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Association of tau protein and Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is a kind of neurodegeneration disease and often happens in older people. Age is an influencing factor in the prevalence of AD. Up to now, AD is still difficult to cure and only limited medications can relieve some of the symptoms. Therefore, research on the pathology of neurodegenerative diseases has become more and more popular in recent years. Multiple studies offer some proof that the tau protein mutation and AD are related. This review described the structure and the purpose of the tau protein. The linkage between abnormal tau mutation and AD is further clarified, and a summary of two medications for AD is also included.

Keywords: Alzheimer's disease, AD, tau protein, abnormal amyloid beta, Acetylcholinesterase inhibitors.

1. Introduction

Alzheimer's disease (AD) is a common neurological condition that impairs visual sight, causes memory loss, and leads to problems with reasoning. It is also quite common for AD to happen in people over 65, with one in nine occurrences. This has made the disease's frequency in this age group up to 11% [1]. The study of AD has gained popularity recently. Two major goals of this paper are to summarize the pathogenesis of AD and then clarify an aberrant and hyperphosphorylated tau protein. It is important to note that this paper also discusses two medications, donepezil and rivastigmine, which are useful for treating AD. Both of these medications are inhibitors. Donepezil is an Acetylcholinesterase inhibitor (ACHE) and Rivastigmine is a carbamate inhibitor (BuChE). They both work by deferring the development of amyloid plaques [2]. However, none of these medications can entirely cure the disease.

2. Structure of tau protein

The MAPT gene on the long arm of chromosome 17 produces the microtubule-associated protein tau, which is only encoded by a single gene. The main function of tau protein is to boost the aggregation of microtubule proteins and has a stabilizing effect on microtubules. An early study finds that tau protein is an essential factor in microtubule assembly and dynamics in regulating the shape of neurons [3]. The four subregions that make up tau are an N-terminal projection area, a proline-rich domain, a microtubule-binding domain, and a C-terminal region. Moreover, Adult brains create six primary isoforms by alternative splicing close to the microtubule-binding domain and N-terminal region. The names of tau isoforms are determined by the expression of microtubule binding repeat sequences and the number of N-terminal exons [4].

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The tau gene contains three different tau transcripts. 2kb tau gene is one of tau transcripts and it combines the full series of tau coding seats in the nucleus. The 6kb tau transcripts are also widely distributed in neurons and are mostly found in the human brain. The peripheral nervous system and retina contain the 8kb tau transcript [5]. Previous review study has established that the neuronal axon is formed and maintained in large part by the tau protein. Pathological tau structures are formed when tau expression is disrupted, and these structures are detected in dementia patients' brains [6].

According to a number of earlier studies, the tau gene has 16 exons, 8 of which are alternately spliced [6]. A review indicates that exon 1 is transcribed but not translated since it is an element of the promoter. Noteworthy, exon 14 belongs to the 3' non-coding part, which is regulating the tau protein expression [7]. Exons 4A, 6, and 8 are always absent from human brain mRNA but are present in the peripheral tissue. Moreover, the majority of exons 2, 3, and 10 are found in human brains, especially located in the adult brain. Noteworthy, exon 2 and exon 3 usually appear together, forming an "augmented combinatorial" pattern that combines the Kunitz domain of the amyloid precursor protein and the neuronal-specific exons [6,8]. Exon 10 is one of the main causes of the dysfunction in the pedigrees of several neurodegenerative diseases. Some tauopathies, such as FTDP-17, Huntington's disease, and AD are brought on by mutations that modify the alternative splicing of exon 10 of microtubule associated protein tau. Nonsynonymous mutations that change microtubule binding are also present [9,10].

3. Tau phosphorylation

Various studies have shown that disruption of typical phosphorylation events contributes to tau loss of function in neurological diseases like AD and it is a source of the pathogenic processes. Since tau is a phosphoprotein and the phosphoprotein inhibits its capacity to promote microtubule assembly. According to Gail's review, an early study made the crucial discovery that tau is an essential aspect of the dual helical filaments that make up the plaques and tangles in the brains of Alzheimer's patients. Additionally, the tau is abnormally phosphorylated in the neurofibrillary tangles and associated helical filaments [11].

Tau is produced by alternative mRNA splicing into six main isoforms in the brain of an adult. It contains N-terminal inserts and microtubule-binding domains. Both tau's splicing and its level of phosphorylation are controlled by developmental processes. A study finds that only the shortest tau isoform and a higher level of phosphorylation than adult tau are seen in the prenatal brain [11]. Furthermore, Goedert's study demonstrates that about 20% of the molecules in the adult brain are probably phosphorylated. In addition, multiple various protein kinases use tau as a substrate. Numerous protein kinases can phosphorylate tau when it is present in vivo, however, this number is likely to be much smaller than it is in vitro. Furthermore, there is significant evidence that tau dysfunction brought on by inappropriate phosphorylation reduces cell survival. In fact, aberrant phosphorylation of the tau has been seen in all neurodegenerative disorders. Another early study finds that frontal lobes degeneration is connected to FTDP-17, a group of uncommon autosomal dominant neurodegenerative diseases brought on by mutations in the tau gene on chromosome 17q21 [11].

4. The pathogenesis of Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease and it is one of the main factors in the development of dementia. Sneham's study indicates that there are already 47 million dementia sufferers globally, and by 2050, experts predict that this figure will have more than tripled [12]. This demonstrates that treating Alzheimer's disease is still quite challenging.

