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Analyzing Different Hypotheses for Alzheimer's Disease

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Abstract: *There are many existing hypotheses for the pathogenesis for Alzheimer's disease (AD), but none are fully verified. The most widely accepted hypothesis is the amyloid-beta hypothesis, which is partially due to the fact that it has been around for relatively long time. The foundation for this hypothesis is the fact that AB tangles have been found in the brains of patients with AD. Therefore, many have come to the conclusion that AB tangles prevent healthy cell function and trigger inflammation in the brain. Despite the plethora of research supporting the AB hypothesis, there have been little to no advancements in the treatments and therapies for AD. Another hypothesis for AD that opposes the AB hypothesis is the presenilin hypothesis. The presenilin hypothesis claims that AD is not caused by the production of AB peptides, but rather stalled ES complexes, which limits the amount of cuts y-secretase makes on APP substrate. This hypothesis proved that AB is merely a byproduct of AD. Lastly, researchers have also looked into how insulin resistance affects AD-related processes in the brain, and have gathered substantial evidence for the insulin resistance hypothesis. The link between Tau protein tangles and insulin resistance has been uncovered, suggesting the relevance of insulin in cognition and neurosynaptic health. Additionally, researchers found that insulin can trigger the non-amyloidogenic pathway, that is, the pathway that does not produce harmful AB peptides. In this review, I will criticize the limitation of each hypothesis, and finally select the most valid one.*

Keywords: *Alzheimer's disease; Dementia; Insulin resistance; Amyloid-beta; Presenilin; Neurodegeneration*

1. Introduction

Alzheimer's disease is a neurodegenerative disorder and a type of dementia that is characterized by symptoms such as but not limited to memory loss, impaired cognition, and poor judgment. It is caused by neuronal cell death, which leads to increased brain atrophy over time. One type of AD is sporadic AD, which is the most common form of AD. Risk factors for sporadic AD include aging, environment, and lifestyle[1]. Sporadic AD generally only affects people aged 60 to 65 years old. The other type of AD is familial AD, which is caused by gene mutations that are inherited. Patients with familial AD typically develop it at around 30-50 years old. Familial AD is the least common type of AD, accounting for less than 5% of all AD cases. There is currently no cure for AD; hence, the search for treatments, drugs, and therapies is still ongoing as of today.

The AB hypothesis has long been the most accepted hypothesis to explain Alzheimer's disease (AD). This hypothesis explains that AD is caused by the buildup of amyloid-beta (AB) plaques in the brain, which prevent normal brain function. For 40 years, researchers have relied on this hypothesis to initiate studies on humans and animals, develop therapies, and produce drugs. However, many of these AB-inhibiting drugs and therapies have not produced the desired result in AD patients, which introduced the possibility that AB plaques are not the true cause of AD. Hence, the search for the true etiology of AD is still ongoing. Many alternative hypotheses have been created, such as the presenilin and insulin resistance hypothesis. But as of today, there is still no confirmed hypothesis for AD.

2. Presenilin Hypothesis

The recently discovered presenilin hypothesis directly opposes the previously conventional hypothesis, the amyloid-beta hypothesis. Recent studies have produced enough evidence to prove that the presenilin hypothesis for familial Alzheimer's disease (FAD) can be considered a potentially groundbreaking discovery. Presenilin is a membrane protein that is also the catalytic component of y-secretase. y-secretase is responsible for cleaving amyloid precursor protein (APP) substrate to make

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amyloid beta (AB) peptides (Gu Y. et al., 2001). To do this, y-secretase cuts the C99 substrate, which is found in the cell membrane, to produce long AB peptides such as AB48 and AB49, and APP intracellular domain (AICD). The longer peptides conjoin with the cell membrane, while the shorter peptides like AB40 and AB42 are[2]. Peptides are cleaved by y-secretase three amino acids at a time, or in tripeptide groups because y-secretase has three binding spots (P1', P2', P3') for the amino acids. This helps y-secretase make cuts on the accurate spots. Researchers wanted to find out if alterations in the functions of y-secretase would affect symptoms of FAD since previous research has suggested that AB tangles may not be the cause of Alzheimer's disease.

Although the primary foundation of the amyloid beta hypothesis was based on the evidence that Alzheimer's disease is caused by an increase in the AB42 to AB40 ratio, recent studies done by Yasuo Ihara et al. (2009) overthrow this claim. The methods researchers used were tandem mass spectrometry and liquid chromatography to identify and separate peptides, along with western blot and mass spectrometry to measure the AICD byproducts of the initial cleavage of APP. They first tested the effects of pairing wild-type y-secretase with a purified recombinant type C99 substrate, then did the same but with a mutated C99 substrate. The latter was mutated with one of the 14 FAD mutations at a time. The findings showed that two mutations did not lead to more AB42 than AB40, and most mutations only increase the AB42/AB40 ratio by decreasing AB40. For all 14 mutations, they found that the mutated C99 substrate's ability to cleave the first and/or second tripeptide groups was inhibited, resulting in long AB45-49 peptides. Therefore, it is logical to conclude that the increase of the AB42 to AB40 ratio is not a reliable biomarker for FAD since this doesn't always mean that the amount of harmful AB42 peptides will increase.

