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A Vision for Treating Alzheimer's Disease

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Abstract. A β is a type of amyloid that is the main component of the senile plaques found in the brains of people with Alzheimer's disease. It is generally thought to be associated with various neurodegenerative behaviors. At the same time, cellular autophagy disorders have also been observed in large numbers in Alzheimer's patients. However, due to technical obstacles, humans have not been very clear about the specific mechanism of Alzheimer's. Previously, the mainstream view has been that A β causes autophagy disorder, which leads to Alzheimer's disease. However, emerging evidence points to the fact that A β is actually a downstream event of autophagy disorder. In the experiment, they observed the specific process of autophagy in the brain by using a dual fluorescent labeling method and a variety of high-end imaging techniques at the same time. In addition, through this method, they also found that A β accumulates in the cell in the early stage of the disease, rather than outside the cell as we generally think. So our goal should also shift from A β removal to how to prevent autophagy disorder. While describing this situation, this paper also proposes some possible methods that have been discovered so far to prevent autophagy disorders.

Keywords: A β , autophagy disorders, Alzheimer's disease, fluorescent labelling, CREG1.

1. Introduction

Alzheimer's disease is one of the most difficult diseases to treat. It is a neurological disorder, and if neurological dysfunction occurs, there is usually irreversible damage. The typical age of onset of human Alzheimer's disease is after reproductive completion, so from a biological point of view, this disease does not affect the normal reproductive or reproductive behavior of species, so despite a long process of evolution and screening, the deadly disease was preserved. Nowadays, medical conditions are getting better and better, people's average life expectancy is gradually getting longer, and the number of patients with Alzheimer's disease is also increasing rapidly. This led to the rapid attention of the disease. 5.8 million Americans are suffering from Alzheimer's disease, compared with 15 million in China. There are now 55 million Alzheimer's patients in the world, which is a very large number. In general, the average age of onset of the disease is over the age of 65, but now the disease has even appeared in people under the age of 40. If a family member who is financially responsible for the disease suffers from the disease, it can be a huge blow to the entire family. At the same time, the elderly suffering from this disease will also bring a lot of financial burden and disputes to the family. Famous figures such as former US President Ronald Reagan and Margaret Thatcher have been diagnosed with the disease. The minds of these characters are arguably their strongest weapon, and Alzheimer's disease keeps them from serving their country. This is a huge loss for humanity. However,

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despite the above-mentioned harm caused by Alzheimer's disease, human beings are currently helpless, because human beings do not even know the real cause of Alzheimer's disease. But the treatment of Alzheimer's remains an extremely serious problem, as it is one of the biggest obstacles to high-quality human longevity. At the same time, despite the unknown pathology, scientists have managed to identify some possibilities to treat the disease.

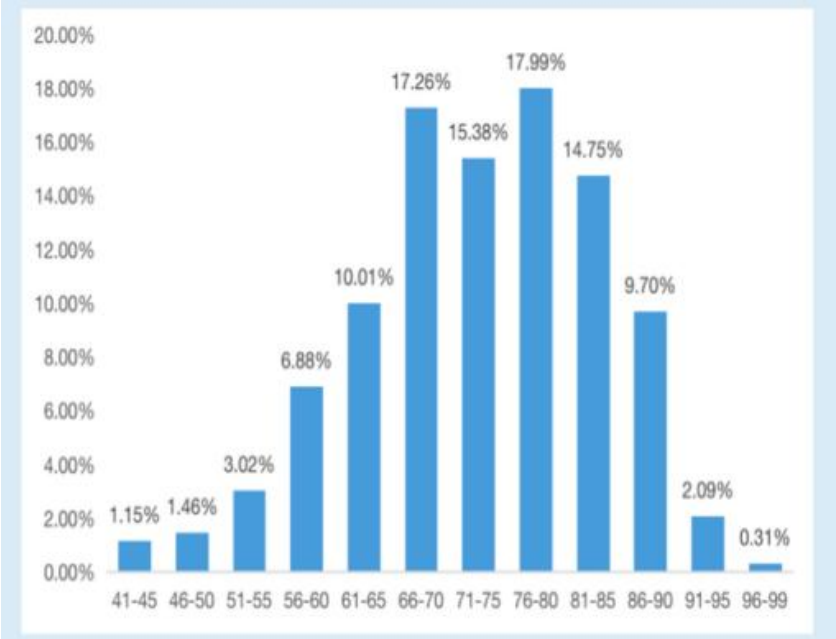

Figure 1. Proportion of Alzheimer's disease by age group in China (Source:WHO)

