Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/59/20241401

Study on hypothesis of amyloid beta protein being the causative factor of Alzheimer's disease

Yinuo Liu

Xi'an Jiaotong-Liverpool University, Wisdom Lake Academy of Pharmacy, Suzhou, 215000, China

noahlyn@163.com

Abstract. At present, people have many hypotheses about the cause of Alzheimer's disease, AD is used in the following text, among which the amyloid beta protein hypothesis is one of the most famous hypotheses about the cause of AD. Therefore, to study the method of completely curing AD, amyloid beta protein, Aβ is used in the following text, is the most important research object, and the study of drugs targeting Aβ has become the hope of people's treatment of AD. The research topic of this review is whether Aβ is the cause of AD, that is, whether the amyloid beta hypothesis is valid. By reading literature and analyzing several drugs that have been developed and have effects on Aβ, this paper proves whether Aβ is related to AD. The results showed that the number of Aβ had an important relationship with the severity of AD that is, the amyloid beta hypothesis was established.

Keywords: Alzheimer's disease (AD), Amyloid beta (Aβ), Aducanumab, clinic trial, bio-pharmaceuticals.

1. Introduction

Alzheimer's disease has been studied for a hundred years. In this long time, many causes have been proposed, and many drugs have been developed, but there is still a lot of confusion about AD. Many of the causes that have been identified are mere conjecture, making it difficult to develop a cure for Alzheimer's [1]. Two of the most well-known hypotheses about the causes of AD today are the amyloid beta protein hypothesis and the tau protein hypothesis [2]. The research topic of this paper is whether Aβ may be the cause of AD. At present, some research results can help people to prove this hypothesis. This paper will summarize the existing results, through the formation mechanism of Aβ, the pathogenic principle, and the mechanism of Aβ And the effect of drugs targeting Aβ on AD, etc., to prove that amyloid beta is the cause of AD. Studying whether Aβ is the cause of AD is of great significance for the cure of AD, it can help people to deeply understand the pathogenesis of AD, take targeted prevention and treatment, formulate more advanced medical strategies, can aid in the creation of fresh therapeutic targets. Under the current trend of global population ageing, Alzheimer's disease is bound to become a high-incidence disease worldwide. Research on the relationship between Aβ and AD is likely to become an important area of future medical development, contributing to public health and prevention. And it can lay a certain foundation for clinical medicine.

DOI: 10.54254/2753-8818/59/20241401

2. The Introduction Of AD And AB

2.1. The Pathogenesis of Alzheimer's Disease

Alzheimer's disease, a progressive neurodegenerative disease, was described by the German doctor Alzheimer's. Memory loss, cognitive decline, behavioural abnormalities, and a progressive loss of the capacity to carry out daily activities are the hallmarks of AD. As the disease progresses, the patient's mental function will gradually decline and eventually lose the ability to take care of themselves. At present, there is no definitive answer for the cause of AD, nor is there a radical cure. Through research, people have put forward many hypotheses about the causes of AD. Based on the analysis of structural abnormalities in the brains of patients, two hypotheses are best known: the amyloid beta protein hypothesis and the tau protein hypothesis.

2.2. The Concept of AB

Aβ is A protein that occurs naturally in the human brain, but in the brains of people with Alzheimer's disease, this protein accumulates excessively into plaques, which are suspected to be the cause of Alzheimer's disease. The human brain has a short peptide of 42 amino acids. It is sliced from a bigger protein precursor. Although the Aβ is involved in numerous cellular activities, its aberrant metabolism causes peptides to build up in the brain as plaques, which may eventually cause AD. Therefore, further research on the drugs targeting amyloid beta will have a profound impact on the treatment of AD. Aβ is A protein fragment produced by the amyloid precursor protein, referred to later by APP [3]. Apps play important physiological functions in the human body, such as helping the development of neurons and promoting signal transmission and communication between different neurons. In a normal physiological environment, Aβ plays a crucial part in helping to the brain, such as participating in the regulation of plasticity, maintaining the normal function of neurons, anti-oxidation (preventing neurons from being damaged by free radicals), and so on. In addition, studies have shown that Aβ has the function of enhancing memory at A certain physiological concentration [4].