Several labs prove the validity of the presenilin hypothesis and further overthrow the amyloid-beta hypothesis. One of these labs included experimenting with six FAD presenilin mutations and wild-type (WT) C99[3]. They found that all six mutations were deficient in initial cleaving, meaning they inhibited the initial cleaving of APP. Moreover, two mutant enzymes caused a decline in the production of AICD, which correlates to less production of AB peptides. As expected, every FAD mutation also inhibited at least one tripeptide trimming step, which is also a part of the initial cleaving of APP. From this, it can be concluded that FAD mutations in presenilin only cause dysfunction in the initial cleaving steps, rather than the later steps when AB peptides are produced.

Another way researchers found more evidence to back up the presenilin hypothesis was through molecular dynamics simulations[4] . Using 2D free energy diagrams, they discovered that the mutant enzyme-substrate (ES) complexes have a smaller chance of getting active conformation from the three binding spots of y-secretase. They also found that FAD mutations moved the conformation sites, or energy wells, away from the correct location for catalysis. This reduced the number of cuts on the substrate. They then used root mean square fluctuations to measure flexibility of enzyme, and found that the mutated enzyme had limited flexibility, meaning it has more difficulty carrying out reactions and cleaving APP. Since the transmembrane domain of APP substrate is surrounded by presenilin during cleaving, if the ES complexes were mutated, then they would effectively prevent cleavage, and thus prevent the creation of supposedly harmful AB42 peptides. In order to prove that this hypothesis applies to living cells, another study was conducted on human cells using fluorescent lifetime imaging microscopy (FLIM) [23]. The process of this included having fluorescent-labeled antibodies target the AB region of the APP substrate and to an enzyme epitope near the y-secretase ES complex substrate, then measuring the fluorescent lifetime. They did this with human embryonic kidney 293 cells that were altered using CRISPR to remove the PSEN1 and PSEN2 genes, and were later transfected with the PSEN1 gene. The results showed that when C99 and PSEN1 have FAD mutations, there were shorter fluorescent lifetimes in C99 and AB-enriched regions, meaning FAD mutations stabilize interactions between y-secretase and its substrate. When y-secretase is stabilized in a certain way, it can become less flexible and therefore be unable to carry out its usual functions.

Lastly, researchers also tested inhibiting y-secretase's functions on a genetic model made with Caenorhabditis elegans (C. elegans). They first introduced human C99 and PSEN1 into C. elegans. They found that WT C99 and PSEN1 had no effect on synapse integrity and lifespan. On the other hand, when the I45 FAD mutation presented in C99, they found reduced lifespan and degeneration in synapses. They tried this again but this time inhibited AB42, and still, the synapses experienced the same negative effects, meaning that stalled E-S complexes are harmful even without AB42; thus, AB42 is merely a byproduct. Researchers then mutated PSEN1 with the L166P mutation and found that synaptic degeneration took place even without coexpression with C99. This helped them lead to the conclusion that stalled E-S complexes can cause harm in any substrate. To conclude, in every lab done by the researchers, the final verdict was that stalled E-S complexes alone are to blame for neurodegeneration in FAD patients.

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There are some limitations in the studies that the researchers conducted. For instance, although they were able to prove the validity of the presenilin hypothesis in eukaryotic cells (human kidney cells and C. elegans cells), they haven't been able to study the effects of the stalled E-S complex in neurons. Without stalling E-S complexes in human neurons, we cannot fully approve the presenilin hypothesis. Another limitation is that these studies are relatively recent; therefore, more research needs to be done before this hypothesis can lead to implications in drug discovery.

3. AB Hypothesis

Amyloid beta (AB) is a protein that is produced through the cleavage of APP. The first time researchers assumed that AB plaques were the cause of neurodegenerative diseases was in 1984, when the AB amino acid sequence was discovered as a main component in meningovascular polymorphic deposits, which is found in patients with Down syndrome[5] . Furthermore, by determining the APP gene's sequence, it was confirmed that AB is produced due to the enzymatic processes of APP[6] . In patients with Alzheimer's disease, there is an imbalance between how much AB is produced and how much is cleared out; this imbalance is called AB dyshomeostasis (Hardy J. et al., 2002). In early-onset Alzheimer's disease (EOAD), AB dyshomeostasis is caused by certain genes that produce an excessive amount of AB. However, in late-onset Alzheimer's disease (LOAD), AB plaques are caused by the dysfunction of proteostasis networks, leading to incomplete clearance of AB from the brain[7].

In a thorough study of a family with single gene EOAD, they found common mutations in the APP, PSEN1, and PSEN2 gene. Additionally, the offspring inherited these mutated genes through autosomal dominant inheritance; or in this case, autosomal dominant Alzheimer's disease (ADAD). When studies were conducted on mice with ADAD, researchers found that each mutation directly caused protein folding, aggregation, and an accumulation of AB plaques. This direct causation supported the development of the "amyloid cascade" concept.

