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A review on the β-amyloid precipitation hypothesis

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Abstract. Alzheimer's disease (AD) is a well-known mental illness and memory loss is its most common symptom. Until now, the reason of AD has been an unsolved mystery, with the two most prominent previous hypotheses being β-amyloid deposition and Tau protein phosphorylation. However, this year, a seminal paper studying the β-amyloid precipitation hypothesis was found to be falsified, therefore, a large number of scientists have questioned the research value of this hypothesis. This paper is a review of the β-amyloid precipitation hypothesis. The development of β-amyloid precipitation hypothesis is described and previous studies on Aβ*56, Aβ42, and Aβ40 are reviewed. It is concluded that β-amyloid precipitation should continue to be studied. The author also argues that the falsification does not mean that the "amyloid" hypothesis is wrong; the only protein suspected of falsification is Aβ*56. The Aβ hypothesis can still be pursued because there are many other Aβ oligomers that have been shown to be neurotoxic.

Keywords: Alzheimer's disease (AD), β-amyloid hypothesis, Aβ42, Aβ*56.

1. Introduction

Alzheimer's disease (AD) is a central nervous system degenerative condition that typically affects elderly people and is characterized by gradual cognitive dysfunction and behavioral impairment. As the average human lifetime rises, AD is becoming more and more common. β-amyloid deposition is currently the most influential hypothesis in the study of the pathogenesis of AD. In 2021, when investigating Simufilam, an experimental drug for AD, Matthew Schrag found that a Nature article published in 2006 with Lesné as the first author and Karen Ashe, a renowned neuroscientist and professor at the University of Minnesota (UMN), as the corresponding author, appeared to contain multiple doctored images [1]. At that time, the attack on the Aβ deposition hypothesis was overwhelming and many neurobiologists began to question the Aβ deposition hypothesis. This review paper describes the development of β-amyloid precipitation hypothesis and introduces what Aβ42 and Aβ*56 are. Besides, the effects of Aβ42 and Aβ*56 on the human body is also analyzed. This paper helps prove that β-amyloid precipitation can be studied further.

2. The development of β-amyloid precipitation hypothesis

Memory loss, frequent lying to cover up negligent behavior, confusion, agitation and anxiety, and mania are typical symptoms of AD. Originally, scientists discovered through autopsy that patients with AD had reduced brain size, tangled neurogenic fibers, and degenerated neuronal cells [2]. To this day, scientists have named the deposits in the brains of Alzheimer's patients beta-amyloid, and they think

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that the deposition of β amyloid (Aβ) is one possible biomarker for Alzheimer. With the development of many novel radiotracers that bind to fibrillar Aβ, sensitive estimations of amyloid deposition in diverse brain areas are now possible [3].

According to the author of the article "A particular amyloid-protein assembly in the brain impairs memory" published in 2006, when given to young rats, A*56 isolated from the brains of damaged Tg2576 mice damages memory. A*56 affects memory in a way that is unrelated to plaque formation or neuronal death and may be a factor in the cognitive deficits associated with AD [4]. Cited more than 2,200 times, this article is the seminal work in the field of the "amyloid" hypothesis of AD (Figure 1). What Figure 2 is trying to convey is that, as the mice in the AD model get older, the expression level of the Aβ*56 protein increases [1]. In fact, the falsification may not mean that the "amyloid" hypothesis is wrong since only the Aβ*56 protein is suspected to be falsified, and there are many other Aβ oligomers that have been shown to be neurotoxic. The group of Sylvain Lesné points out that Aβ*56 is the culprit [4]. Steven and Qin put forward that Aβ42 will cause Alzheimer's disease [5,6]. The following sections mainly argue about these views.

