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Perspective

The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease

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Abstract The "amyloid hypothesis" has dominated Alzheimer research for more than 20 years, and proposes that amyloid is the toxic cause of neural/synaptic damage and dementia. If correct, decreasing the formation or removing amyloid should be therapeutic. Despite discrepancies in the proposed mechanism, and failed clinical trials, amyloid continues to be considered the cause of a degenerative cascade. Alternative hypotheses must explain three features: (*i*) why amyloid toxicity is not the etiology of Alzheimer's disease (AD), (*ii*) what alternative mechanisms cause the degeneration and dementia of AD, and (*iii*) why increased amyloid accumulates in the brain in AD. We propose that AD, which occurs in elderly, already vulnerable brains, with multiple age-related changes, is precipitated by impaired microvascular function, resulting primarily from decreased Notch-related angiogenesis. With impaired microvasculature, a lack of vascular endothelial-derived trophic factors and decreased cerebral blood flow cause the atrophy of neural structures. Therapeutic strategies should focus on supporting normal angiogenesis.

Keywords: Alzheimer's disease; Amyloid; Microvascular; Endothelium; Notch; Trophic factors; Angiogenesis; Presenilin; Gamma secretase.

1. Introduction

For more than 20 years, the "amyloid hypothesis" of Alzheimer's disease (AD) has been the leading scientific explanation for this degenerative disorder [1,2]. This hypothesis proposes that excess toxic accumulation of amyloid-β (Aβ) in one or more forms [3]—compact plaques, diffuse plaques, soluble oligomers [4,5], fibrils, protofibrils—is the specific cause of AD. The hallmark neuropathological changes, the neuronal and synaptic losses, and the cognitive impairment are considered to result from amyloid-related damage. Evidence for this hypothesis includes the presence of amyloid in neuritic plaques in AD; the genetics of dominantly inherited familial AD, involving mutations of amyloid precursor protein (APP) and presenilin (PS) genes; the occurrence of Alzheimer-like changes in middle-age patients with Down syndrome; the molecular biology of Aβ production from APP; the neurotoxicity of amyloid in tissue culture; positron emission tomographic (PET) imaging of amyloid markers in the brain of patients with AD; and observations on transgenic mouse models of AD with human mutant genes. During the past two decades, more than 18,000 articles on the association of Aβ and AD have been published, and most current therapeutic trials designed to modify disease in AD attempt to prevent the production and accumulation of Aβ in the brain.

Scientific and clinical information makes it clear that Aβ is *associated* with AD. The critical question, however, relates to *causality*: Is Aβ the primary cause of late-onset sporadic Alzheimer's disease (LOSAD)? If so, modifying the production, accumulation, circulation, fixation, or removal of Aβ should be the most appropriate strategies for preventing and/or treating AD [6]. If Aβ is an epiphenomenon associated with the process or processes that cause late-onset sporadic dementia—or a minor contributing factor to LOSAD—therapeutic efforts should be directed at other targets. The evidence for and against the amyloid hypothesis must be evaluated, and alternative explanations considered. Current treatments for AD are of modest,

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symptomatic benefit; disease-modifying therapies will depend on an accurate understanding of the molecular mechanisms that cause AD.

2. Origin of the amyloid hypothesis

In 1907, Alois Alzheimer described the clinical and pathological features of a single patient whose dementia started at age 51 [7]. In 1910, Emil Kraepelin named this *pre*senile dementia "Alzheimer's disease" after his junior associate [8] in his authoritative psychiatric textbook. Neuritic plaques had been described 15 years previously [9], and neurofibrillary tangles earlier in 1907 [10], but the "Alzheimer's disease" eponym from Kraepelin's writing has stuck [11]. For 70 years, AD was considered to be *pre*senile dementia, and was considered very rare. In 1976, Robert Katzman's seminal editorial in the *Archives of Neurology* stated that presenile and senile dementia were sufficiently similar clinically and neuropathologically to be considered a single condition, identified as AD [12]; this designation has been accepted universally.

