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An Overview of Current Research on Alzheimer's Disease

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Abstract. Alzheimer's disease, a typical neurodegenerative disease, has been one of the most challenging problems for researchers and doctors. Having known many of its negative impacts such as cognitive decline and disturbed sleep, researchers are yet unable to figure out what specifically causes it and how to effectively cure it. In other words, the underlying mechanisms of the disease seem to be very complex, contributing to an incomplete understanding of the disease and an increasing number of patients who cannot be fully recovered. Therefore, the purpose of this article is to summarize current findings about the disease and to provide suggestions for future research. It seeks to answer the question of what can be done to find a cure for the disease. To conduct this research, information and data from academic journals will be analyzed. Some relevant theories such as the amyloid cascade hypothesis will also be covered. As a result of this research, it is suggested that researchers should focus on causes of the abnormalities of different proteins, treatments for tau pathology as well as the specific relationship between healthy lifestyle and cognitive health.

Keywords: Alzheimer's disease, neurodegenerative disease, AD pathology, beta-amyloid protein, tau protein

1. Introduction

Alzheimer's disease, typically defined as a progressive neurologic disorder that causes brain cells to die [1], is a common issue for most elders. According to statistics in 2021, approximately 6.2 million Americans aged 65 or more had Alzheimer's disease [2], which negatively affected their thinking and memory. At present, researchers propose that aggregation of beta-amyloid protein and abnormal phosphorylation of tau protein are related to the disease. They also suggest people to use protein inhibitors to slow down the progression of the disease. However, they do not yet have a comprehensive understanding of what causes this disease as well as how to cure it. Therefore, the topic of this article will be Alzheimer's disease, and the main question this article attempts to answer is what researchers should do to find a cure for Alzheimer's disease. Also, this research will be conducted by collecting data and information from academic journals. The collected data will be analyzed, and the information will mainly include cellular mechanisms, preventions and treatments. The research aims to provide ideas about treatments for Alzheimer's disease and to give suggestions for future research. By carefully considering the research question, elder patients who suffer from Alzheimer's disease will be likely to be cured.

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2. Cellular mechanisms in alzheimer's disease

2.1. A subsection

Recent genetic studies and biochemical data have shown that the aggregation of beta-amyloid proteins, or the formation of amyloid plaques, is a major hallmark of Alzheimer's disease. Before explaining this aggregation, some basic information of beta-amyloid proteins will be given. First of all, a beta-amyloid protein is a protein fragment of an amyloid precursor protein (APP), and it contains 36-42 amino acids that form amyloid plaques. Usually in healthy brains, beta-amyloid protein fragments are eliminated; however, in brains of people with Alzheimer's disease, those fragments form hard and insoluble amyloid plaques that lay between neurons [3]. Researchers have discovered a general process of the formation of beta-amyloid proteins: During the degradation of an amyloid precursor protein, the enzyme beta secretase instead of an alpha secratase, works with a gamma secretase to eventually produce an insoluble beta-amyloid protein rather than a soluble P3. For the aggregation of beta-amyloid proteins, a current explanation is: The protein peptides spontaneously aggregate into soluble oligomers and polymerize into fibrils, which then "induces oxidative injury, microglial and astrocytic activity as well as alters kinase/phosphatase activity, eventually leading to the neuronal death" [4]. From the research results shown above, it appears that there are still unsolved questions. For example, people do not know whether the formation of amyloid plaques is a cause or result of Alzheimer's disease, despite the proposal of some unverified hypotheses. Proposed in 1992, the amyloid cascade hypothesis claimed that the aggregation of beta-amyloid proteins is a cause. However, this hypothesis was later contradicted by failures of anti-Aβ therapies. Apart from the "cause or effect" question, the cause of the aggregation is also unknown. In other words, the process of the buildup may not necessarily be spontaneous, and there should be some factors contributing to it. If these two questions above are figured out, people may gain a more complete understanding of the mechanisms or principles of Alzheimer's disease.

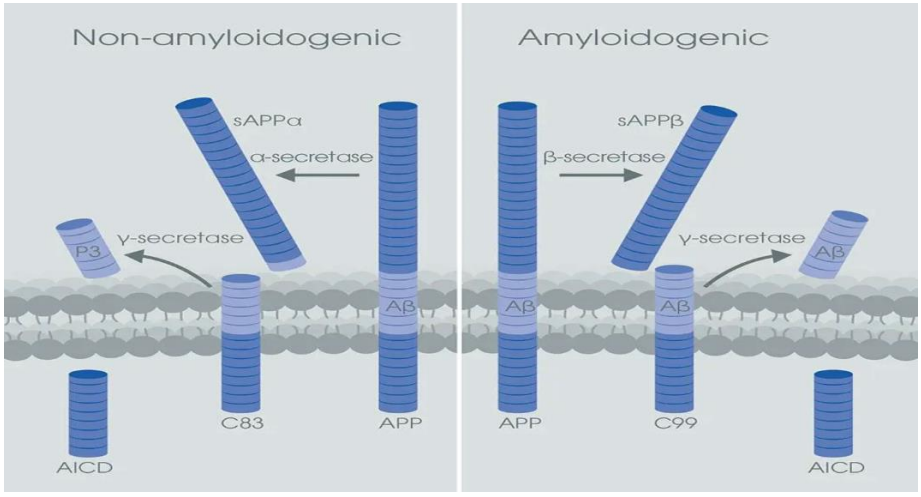


Figure 1. Difference between non-amyloidogenic pathway and amyloidogenic pathway [5]

