Review Article

The Amyloid Beta Cascade Hypothesis in Alzheimer's Disease

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ABSTRACT

The amyloid-β cascade hypothesis has served for decades as the foremost explanation for the pathology of Alzheimer's disease, and it has served as the basis for much research on the mechanisms of and treatments for Alzheimer's, fostering countless discoveries in the field. This paper will review the historical and current evidence both in support of and challenging the amyloid cascade hypothesis to determine its applicability in modern research. More modern variations of the hypothesis acknowledge the importance of other factors and focus on the role of soluble amyloid oligomers have been able to explain many criticisms of the hypothesis, such as the presence of plaques in healthy individuals, and the weak correlation with cognitive decline, and additionally support has come from new amyloid-targeting drugs. However, while amyloid-β likely plays some role in Alzheimer's pathology, evidence suggests that amyloid-β alone does not incite pathogenesis. Instead, Alzheimer's results from a great variety of factors of which amyloid-β may be one, though it is far from being fully understood.

Keywords: Alzheimer's Disease; Neuroscience; Amyloid-β; Amyloid Cascade Hypothesis; Neurodegeneration

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the main cause of dementia, affecting 60-80% of the more than 55 million people with dementia worldwide. As the elderly population grows, so does the prevalence of AD, only increasing the problem it poses (1). For decades, the amyloid-β cascade hypothesis (ACH) has dominated AD research both as a disease mechanism and as a target for treatments (1). Recently, evidence refuting the hypothesis has grown, while more has also been found in support of it. In light of this, it is critical to review all the evidence not only to improve understanding of AD but also to properly guide the development of future treatments.

OVERVIEW OF THE AMYLOID CASCADE HYPOTHESIS

The Original Hypothesis

The ACH was originally devised in the early 1990s by Hardy and Allsop and Hardy and Higgins (2,3). The original hypothesis was that the deposition of the amyloid-β (Aβ) protein is the disease-causing event, resulting in the onset of AD, via a cascade of events including tau phosphorylation, neuroinflammation, neuronal dysfunction, and neuron death (2, 3). Aβ is a short peptide fragment that is produced from amyloid precursor protein (APP), a transmembrane protein

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found in high density within the brain. Though its exact function is unknown, it is believed to play a role in neuronal development and plasticity (4). APP can be processed through one of two pathways. The first, the non-amyloidogenic pathway, involves APP being cleaved by α-secretase in the middle of the Aβ sequence of the protein, preventing its formation. In the amyloidogenic pathway, APP is cleaved by β-secretase, producing a C-terminal fragment, which is cleaved by γ-secretase, producing Aβ peptides, mainly Aβ40 and Aβ42 (1, 4). Of these two, Aβ42 is more hydrophobic and more likely to aggregate, and thus it is the major suspect in the creation of toxic oligomers and plaques (5, 6).

Amyloid-β

Once they are synthesized, Aβ peptides exist in various forms, including monomers, soluble oligomers, protofibrils, and insoluble fibrils (6). The Aβ plaques form in the extracellular space of the brain from insoluble fibrils, and early ACH models focused on plaques as the central toxic form of Aβ (2, 3). However, more recent discoveries suggest that soluble Aβ oligomers may be more neurotoxic than plaques and are mainly responsible for neurodegeneration (1, 7). These soluble oligomers have been reported to interact with various protein receptors, causing their neurotoxic effects. Among these are multiple receptors of the neurotransmitter glutamate, which plays a vital role in learning and memory, and Aβ oligomers' interactions with these receptors can cause an influx of calcium, leading to neurotoxicity. Aβ oligomers have also been found to interact with neurolignin, possibly resulting in synaptic degeneration, as neurolignin plays a critical role in the structure and function of synapses (8).

Evidence Supporting ACH

The primary evidence for this hypothesis was that familial AD had been linked to mutations in the APP gene and later the presenilin (PSEN) 1 and 2 genes, which are components of γ-secretase, and these mutations had been shown to increase the production or aggregation of Aβ42, suggesting that Aβ accumulation was a cause of AD rather than simply a marker (3, 9, 10). Another APP mutation was also discovered which lowers production of Aβ and was found to be protective against AD (11). Additional support came from transgenic animal models. Mice engineered to express mutations of APP or presenilin from familial AD developed Aβ plaques, synaptic loss, neuroinflammation, and impairments of spatial memory (6, 9). Additionally, pharmacological and immunological removal of the plaques decreased synaptic loss and improved spatial memory (9). In humans, positron emission tomography (PET) imaging has shown that the presence of Aβ plaques increases the chances of mild cognitive impairment progressing to AD by four times, supporting the idea that Aβ is an early and possibly an initiating factor in AD (11).