3. The Pathogenesis of Aβ

APP is cut into different fragments after A series of enzyme digestion reactions, and these fragments are Aβ, which is cut into A different type of Aβ. Depending on the length, there are two main subtypes of Aβ-atmosphere: Aβ-40 and Aβ-42 [5]. Aβ40 is more abundant, and Aβ42 is more likely than the former to form insoluble fibrous deposits in the brain, which are the plaques deposited in the brains of AD patients. At the same time, the toxicity of Aβ is also thought to be the cause of Alzheimer's disease in people. Aβ forms soluble oligomers before aggregating into large plaques, and these oligomers are more neurotoxic than the plaques they form [6]. Aβ oligomers can bind to the receptor cells on the neuronal membrane to destroy the normal physiological function of the neuronal structure, and finally lead to apoptosis. They can also establish ion channels in the cell membrane, causing the loss of other ions such as calcium ions to cause the loss of cell ion balance, leading to further cell apoptosis. Moreover, Aβ oligomers can promote the production of Reactive oxygen species, promoting oxidative stress responses, which can lead to severe damage to proteins, lipids, DNA and other substances within cells, ultimately leading to the death of neurons [7]. The Aβ proteins themselves have also been shown to be somewhat toxic, activating microglia and astrocytes in the brain to release inflammatory factors. These inflammatory factors trigger a chronic inflammatory response, leading to neuronal damage and exacerbating the symptoms of neurodegenerative diseases. The Aβ protein also acts on another protein important for studying AD: tau. Aβ protein can induce abnormal phosphorylation of tau protein to form Neurofibrillary tangles. Neurofibrillary tangles can disrupt the microtubule structure of neurons, causing certain obstruction to intracellular material transport and ultimately leading to neuron death. In addition, the accumulation of Aβ protein in the case of excessive damage to the human blood brain barrier, so that the integrity of the blood brain barrier is affected. It also causes increased permeability of blood vessels, resulting in the gradual failure of the blood-brain barrier, in order for a variety of dangerous chemicals to penetrate the blood-brain barrier, enter the human brain, and worsen neuronal damage.

DOI: 10.54254/2753-8818/59/20241401

Just like this, Aβ can cause damage to neurons through A variety of mechanisms, and these mechanisms interact with each other to cause damage to the brain, eventually leading to the gradual impairment of brain function [8], cognitive function, memory function in AD patients, which is why people believe that Aβ is the main cause of AD.

4. Use of Drug Certification

In addition to illustrating the effects of the toxicity of the Aβ protein itself on the human brain, drugs can also be used to prove that Aβ is the cause of AD. The effect of drugs targeting Aβ on the remission of AD can be an important basis. Drugs targeting Aβ can reduce the amount of oligomers of Aβ protein and plaques deposited by Aβ in the human brain, and if the amount of these substances is reduced, if the symptoms of AD patients are alleviated or the development of AD disease is delayed, it indicates that Aβ is associated with AD. Many new drugs target Aβ, such as Anhui protein [9], Gantenerumab [10], Tarenflurbil and so on. In this paper, Aducanumab, the latest Aβ-targeting drug in recent years, was selected as an example.

The U.S. Food and Drug Administration authorized aducanumab, a new human monoclonal antibody against amyloid beta protein, in June 2021 for the treatment of Alzheimer's disease. This is the first medication for humans to be licensed since 2003. It targets other Aβ selectively, including soluble oligomers and insoluble fibres. in this paper, the procedure, data and results of Two randomized phase 3 studies of aducanumab in early Alzheimer's disease were selected for reference, so as to discuss the research topic.

4.1. The Experimental Information of the Trial

To test this hypothesis, a trial was set up called Two randomized phase 3 studies of aducanumab in early AD. The first question is how to design the trial. First, divide the subjects into EMERGE AND ENGAGE, they were two randomized, double-blind, placebo-controlled, global, phase 3 studies of aducanumab in patients with early AD. As shown in the table, it has been made that about gender, nationality, clinical stage and some other information of subjects in both groups. EMERGE started earlier than ENGAGE for a month. Then divide equal amounts into three groups. Separate injection high concentration of aducanumab, low concentration and placebo. Then record the results. Among them, the high dose is 10 mg/kg, The low dose is 3 or 6 mg/kg. For 76 weeks, the injection schedule was once every four weeks. The major end measure, known as the clinical dementia rating sum of boxes (CDR-SB) in the text that follows, was the change from baseline to 78 on this composite evaluation of cognitive and functional ability. Biomarker endpoints, secondary and tertiary clinical outcomes that assessed behavior, function, and cognition, and safety assessments were additional measurements. The whole experiment was double-blind [11].