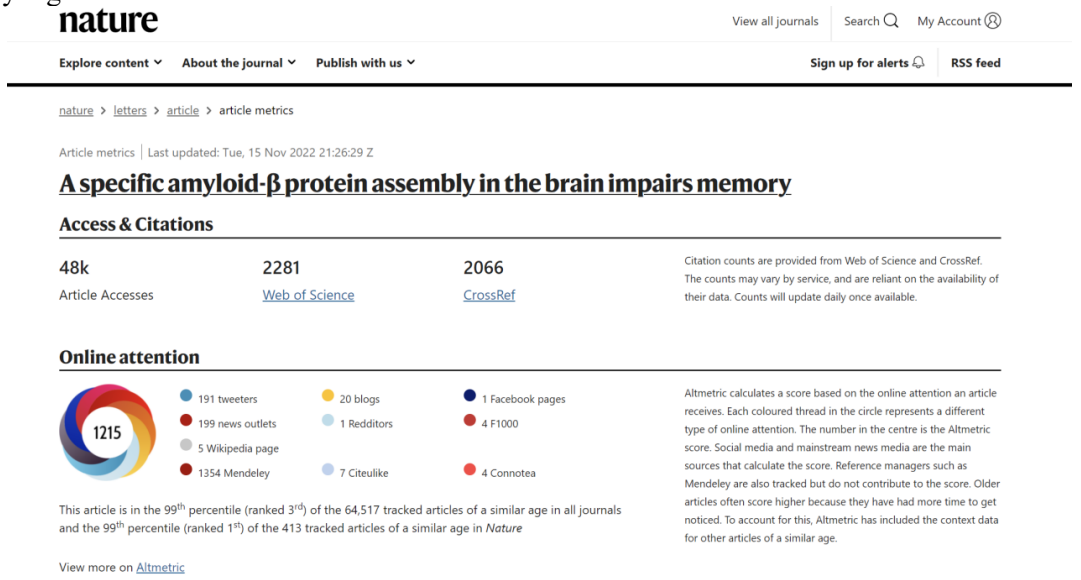

Figure 1. Number of citations of articles that found to be image falsified [4].

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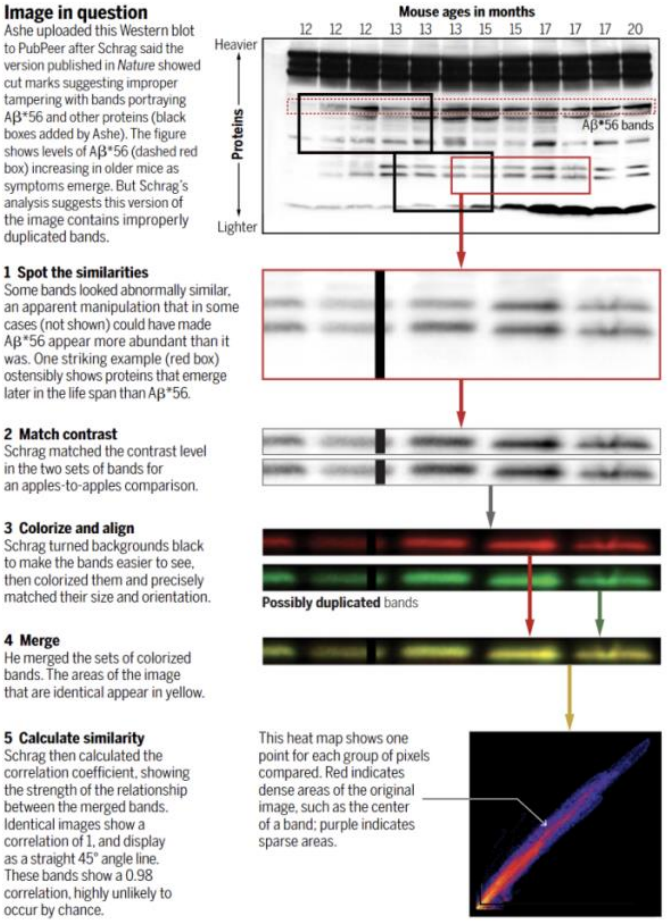

Figure 2. The data Ashe provided on PubPeer after Schrag challenged the original paper's data, which still shows signs of copying [1].