RECENT DEVELOPMENTS IN DRUGS AND THEORIES OF AD

AD Drug development

Some renewed support for the ACH has come from two recent anti-Aβ monoclonal antibodies: lecanemab and donanemab. In Clarity AD, a phase 3 clinical trial comparing lecanemab to a placebo in patients with early AD, lecanemab saw moderately less cognitive decline, with an increase of 1.21 on the CDR-SB, compared to 1.66 with the placebo (12). Additionally, in TRAILBLAZER ALZ, a phase 2 trial comparing donanemab to a placebo in early AD, donanemab saw less decline in Integrated Alzheimer's Disease Rating Scale scores, with a change of -6.86 compared to -10.06 with the placebo (13). However, clinically meaningful differences have not been established for either scale, and these results are not superior to those seen with symptomatic treatments such as the acetylcholinesterase inhibitor donepezil, which, in a phase 3 trial, saw scores ADAS-cog 2.5 and 3.1 points better than the placebo, while in the previously mentioned lecanemab trial, lecanemab saw ADAS-cog scores only 1.44 points better than placebo (1, 12, 14). Despite this, the moderate success of these two anti-Aβ monoclonal antibodies lend credibility to the ACH and the importance of Aβ as a target for therapies (13, 14).

Oligomer Hypothesis

In response to criticisms, the ACH has changed over time, being refined and expanded rather than entirely discarded. One of the most important shifts has been the recognition that soluble Aβ oligomers, rather than insoluble plaques, may be the most neurotoxic form. These have been shown to be capable of disrupting synaptic transmission, impairing plasticity, and triggering downstream events like tau hyperphosphorylation and inflammation, even in the absence of visible plaques through interactions with various receptors, including glutamate receptors, prion protein, and neurolignins (6, 8, 9, 11). This "oligomer

hypothesis" helps to explain the lack of correlation between Aβ plaques and cognitive decline, as the plaques may not cause any harm on their own, possibly being an incidental result of oligomers or a reservoir for them. The latter theory may also explain why plaques can remain in cognitively healthy individuals for years (1, 8, 10).

Amyloid-tau Interaction

Another modification to the original theory is the "amyloid-tau interaction" model, which suggests that Aβ accumulation may initiate the disease but that tau pathology drives neurodegeneration and clinical decline. In this model, Aβ is necessary but not sufficient. Tau, inflammation, and other factors determine the pace and severity of the disease (1, 7, 9). This is another possible explanation for the stronger correlation of cognitive decline with neurofibrillary tangles than Aβ plaques and the presence of plaques in cognitively normal individuals (1, 10)

CRITICISM AND LIMITATIONS

Gaps in Evidence

Despite its initial promise, the ACH has been increasingly scrutinized due to clinical trial failures and gaps between pathology and symptoms. One of the most significant criticisms is the weak correlation between an individual's amount of Aβ plaques and cognitive decline (1, 11). While there does exist a modest correlation between the two. Multiple autopsy studies and PET scans have shown that some individuals with extensive Aβ deposits, even enough to satisfy AD diagnosis criteria, still show few dementia symptoms (11, 15-17). These individuals are also quite common, making up 30% or more of older individuals with normal cognitive function, and although these individuals may be more likely to develop AD, many remain cognitively healthy, even after 5 years (1, 11, 16). Meanwhile, other factors such as neurofibrillary tangles correlate more closely with cognitive decline and are rarely seen in cognitively normal individuals (6, 15, 16). These results suggest that while Aβ may play some role in cognitive decline, it alone is not sufficient to cause dementia symptoms.

Clinical Trials

Perhaps the most significant setback to the hypothesis has come from clinical trials targeting Aβ. Numerous drugs designed to reduce Aβ production, aggregation, or deposition, including solanezumab, bapineuzumab, and gantenerumab, have failed to demonstrate meaningful cognitive improvement (1, 7, 9, 10). Two phase 3 trials, EXPEDITION 1 and 2, which compared solanezumab to a placebo found no significant differences in scores on the ADAS-cog or the Clinical Dementia Rating–Sum of Boxes (CDR-SB) between the two groups (18). Additionally, two other phase 3 trials comparing bapineuzumab to a placebo found no significant differences in scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), despite the bapineuzumab having a significant reduction in Aβ accumulation on a PET scan (19). For gantenerumab, two phase e trials, GRADUATE 1 and 2, which compared it to a placebo saw no significant difference in change from baseline CDR-SB scores between the groups, despite partial removal of Aβ plaques (20). These outcomes led many researchers to reconsider whether Aβ plaques are a driver of AD that should be targeted for therapy, or they are simply a byproduct of it.

CONCLUSION

The ACH has arguably been the most important framework in the history of Alzheimer's research. It was able to explain the genetic, biochemical, and pathological findings associated with the AD at the time of its creation, and it has served as the basis for AD research and treatment for decades. Despite all this, while Aβ in some form is likely a necessary component of AD pathology, the existing evidence suggests that it is certainly not sufficient on its own, nor is it the sole causative factor. While the oligomer hypothesis and theories of tau interaction provide promising steps forward, in order to truly understand the pathology of AD, much more research is required to investigate these complex pathways and interactions that drive this multifactorial disease. With promising results from new anti-Aβ monoclonal antibodies, though Aβ may not be the initiating factor, it could still as an effective target for future AD treatments, and as the pathology of AD is increasingly understood, more focus ought to be placed on multi-targeted approaches to treatment to manage all factors of the disease.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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