Table 1. Demographic and baseline disease characteristics [11]

	Placebo n=548	Low dose n=543	High dose n=547	Placebo n=545	Low dose n=547	High dose n=555
Age,mean±SD,years	70.8 ±7.4	70.6±7.4	70.6±7.5	69.8±7.7	70.4±7.0	70.0±7.7
Female,n(%)	290(53)	269(50)	284(52)	287(53)	284(52)	292(53)
Race,n(%)						
American Indian or Alaska	1(0.2)	0(0)	0(0)	0(0)	0(0)	0(0)
Asian	47(9)	39(7)	42(8)	55(10)	55(10)	65(12)
Black or African American	1(0.2)	6(1)	4(1)	5(1)	1(0.2)	2(0.4)
Native Hawaiian or other Pacific Islander	0(0)	0(0)	0(0)	0(0)	1(0.2)	0(0)
White	431(79)	432(80)	422(77)	413(76)	412(75)	413(74)
Not reported due to confidentiality regulations	67(12)	65(12)	75(14)	69(13)	74(14)	72(13)
Other	1(0.2)	1(0.2)	3(1)	3(1)	4(0.7)	3(1)

DOI: 10.54254/2753-8818/59/20241401

Table 1. (continued).

thnicity,n(%)						
Hispanic or Latino	22(4)	22(4)	23(4)	13(2)	11(2)	13(2)
Not Hispanic or Latino	470(86)	470(87)	461(84)	489(90)	492(90)	499(90)
Not reported due to confidentiality regulations	56(10)	51(9)	62(11)	43(8)	44(8)	43(8)
Education,mean±SD,years	14.5±3.7	14.5±3.6	14.5±3.6	14.7±3.7	14.6±3.8	14.6±3.7
Alzheimer's disease medications used,n(%)	282(51)	281(52)	285(52)	299(55)	317(58)	313(56)
ApoE ε4,n(%)						
Carriers	368(67)	362(67)	365(67)	376(69)	391(71)	378(68)
Noncarriers	178(32)	178(33)	181(33)	167(31)	156(29)	176(32)
Clinical stage,n(%)						
MCI due to Alzheimer's disease	446(81)	452(83)	438(80)	443(81)	440(80)	442(80)
Mild Alzheimer's disease	102(19)	91(17)	109(20)	102(19)	107(20)	113(20)
BANS delayed memory score,mean±SD	60.5±14.2	60.0±14.0	60.7±14.2	60.0±13.6	59.5±14.2	60.6±14.1
MMSE score,mean±SD	26.4±1.8	26.3±1.7	26.3±1.7	26.4±1.7	26.4±1.8	26.4±1.8
CDR global score,n(%)						
0.5	545(99)	543(100)	546(100)	544(100)	546(100)	554(100)
	3(1)	0(0)	1(0)	1(0)	1(0)	0(0)
CDR-SB score, mean±SD	2.47±1.00	2.46±1.01	2.51±1.05	2.40±1.01	2.43±1.01	2.40±1.01
ADAS-Cog13 score,mean±SD	21.87±6.73	22.49±6.76	22.25±7.07	22.48±6.56	22.52±6.30	22.40±6.54
ADCS-ADL-MCI score,mean±SD	42.6±5.7	42.8±5.5	42.5±5.8	43.0±5.6	42.9±5.7	42.9±5.7
ET substudy population	n=159	n=159	n=170	n=204	n=198	n=183

4.2. The Results of the Trial

Both trials were stopped early as a result of a futility analysis of provisional data, which is an early assessment of whether an experiment is worth going forward. While meeting the pre-set futility criterion that the experiment is unlikely to demonstrate clinical benefit, it violates two assumptions of the futility analysis. One is that the two studies' treatment effects are comparable, and the other is that the impact is continuous, that is, the patients enrolled in the late period have the same effect as the patients enrolled in the early period. So the next step is to reanalyze the data. From the table, it is obvious to see that the value of CDR-SB in the EMERGE group decreased by 15% compared with the baseline in the low-dose group and 22% in the high-dose group. In the ENGAGE group, the low dose group decreased by 12%, but the high dose group not only did not decrease, it even increased by 2% above the baseline. In the engage, the trial failed to meet its primary endpoints, showing no statistically significant difference in slowing cognitive decline between the treated and placebo groups. But conversely, this study met its primary endpoints, indicating that patients treated with aducanumab experienced a slower rate of cognitive and functional decline than those who received the placebo. But the point that is needed to make is that in the trial, some people showed adverse reactions, which can be strong or weak, including headache, dizziness and so on.