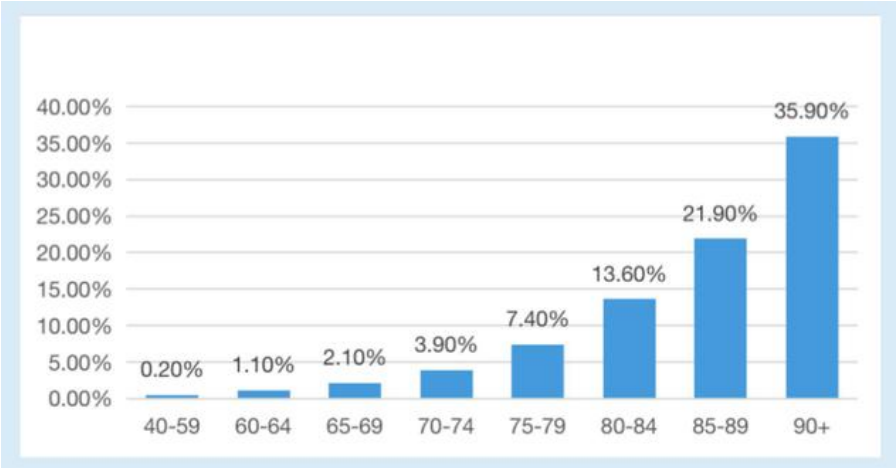

Figure 2. Global prevalence of Alzheimer's disease
Source: Global status report on the public health response to dementia

2. The brief information on Alzheimer's disease

It is difficult to prevent Alzheimer's disease effectively because of the many causes and the difficulty in finding out the pathology. Alzheimer's is a neurological disease, and researchers have largely dissected dead cases to find the causative component. However, since neurodegeneration will lead to the disappearance of nerves, and certain proteins and other substances that are related to Alzheimer's disease may also be rapidly decomposed after the death of the human body, so far we can only speculate on the cause of Alzheimer's disease based on early signs and the corresponding symptoms of

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patients. Among the various research hypotheses, the most mainstream explanations are genetic theory, acetylcholine theory, tau protein theory and beta amyloid peptide (A β) theory. Yet until now, none of the hypotheses has been confirmed, but among them the A β theory is relatively the most widely accepted. The A β theory holds that A β is the culprit behind many neurological problems. At the same time, the study found that A β β can cause ER-stress, resulting in unfolded protein response (UPR), and confirmed that A β can lead to activation of astrocytes and microglia, breakdown of the blood-brain barrier (BBB), and can cause changes in the microcirculation. So For A β , scientists have studied many drugs against A β , but all the current drugs based on A β theory have all failed. This is also the reason why the A β theory is opposed by many people. In order to reduce this phenomenon, scientists have envisioned some ways such as β -Secretase inhibitors, γ -Secretase inhibitors and selective A β 42 lowering agents to inhibit the production of a β , especially a β -42, to make nerve cells live longer. But then there is the question: Since A β is a naturally occurring protein, can it be so harmful? After all, this substance is very common, and similar age spots are often found on the skin of people without Alzheimer's disease. However, a recent article seems to explain this phenomenon. In the article, the researchers used fluorescent labeling to confirm that the massive accumulation of A β follows neurodegeneration. From this, we can conclude that perhaps blocking the production of A β does not prevent Alzheimer's disease.

3. Literature Review

Although the most mainstream hypothesis at present is the A β theory, all the drugs developed based on this hypothesis have failed. This has led many researchers to turn their attention to other theories. But as the most widely accepted theory, the A β theory itself seems to be the most plausible argumentation process: First, some animal experiments have shown that the lack of A β does not lead to any significant loss of physiological function. [1] And many proteases are involved in the recognition and degradation of A β . And A β is also a major component of amyloid plaques (also called senile plaques). Amyloid plaques are also extracellular deposits found in the brains of Alzheimer's patients. Meanwhile, A β has been found to cause multiple damages in the human body: A β oligomers induce certain Alzheimer's symptoms by competing with insulin for binding sites, thereby impairing glucose metabolism in the brain. [2] A β also damages or causes neuronal death by producing reactive oxygen species during its self-aggregation, and when this happens on neuronal membranes in vitro, it produces a toxic aldehyde called 4-hydroxynonenal, This promotes synaptic membrane depolarization, excessive calcium influx, and mitochondrial damage. [3] At the same time, reactive oxygen species produced by A β can also damage DNA in the brain. At the same time, research on Down syndrome has also justified these studies. Because the pre-amyloid protein (APP) gene that controls the expression of A β is located on chromosome 21, the root cause of Down syndrome is an extra repeat of chromosome 21. Almost all patients with Down syndrome will show the features of Alzheimer's disease around the age of 40. [4] Furthermore, further evidence comes from experiments conducted by a group of researchers. The researchers transcribed the human APP gene in experimental mice and found that the mice also produced amyloid plaques in their brains and exhibited brain pathological changes and states similar to Alzheimer's disease. [5] There is also significant autophagy damage in Alzheimer's disease, and many studies have shown that mutations in autophagy or lysosomal function can cause neurodegeneration in humans. [6] Due to the prosperity of the A β theory, the mainstream view is that autophagy is also one of the results triggered by A β deposition. But even with the above theoretical support, after the advent of a vaccine that can clear A β at an early stage, it has not had a significant effect on the treatment of Alzheimer's disease. This can't help but make people wonder where the loopholes in this theory are. Indeed, there are still some very obvious irrationalities in the A β theory: as a protein naturally produced by the human body, why must A β be contained from the source? At the same time, since the body has so many ways to