3. Previous studies on Aβ*56

*3.1. How Aβ*56 was found to be damaging to memory*

The decline in memory function that occurs with aging is thought to be caused by changes in synaptic function. It is also believed that some individuals with AD develop the disease through neurodegeneration. To study the causes of this loss, Sylvain Lesné and other biologists used a mouse that has a variant of the human amyloid precursor protein. The young Tg2576 mice had normal memory, while the older ones had neuritis plaques that were filled with amyloid-β. Middle-aged Tg2576 animals, on the other hand, developed memory deficits without loss of neurons. Sylvain Lesné and other biologists discovered that the deficits in these animals were caused by the accumulation of 56-kDa of soluble amyloid-β in the extracellular matrix. In the brains of damaged Tg2576 mice, Aβ*56 was purified. When purified Aβ*56 was given to young rats, the animals exhibited memory deficits. Therefore, scientists are believed that this substance can contribute to the development of AD [4].

*3.2. The effect of Aβ*56*

It is thought that the primary beginning component in neurodegenerative illnesses, such as AD, is the production of oligomers of amyloid-forming proteins. These have been linked to the phosphorylation and aggregation of tau. From the AD model Tg2576 mice, several Aβ variants were identified. Amar and more researchers found that modifications in neuronal signaling were induced by the 56-kDa oligomer A*56, which is known to be detected prior to the onset of illness symptoms in patients. A*56

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interacts with N-methyl-d-aspartate receptors in primary cortical neurons. This interaction increases the Ca2+ influx and the concentration of Ca2+ in the cytoplasm. It also activates the CaMKII protein, which is known to be involved in the development of AD. In Tg2576 mice, the activation of this protein was linked to an increase in the site-specific phosphorylation and the mis sorting of tau. In contrast, the effects of exposure to other oligomers, such as trimers and dimers, were not detected in cultured primary cortical neurons. These findings suggest that the various pathways that are involved in the activation of neurons can be efficiently targeted by the different Aβ assemblies [7].

4. Previous studies on Aβ42

4.1. The formation of Aβ 42

Studies have shown that the amyloid β-protein, which is a component of AD, plays a central role in the development of the disease. As shown in Figure 3, it is produced by two aspartic enzymes, β- and γ-secretases. The former cleaves APP and allows it to be shed into the extracellular fluid and luminal. The latter leaves a C-terminal residue. After the amino acid long stub is cleaved by γ-secretase, the resulting Aβ is released [8].

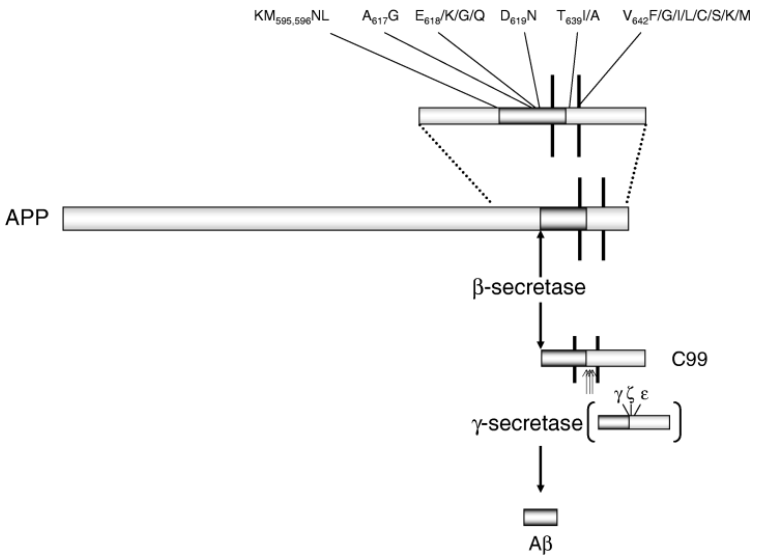

Figure 3. β-Amyloid precursor protein (APP) mutations and processing [8].