DOI: 10.54254/2753-8818/59/20241401

Table 2. Week 78 primary and secondary endpoints [11]

	Placebo decline ±SE (n=548)	Difference vs placebo(%)ll 95% CI P		Placebo decline ±SE (n=545)	Difference vs placebo(%)11 95% CI P	
		Low dose (n=543)	High dose (n=547)		Low dose (n=547)	High dose (n=555)
Primary						
CDR-SB*	1.74±0.11	-0.26(-15%)	-0.39(-22%)	1.56±0.11	-0.18(-12%)	0.03(2%)
		-0.57,0.04	-0.69,-0.09		-0.47,0.11	-0.26,0.33
		.090	.012		.225	.833
Secondary						
MMSE+	-3.3±0.2	-0.1(3%)	0.6(-18%)	-3.5±0.2	0.2(-6%)	-0.1(3%)
		-0.7,0.5	0.0,1.1		-0.3,0.7	-0.6,0.5
		.758	.049		.479	.811
ADAS-Cog 13	5.16±0.40	-0.70(-14%)	-1.40(-27%)	5.14±0.38	-0.58(-11%)	-0.59(-11%)
		-1.76,0.36	-2.46,-0.34		-1.58,0.42	-1.61,0.43
		.196	.010		.254	258
ADCS-ADL-MCIS	-4.3±0.4	0.7(-16%)	1.7(-40%)	-3.8±0.3	0.7(-18%)	0.7(-18%)
		-0.3,1.7	0.7,2.7		-0.2,1.6	-0.2,1.6

4.3. The Discussion of the Trial

The results of this trial provide some key insights and implications for early AD. First is the inconsistency of the experimental results between the two groups. As shown in the table, in Emerge, the three secondary objectives and the primary endpoint showed statistically significant reductions in clinical deterioration. However, neither the primary nor secondary goals were reached in Engage. This difference could be due to factors such as differences in trial design, execution, or baseline characteristics of the participant population. The positive results of the emerging trial shows the positive results of a statistically significant reduction in the rate of cognitive decline suggesting that aducanumab may be effective for some patients with early-stage AD. This suggests that Aducanumab has the potential to reduce the Aβ burden in the brain, possibly through this mechanism to slow the progression of the disease. However, because of the difference between the two sets of results, we can't really say whether it works, only that it can agree with our conjecture to a certain extent, and support the hypothesis that amyloid beta is the causative agent of AD.

While the results of the EMERGE trial provide support for therapeutic strategies targeting amyloid beta, the results of the ENGAGE trial remind us that the understanding of the pathogenesis of AD still needs to be further depended, and other therapeutic targets may need to be explored. In addition, from the results between the two groups, after adding the same dose of aducanumab, the decrease of amyloid beta protein volume in the ENGAGE group was 16.5% lower than that in the EMERGE group, which means that under the same dose, aducanumab also works differently in people, which is also a point worth discussing. It is still needed to study why the treatment works differently at the same dose.

DOI: 10.54254/2753-8818/59/20241401

However there is still some room for improvement in the design and conjecture of the experiment. It is likely different genetic backgrounds for participants, different rates at which they develop resistance to aducanumab, different lifestyles and habits, and whether other diseases affect the effectiveness of aducanumab. However, further research is needed to establish the exact rules that would make aducanumab a consistent benefit for most people. These trial results also highlight how to select and define the most appropriate participants, assessment measures, and efficacy criteria when conducting clinical trials for AD to accurately reflect the potential benefits and risks of drugs. The above experiment can be used as a strong argument to prove that Aβ is the cause of AD.