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get rid of Aβ, why does it still accumulate in excess in old age? These questions also trouble many scholars who support or oppose the Aβ theory. However, a recent study appears to have significantly downgraded the Aβ theory. Despite the above harmful phenomenon caused by the massive accumulation of Aβ, in this study, the researchers confirmed that the deposition of Aβ protein is after the occurrence of autophagy, contrary to the current traditional view.

4. Methodology

In this study, in order to observe the process of autophagy in the brain, the researchers developed a dual-fluorescent probe and adopted a more advanced method. There are many types of autophagy, and in the macroautophagy observed in this experiment, there are several key steps: first, autophagic vesicles are formed, and then autophagic vesicles will capture the aging organelles or proteins that need to be degraded, and at the same time form Autophagosomes. Autophagosomes then combine with lysosomes to form autophagolysosomes. At this time, a protein called LC3 binds to it, so it was used as a tracer of autophagy in this experiment.

In this experiment, the mRFP-eGFP-LC3 fusion protein was used for tracking. This is a common method for studying autophagy. mRFP is a stable fluorescent expression group and appears in red, while GFP is an acid-sensitive protein and appears in green. At the beginning of the experiment, when the autophagosome and the lysosome were just fused, the two fluorescences combined to give a yellow color. However, when the lysosomal environment is normal (acidic), GFP is broken down and only appears red. The research team also labeled lysosomes with blue fluorescence. Thus, when the two are combined, they will appear purple. In cells with lysosomal acidification dysfunction, because GFP is not decomposed and remains yellow, when lysosomes bind, it will appear white. In this study, the researchers also bred TRGL mice to specifically express mRFP-eGFP-LC3 in neurons, and then crossed these mice with Tg2576 mice. Tg2576 mice are mice with human APP gene transfer, and this model is generally used for early AD research. Finally, using this hybrid mouse model, autophagy progression in AD mice can be monitored. At the same time, under the stress of autophagy, a large number of autophagy-disordered autophagosomes aggregated in neurons, forming a flower-like shape, which the researchers called PANTHOS. After detection with the Aβ antibody, it was found that Aβ plaques and PANTHOS completely overlapped, which means that PANTHOS is composed of Aβ. To see where PANTHOS goes, the research team tagged it with thioflavin S. The final result was that these PANTHOS would gradually aggregate, expand, and eventually evolve into what we think of as senile plaques[7].

5. Result

Through this experiment, the researchers have the following important conclusions.

First, autophagy impairment was already present in mouse neurons before Aβ plaque formation, apparently due to insufficient lysosomal acidification. In particular, it was observed by fluorescent labeling that at 5 months, mice already developed under acidified lysosomes and only developed Aβ plaques at 10 to 12 months. This is sufficient to prove that autophagy disorders appear before Aβ plaques.

Secondly, autophagic neurons exhibit a "poisonous flower" phenomenon, which was observed for the first time in this study. The remains of such neurons are the amyloid senile plaques we observe in the brain.

Finally, the appearance of the "poisa onous flower" also proves that Aβ accumulates in neurons rather than extracellularly in the early stage of AD. This basically denies the previous view that "Aβ causes cell death and lysis", and makes Aβ less harmful to cells.

6. Conclusions

These findings imply that regardless of whether Aβ is the culprit in AD, we should focus on lysosome acidification, rather than Aβ itself. The research team also proposed that autophagy impairment in AD

models could be improved by repairing PSEN1-related genes. Meanwhile, in Earlier studies, it was also found that CREG1 can promote the biosynthesis, acidification, and degradation of lysosomes [8]. These studies are relatively early studies, but after the publication of this paper, this study is likely to have some more relevant human value in development. We can turn the door to select some genes that play a role in the abnormal acidification of lysosomes and try to treat Alzheimer's disease from the direction given in this paper. These may be directions we can study in the future.

But then a new question arises: Aβ usually begins to deposit 10-20 years before AD, so if the autophagic acidification disorder is earlier, what is the root cause of AD? When did it start working? There is currently no solution to these fundamental questions in this study. The above are all conclusions based on the research on the harm theory of Aβ. But this research is not limited to Aβ theory. Even if Aβ is not the culprit in AD, acidification of the lysosome may prevent it from causing other damage to the body, such as the ER stress mentioned above. Therefore, the research prospects in this field are very broad.

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