2.2. The role of tau protein

Except from the accumulation of beta-amyloid proteins, another noticeable hallmark of Alzheimer's disease is the abnormal phosphorylation of tau proteins, or the formation of neurofibrillary tangles in brain regions. To begin with, tau proteins are multi-functional proteins whose main role is to stabilize microtubules in axons. Being responsible for axonal transport, postnatal brain maturation as well as neurogenesis, they seem to be closely related to neuronal functioning. In healthy brains, tau proteins usually stabilize microtubules in neurons. In contrast, in brains of people with Alzheimer's disease, the proteins become hyperphosphorylated, which weakens their ability to bind microtubules. These abnor-

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mally folded proteins then detach from the microtubules, forming helical filaments and thereby neurofibrillary tangles that induce cell death. Given the primary function and behavior of tau proteins in brain areas, the next step is to find out how they build up and why they form those harmful tangles. For the buildup, current evidences have shown that the tau proteins "spread through the brain by means of oligomer seeds" that travel across synapses [6]. Moreover, the proteins continuously accumulate accordingly with the progression of the disease. About why they form neurofibrillary tangles, researchers offered an explanation that the formation of tangles is a response to "chemical modifications of the proteins that interfere with their normal function" [7]. This means that the tau proteins are chemically modified, which tiggers their aggregation to form tangles. Furthermore, a recent research conducted by MIT chemists showed that the tangles can randomly recruit any surrounding tau protein to add to the growing filament, making the formation of tangles easier [8]. From these findings, it seems that more detailed research is required to figure out the factors leading to the abnormal phosphorylation of tau proteins. Researchers will need to know what drives a healthy and well-regulated tau protein to a disordered state. The answer to this problem will be a key to cure the disease.

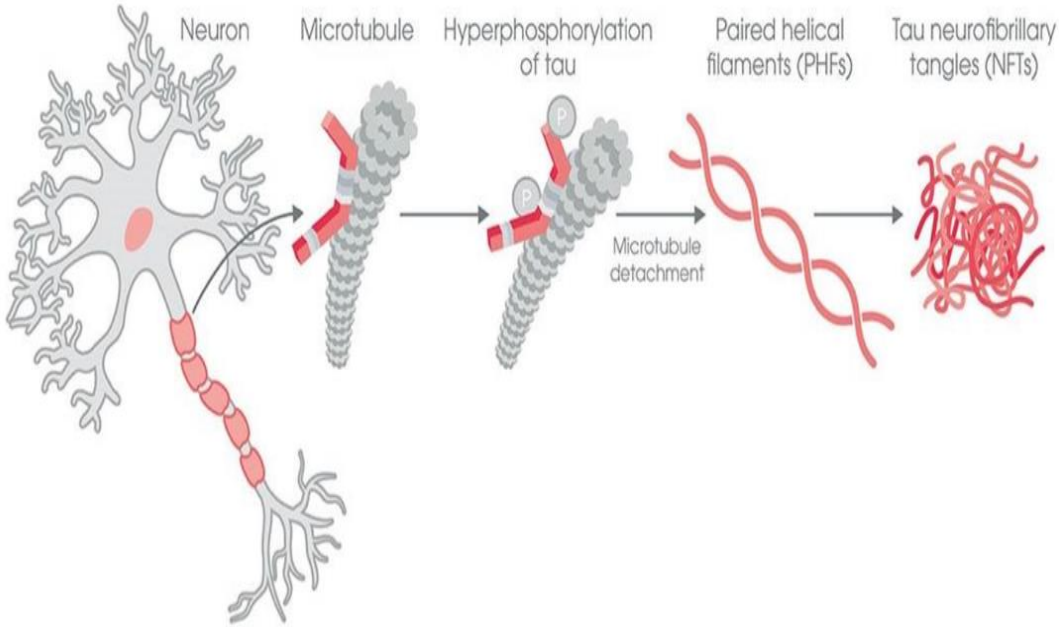


Figure 2. Microtubules detachment and the formation of tau neurofibrillary tangles [9]

2.3. Relationship between amyloid pathology and tau pathology

Current research has shown that there is a link between the two pathologies that contribute to the development of Alzheimer's disease. It was suggested that amyloid pathology is dependent on tau pathology, while tau pathology can act independently of amyloid pathology. In other words, tau pathology can cause neurodegenerative diseases such as Pick's disease and frontotemporal dementia, without amyloid pathology [10]. On the other hand, only amyloid pathology is not sufficient to lead to any neurodegeneration. This discovery of the link between two pathologies raised a proposal that alleviating the pathological effects of tau proteins may be defensive against that of amyloid. This can be a main focus for future research on treatments for the disease.