5. Conclusion

From the above introduction, there are several ways to prove the hypothesis that Aβ is the cause of AD. Through the analysis of the pathological mechanism of AD, the structure of Aβ, the pathological mechanism of pathogenesis, in addition to the thorough explanation of how medications targeting Aβ affect individuals with AD, the relationship between Aβ and AD was explained in more detail, once to support the hypothesis that Aβ is the cause of AD. However, in order to confirm that Aβ is the cause of AD, the current research results are still lack of practical proof. For example, Acanumab in early AD was the subject of two randomized phase 3 trials. Aβ levels were not reduced in the ENGAGE group. Finding out the cause and principle is the key to the thorough treatment of AD. Therefore, the follow-up research direction should still focus on further demonstrating the hypothesis that Aβ is the cause of AD, while other hypotheses such as tau protein hypothesis, Heredity hypothesis [12] should not be abandoned. At the same time, the study of multiple hypotheses is conducive to the improvement of the cause of AD in the AD field, and multiple viewpoints complement each other. Studying multiple hypotheses at the same time can help accelerate the breakthrough of AD field. In this paper, although the current famous theories are listed, there are still many theories and research results that are not presented, and the conclusions are also limited to a certain extent. In the follow-up research process, it is still necessary to summarize more research results to support this conclusion.

References

[1] 2023 Alzheimer's disease facts and figures. (2023). Alzheimer's & dementia : the journal of the Alzheimer's Association, 19(4), 1598–1695. https://doi.org/10.1002/alz.13016

[2] Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules (Basel, Switzerland), 25(24), 5789. https://doi.org/10.3390/molecules25245789

[3] Chen, G. F., Xu, T. H., Yan, Y., Zhou, Y. R., Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: structure, biology and structure-based therapeutic development. Acta pharmacologica Sinica, 38(9), 1205–1235. https://doi.org/10.1038/aps.2017.28

[4] Morley, J. E., & Farr, S. A. (2014). The role of amyloid-beta in the regulation of memory. Biochemical pharmacology, 88(4), 479–485. https://doi.org/10.1016/j.bcp.2013.12.018

[5] Chau, E., & Kim, J. R. (2022). α-synuclein-assisted oligomerization of β-amyloid (1-42). Archives of biochemistry and biophysics, 717, 109120. https://doi.org/10.1016/j.abb.2022.109120

[6] Ashe K. H. (2020). The biogenesis and biology of amyloid β oligomers in the brain. Alzheimer's & dementia : the journal of the Alzheimer's Association, 16(11), 1561–1567. https://doi.org/10.1002/alz.12084

[7] Arbor, S. C., LaFontaine, M., & Cumbay, M. (2016). Amyloid-beta Alzheimer targets - protein processing, lipid rafts, and amyloid-beta pores. The Yale journal of biology and medicine, 89(1), 5–21.

[8] Aleksis, R., Oleskovs, F., Jaudzems, K., Pahnke, J., & Biverstål, H. (2017). Structural studies of amyloid-β peptides: Unlocking the mechanism of aggregation and the associated toxicity. Biochimie, 140, 176–192. https://doi.org/10.1016/j.biochi.2017.07.011

[9] Hosoi, T., Yazawa, K., Imada, M., Tawara, A., Tohda, C., Nomura, Y., & Ozawa, K. (2023). Alkannin Attenuates Amyloid β Aggregation and Alzheimer's Disease Pathology. Molecular pharmacology, 103(5), 266–273. https://doi.org/10.1124/molpharm.121.000468

[10] Söderberg, L., Johannesson, M., Nygren, P., Laudon, H., Eriksson, F., Osswald, G., Möller, C., & Lannfelt, L. (2023). Lecanemab, Aducanumab, and Gantenerumab - Binding Profiles to Different Forms of Amyloid-Beta Might Explain Efficacy and Side Effects in Clinical Trials for Alzheimer's Disease. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics, 20(1), 195–206. https://doi.org/10.1007/s13311-022-01308-6

[11] Budd Haeberlein, S., Aisen, P. S., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., Dent, G., Hansson, O., Harrison, K., von Hehn, C., Iwatsubo, T., Mallinckrodt, C., Mummery, C. J., Muralidharan, K. K., Nestorov, I., Nisenbaum, L., Rajagovindan, R., Skordos, L., Tian, Y., van Dyck, C. H., … Sandrock, A. (2022). Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. The journal of prevention of Alzheimer's disease, 9(2), 197–210. https://doi.org/10.14283/jpad.2022.30

[12] Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. Lancet (London, England), 397(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4