Depending on the point at which the cleavage occurs, three different forms of Aβ are produced. These include 38, 40, and 42 amino acid residues. The relative quantity of A42 formed is noteworthy because it is more prone to forming amyloid fibrils and oligomerizing than the more abundantly produced A40 peptide [8].

4.2. The effect of Aβ42

Although it is known that the accumulation of Aβ can lead to AD, it is also believed that the protein can function as a neurotrophic factor. Some studies suggest that it can stimulate the growth of neurons and promote the development of antimicrobial peptides in the innate immune system. Meanwhile, Aβ could potentially be involved in the activation of phosphokinase and the transportation of cholesterol [5].

According to the amyloid hypothesis, Aβ monomer is not harmful. After aggregation, it can cause harmful effects, though. These include heightened membrane permeability, elevated oxidative stress, altered cell skeleton, apoptotic pathway activation, and memory retention deficits. Blood, brain, and CSF samples containing stable low-molecular-weight A-42 oligomers were found to be related to the prevalence of AD [5].

A basic consequence of mutations linked to familial Alzheimer's disease (FAD) is an increase in Aβ42 extracellular concentration. Aβ42 is deposited early and selectively in senile plaques, which are

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an unchanging hallmark of all forms of AD, suggesting that this action of FAD-associated mutations may be directly related to the pathophysiology of the disease. The findings of Steven support the idea that brain Aβ deposition is a crucial early event in the etiology of all forms of AD and provides strong evidence that FAD-associated mutations all contribute to Aβ deposition by raising the extracellular concentration of Aβ42 [6].

5. The difference between Aβ42 and Aβ40

The most significant Aβ isomers are seen as being Aβ40 and Aβ42. The only distinction between them is an extra isoleucine and an alanine at the C-terminus of Aβ42 [5].

Because of its link to toxicity caused by the Aβ peptide, copper is recognized as a significant contributor to the pathophysiology of AD. According to Lu Jin's research, copper changes the morphology and structure of A-42 and increases its toxicity, while it has no discernible impact on A-40. They draw the conclusion that copper induces the development of A-42 nanoscale oligomers, which is a crucial process in neurotoxicity [9].

According to the research of Chang's team, a high Aβ40/Aβ42 ratio shields neurons against the harmful effects of Aβ42. This may imply that restoring the proper ratio of Aβ. The potential synergistic interactions between βA42 and Aβ40 in vivo, however, are not well understood [10]. Kim J's group also found that Aβ40 has a strong anti-amyloidogenic effect in the brain of Tg2576 mice and is protective during pathogenesis [11].

6. Diagnosing Alzheimer's disease

The increasing importance of the diagnosis and validation of AD and other forms of dementia has led to the development of new diagnostic tools. Currently, the most common method for determining the presence of β-amyloid (1–42), total tau and phospho-tau-181 in cerebrospinal fluid (CSF) is the ELISA [12].

Hansson, O 's group's finding also suggest that when analyzing CSF AD biomarkers, the CSF Aβ42/40 ratio should be used rather than the absolute value of CSF Aβ42 to increase the proportion of patients correctly diagnosed [13].

7. Conclusion

Although a seminal article on AD was revealed to be a falsification of images, the β-amyloid hypothesis cannot be completely rejected. In addition to Aβ*56, there are various oligomers of beta amyloid, including Aβ42 and Aβ40. These other oligomers of beta amyloid have been suggested by other scientists to have more or less toxic effects on the human brain. This paper also aims to use some previous studies to show that this hypothesis should not be completely abandoned, but more funds and manpower should be devoted to the study of other β-amyloid oligomers. The pathogenesis of AD is still a mystery, so, any research direction should not be given up.

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