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3. Preventions on alzheimer's diseae

Currently, there are no specific ways to prevent this disease. All the temporary methods used to reduce the risk of getting the disease are concerned with reducing the risk of getting cardiovascular diseases and preserving cognitive ability. The main idea is to develop a healthy lifestyle.

3.1. Physical exercises

It is believed that moderate body exercises can effectively protect brain health. Several studies have shown a positive relationship between active physical exercises and a lower risk of getting the disease. For example, by calculating population attributable risks, Barnes and Yaffe have concluded that about 4.3 million AD cases probably resulted from physical inactivity [11]. Simply knowing this relationship is not enough for curing the disease, so researchers further investigated on the effect of physical activities on cognitive functions. Generally, physical activities benefit cognition by alleviating cognitive decline and reducing neuropsychiatric disorders. First, although the specific mechanisms are unclear, it is proposed that exercises may trigger molecular and cellular mechanisms that promote neurogenesis and increase cerebral blood flow as well as the amount of neurotransmitters [12]. The increase of neurons and blood flow will delay cognitive decline. Moreover, moderate exercises may weaken neuropsychiatric symptoms, a typical manifestation of Alzheimer's disease, by transporting afferent neurotransmitters (eg. norepinephrine, serotonin) to hippocampus. Therefore, exercises benefit cognition mainly by increasing blood flow and neurotransmitters, but the exact process of these mechanisms remains to be unclear. Also, further research is needed to find out what type of exercise is most beneficial for cognitive abilities.

3.2. High-quality sleep

Apart from physical inactivity, another possible risk factor for developing Alzheimer's disease is sleep disturbance. This is because sleep disorders may negatively affect metabolite clearance ability, leading to more accumulation of neurotoxic substances [13]. Studies have also shown that sleep disorders and AD pathology may be bidirectionally related: Sleep disorders may stimulate the aggregation of amyloid proteins and tau proteins, while the aggregation of proteins can aggravate the progression of sleep disorders. These findings revealed the importance of getting high-quality sleep, which may help preserve cognitive ability and reduce the likelihood of the accumulation of neurotoxic substances. To learn more about how to prevent Alzheimer's disease, researchers may need to focus on the possible bidirectional relationship between sleep disorders and protein pathologies and conduct studies about it.

3.3. Balanced diet

It is discovered that unhealthy diets with high fat/sugar content may lead to cognitive decline by increasing the level of oxidative stress and inflammatory response, eventually contributing to dementia [14]. This finding implies that a nutritious diet with healthy fats may improve cognitive functioning and prevent neuronal dysfunction. One example of this type of nutritious diet is the Mediterranean diet, which is widely adopted to prevent Alzheimer's disease. It focuses on the intake of healthy fats (eg. olive oil), fruits and vegetables. Another type of diet that modified the Mediterranean diet is called the MIND diet. This diet focuses on the intake of whole grains and vegetables, while minimizing the amount of fast food or sugars. Both diets have displayed a successful defense against cognitive decline. To enhance the preventions against Alzheimer's disease, more similar diets can be promoted.

4. Treatments for alzheimer's disease

4.1. Medication

As mentioned before, although Alzheimer's disease can hardly be cured, there are drugs that either alleviate AD symptoms or slow down AD progression. However, these drugs are only recommended for specific stages of symptoms, and they do not necessarily work for everyone. One of them is the cholinesterase inhibitor, which works by preventing the breakdown of acetylcholine. This is because the

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chemical messenger acetylcholine is responsible for alertness and memory, while it will decrease as the disease proceeds. It is thus revealed that the cholinesterase inhibitor can only temporarily help maintain alertness and memory, based on the fact that the inhibitors cannot stop the damage of cells. Another drug commonly used to treat Alzheimer's disease is memantine, which works by regulating the activity of glutamate involved in learning and memory [15]. It is usually used to treat severe AD symptoms, and it may cause side effects such as headache. From these results, it seems that current drugs are not available for all patients, and they can only delay the progression of the disease for a short period of time. In this way, more studies regarding how to effectively control the amount of neurotoxic substances should be conducted to provide better solutions.

4.2. Self care

In addition to medical treatments, patients also need to take care of themselves under the assistance of their supervisors or caregivers. They need to develop beneficial habits such as keeping their objects in the same place at home and keeping track of their daily schedules. These habits can make them more independent at least when they are at home. They may also need to eat healthy diets and do regular physical exercises, since these actions may lower their blood pressure as well as their level of oxidative stress and inflammatory response, just as what the previous sections suggest. Generally, these methods for patients to take care are quite clear and plausible, so the "self care" part will not need much further research.

5. Conclusion

In summary, it is suggested that researchers should pay more attention to the cause of abnormalities of the proteins, treatments for tau pathology and the specific relationship between healthy lifestyle and cognitive health. Overall, this article identified possible defects of current research on Alzheimer's disease from three perspectives: cellular mechanisms, preventions, and treatments. Among them, cellular mechanisms may be the most worthwhile aspect for researchers to study, since they greatly account for AD pathology. More research is also required to figure out the details of the role of healthy lifestyle in maintaining cognition. After these two aspects are studied extensively, people may gain a clearer idea of how to effectively treat the disease.

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