4.1. Aβ and tau

Amyloid beta plaques and intracellular neurofibrillary tangles made of hyperphosphorylated protein are associated with the pathogenesis of Alzheimer's disease in the human cerebral cortex and limbic areas [12]. Aberrant phosphorylation is one of the primary properties of tau that has been isolated from the brains of patients with AD and other illnesses expressing tau pathology. A large number of reviews highlight that the function and intracellular localisation of tau can be regulated by phosphorylation.

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Improper phosphorylation will result in the development of tau pathology and the incidence of various degenerative neurological illnesses [11].

Accumulating research provides evidence that abnormal tau phosphorylation and amyloid beta (Aβ) play major roles in AD. The major component of the senile plaques seen in the AD brain is amyloid beta plaques, which is a peptide produced by the proteolytic degradation of the amyloid precursor protein. Aβ causes tau-mediated neurotoxicity, which results in dendritic degeneration and spine collapse, by promoting tau hyperphosphorylation in vitro and directing pathogenic tau species into dendritic spines [13]. In addition, a vivo study finds that Aβ increases tau hyperphosphorylation and neuronal toxicity in mice. This evidence implies that there is a functional interaction between tau phosphorylation and Aβ. In addition, the report points out the association between tau toxicity and Aβ. When they immunostained the frontal brain areas of double-transgenic flies for actin, they found that the proportion of amyloid rods had significantly increased. This demonstrates that the synergistic relationship between Aβ and tau toxicity may be caused by alterations to the actin filaments [14].

4.2. Tau oligomers

The essential connection between tau toxicity and the oligomeric aggregation of the tau protein has recently been the focus of many investigations. This is due to the fact that it associates with many neurodegenerative diseases [15]. According to previous research, the pathophysiology of AD and the oligomer production process are strongly associated. The first is nitration, a crucial step for oligomer synthesis and the conversion of oligomers into filaments. This process disrupts the normal MT-binding activity of tau protein. Another mechanism relates to the so-called chaperon molecules. Evidence suggests that molecular chaperone-tau protein complexes may be the source of tau aggregation processing since heat-shock protein levels are inversely linked with those of granular Tau oligomers [15].

5. The treatment of AD

5.1. Acetylcholine and Acetylcholinesterase

Acetylcholine (ACh) plays a vital role in the nerve system as it is a neurotransmitter. Noteworthy, ACh is mainly located in interneurons in the central nervous system and also some research points out that there are a few significant long-axon cholinergic routes that have been discovered. This pathway of degradation of cholinergic projection is a pathology related to Alzheimer's disease [16]. In addition, Acetylcholinesterase (AChE) is a serine hydrolase that is mostly found at neuromuscular junctions and cholinergic brain synapses. For a serine hydrolase, AChE possesses a remarkably high specific catalytic activity [16]. Understanding the high catalytic effectiveness of AChE is essential because it is a base to further understand the mechanism of Acetylcholinesterase (AChE) inhibitors, which is one of the treatments to reduce the diagnosis of Alzheimer's disease.

5.2. Acetylcholinesterase inhibitors

The loss of cholinergic neurons in the brain and a decrease in ACh levels are two pathologies of Alzheimer's disease. Acetylcholinesterase inhibitors (AChE), also known as anti-cholinesterase, are an effective method to stop Acetylcholine from being degraded by the cholinesterase enzyme, extending and amplifying the neurotransmitter's effects [2]. Even though the AChE inhibitor drugs could keep ACh levels stable by lowering its breakdown rate to enhance cholinergic neurotransmission in areas of the forebrain to make up for the death of working brain cells [2]. However, so far, no drugs can completely cure Alzheimer's disease. The following sections describe two drugs that have been widely used to alleviate Alzheimer's disease.

5.2.1. Donepezil. In the treatment of AD, donepezil is a type of reversible AChE inhibitor that binds to the peripheral anionic site and delays the development of amyloid plaque, having both symptomatic and causative effects. Donepezil is widely used as a palliative for mild to moderate AD. However, some

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clinical research suggests that donepezil may enhance cognitive function in patients with severe AD symptoms [16]. Both an oral liquid and a dissolving tablet are options for donepezil. There are various dosage levels of 5 and 10 mg available. Typically, the dosage is increased from 5 mg per day to 10 mg per day over the course of a few weeks. The daily maximum is one dose of 23 mg. Higher doses generally result in a little improvement in cognitive performance but no change in overall functioning in the patients. However, Higher doses of the drug are associated with side effects. Examples include diarrhea, bradycardia, and nausea [2].

5.2.2. Rivastigmine. The slow-reversible carbamate inhibitor (BuChE) rivastigmine inhibits cholinesterase activity by interacting with the esteratic region of the active site. Rivastigmine inhibits BuChE and AChE simultaneously, in contrast to donepezil, which only inhibits AChE. The medication is consumed orally in the form of a liquid capsule, and it is then metabolized and eliminated through urine. The favorable effects seen in terms of the rate of cognitive decline, and severity of dementia are maximized with early ongoing treatment of AD with rivastigmine. Rivastigmine's side effects are comparable to those of donepezil, including headache, nausea, and vomiting [2].

6. Conclusion

This paper identified aberrant tau phosphorylation and amyloid beta (Aβ) deposits as the primary pathological characteristics of Alzheimer's disease. Furthermore, it is discovered that there have been a lot of reliable studies on tau pathology in recent years. By reviewing these studies, a strong correlation between aberrant Aβ and tau and Alzheimer's disease is revealed. Additionally, this paper described the efficacy of two medications for the condition of Alzheimer's disease. Suggesting that further clinical trials are required in order to obtain positive results and more research is necessary in order to fully understand the origins of Alzheimer's disease. Since there are not many medications available to treat Alzheimer's. Hopefully, future research will yield better outcomes.

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