The presence of amyloid in the brain of patients with AD had been known since at least the 1920s [13], particularly as "congophilic angiopathy" in the cerebral and meningeal blood vessels. Until the 1980s, however, the role of amyloid was generally considered to be a secondary product of altered immunoglobulins [14]. In 1984, Glenner and Wong [15] found that the molecular composition of amyloid from patients with AD was distinctive, and proposed that assessment of Aβ had potential value for diagnostic testing and might be related etiologically to AD. In 1991, Alison Goate found that patients in six families with early-onset dominantly inherited AD (EODI AD) had a mutation involving a gene on chromosome 21 [16,17], which was later shown to code for the APP—a large protein from which the smaller amyloid peptides (Aβ40, Aβ42) found in neuritic plaques in AD were derived. During the early 1990s, other patients with EODI AD, but lacking an APP mutation, were found to have different mutations on chromosome 14 or chromosome 1, causing a similar early-onset form of familial AD (FAD) [18,19]. These mutations altered the structure of an enzyme, subsequently named "presenilin," shown to be part of the γ-secretase complex. γ-Secretase cleaves Aβ42 from the APP protein after an initial cleavage by β-secretase. More than 180 mutations in the PS gene have been found to cause EODI AD, with essentially complete penetrance, and were presumed to increase the production of Aβ42 [20,21]. During the 1990s, a transgenic mouse model of FAD was engineered using the FAD mutant APP human gene [22], which resulted in transgenic (TG) mice with amyloid-containing plaques, slight behavioral changes late in life, but little neuronal or synaptic loss in the hippocampus [23].

This evidence focused attention on amyloid (Aβ42) in the brain of patients with AD. Amyloid-related genetic mutations in the rare FAD suggested that amyloid in the brain might cause AD—not only in EODI FAD, but also in LOSAD as well. Clinical research with amyloid-binding radioisotope ligands (Pittsburgh compound B, florbetapir), which can be imaged with PET scanning, has shown increased amyloid in the brain of patients with AD [24,25], providing additional support for this concept. Pharmaceutical companies and investigators have developed drugs and immunological agents to reduce the production of Aβ42 or to remove fixed amyloid in neuritic plaques. To date, a number of clinical trials have been completed; none have improved cognitive function, although several have effectively removed Aβ42 [26,27]. Questions regarding the logic implicating Aβ as the specific, primary cause of LOSAD, and the failure so far to derive clinical benefit from removing brain amyloid in patients with AD, are the subject of this discussion.

3. Is Aβ the cause of AD?

Many published articles address the relationship between amyloid and AD. This is a brief review of the rationale and strength of evidence supporting amyloid as the cause of AD.

1) The genetic abnormalities in EODI FAD and Down syndrome [28], involving amyloid-related mechanisms, provide the most compelling support for amyloid as the *cause* of LOSAD. Whether sporadic AD is a result of the same mechanism as EODI FAD, and whether the genetic abnormalities indicate that amyloid is the cause of the pathology and dementia in FAD, remain unproved.

2) By definition, LOSAD has a different etiology from EODI FAD and Down syndrome, lacking the genetic abnormalities that produce those conditions. It was presumed initially that in LOSAD, as in the other conditions, the amount of Aβ in brain was increased, and that toxicity of Aβ damaged proximate neurons.

3) It is now clear that amyloid plaques are not adjacent to neurons or synapses lost early in AD [29]. Neurons are typically lost initially in the hippocampus and entorhinal cortex, whereas amyloid plaques are first found in frontal regions, basal ganglia, or elsewhere. How distant plaques might damage neurons or synapses remains unclear.

4) The amount of amyloid in AD brain is not related directly to the extent of cognitive decline [30–32]. The absence of an amyloid-related "dose effect" for the amount of neuronal loss and degree of dementia raises questions regarding the toxic effect of amyloid on the brain.

5) Many cognitively normal elderly subjects have relatively large amounts of Aβ in their brain postmortem [33–35]. Recently, imaging Aβ with Pittsburgh compound B and florbetapir, PET studies in cognitively normal subjects showed that almost a third of elderly individuals have major amounts of Aβ in their brain [36,37]. This suggests that cerebral Aβ plaques are *not sufficient*, to cause AD. Suggestions that cognitively normal elderly subjects with neuritic plaques have "preclinical AD" [33]