Another factor that affects the AB pathway in LOAD is the apolipoprotein E (APOE) e4 allele[8]. In a study that used a sample of brain tissue collected from AD patients, it was confirmed that the presence of APOE e4 is associated with misfolded AB, harmful species of AB, and AB plaques[9]. Henceforth, APOE e4 can affect the mechanisms in which AB is produced. For instance, APOE e4 can control y-secretase activity, which is involved in the cleavage of APP. Therefore, APOE e4's contribution to AB metabolism and aggregation is a critical factor to consider when developing clinical treatments. To add on, APOE e4 is the variant that leads to more AB production than any other variant; thus, the effects that APOE have on the brain are isomer-dependent[10]. An important factor in the breakdown of APOE is the presence of low-density lipoprotein receptors (LDLR) [11]. This receptor helps cells absorb APOE and can also regulate the levels of AB in the brain. When there is an excessive amount of LDLRs, the amount of APOE decreases. This idea is supported by studies on mice brains, where researchers found that decreasing LDLR leads to more amyloid accumulation.

Another way that researchers have found evidence supporting the AB hypothesis was by investigating the role of the secretory pathway of APP processing. Two mutations at the b-secretase binding site, the Swedish mutation KM/NL and an Italian variant A673V), created a more soluble N-terminus of APP (sAPPβ), which is associated with AD[12]. These mutations allow beta-site APP cleaving enzyme 1 (BACE1) to cleave APP substrate more and create more AB peptides. To support this claim, researchers have reported high levels of BACE1 enzymatic activity in human AD brain samples[13]. BACE1 is one of the enzymes that cleaves APP substrate to produce amyloid-beta. Additionally, in both mice and human AD brains, a large amount of BACE1 was found near damaged neurites and AB plaques[14]. Hence, the evidence related to BACE1's relevance in APP cleavage backs up the claim that AB plaques cause neurodegeneration in AD patients.

Tau protein tangles are another possible cause of AD. Many studies have found that tau markers are highly correlated with neurodegeneration markers. Furthermore, an increased level of tau protein in the inferior temporal cortex is related to an increased level of AB accumulation. Thus, it can be suggested that AB pathophysiology can instigate tau-related neurodegeneration, and that the main reason for AD is the accumulation of AB and tau protein. Many have used rat neurons to study the effect of AB on the brain as well[15]. By adding AB oligomers in a culture with healthy rat neurons, neuritic dystrophy and AD-type tau hyperphosphorylation were developed in the neurons[16]. Moreover, in a culture system with human neurons, the initiation of EOAD mutations in PSEN1 and APP substrate triggered AB plaques. Using amyloid-PET and volumetric analysis MRI, researchers discovered that higher rates of PET standardized update value ratios (SUVRs) correlated with hippocampal gray matter atrophy[17].

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The average rate of AB clearance in healthy adults is around 8% per hour[18] . It is suggested that AB is cleared through bulk-flow in the CSF and across the blood-brain barrier (BBB), the perivascular circulation, and the glia-lymphatic (glymphatic) system since that is how most brain metabolites are cleared[18]. There is an emphasis on the BBB's role in AB homeostasis, as BBB dysregulation can be worsen AD symptoms. The BBB is a semi-permeable barrier, in which soluble AB passes through to the bloodstream along with the transporter LRP-1. Soluble LRP (sLRP) can prevent soluble AB from binding with advanced glycosidation end products (RAGE), hence inhibiting its entrance into the interstitum[19]. Conversely, in AD patients, LRP is dysregulated while RAGE is upregulated. This suggests that dysfunctions in the process of clearing AB from the brain can be the reason for AB plaques in AD patients. This extensive amount of research has provided substantial evidence for the AB hypothesis.

The controversy surrounding the AB hypothesis is generally due to the fact that a clear causal relationship has not been established between the accumulation of AB peptides and AD. It is unknown whether or not AB causes AD, or if AB is just a byproduct of AD. As mentioned previously, although some research has indicated that in AD the ratio of AB40/AB42 is increased, further investigation has proven that the ratio only increased because AB40 decreased, thereby overthrowing the claim that AD is caused by an increase of AB42. In addition, although many drugs have been developed to limit AB production, such as aducanumab, they all did not have a positive impact on the severity of AD symptoms.

4. Insulin Resistance

Insulin is found in many parts of the brain. Synapses between neurons are an important location for insulin signaling, as many insulin receptors can be found on the presynaptic axon terminal of synapses. With the help of the glucose transporter protein GLUT 3, and occasionally GLUT 4 and GLUT 8, glucose can be transported into neurons[20] . Insulin is imperative for the regulation of neuronal metabolism and energy uptake because GLUT 4 needs to be triggered by insulin in order to be transported from the cytosol to the plasma membrane. Additionally, GLUT 4 needs to be transported to the neuronal cell membrane through the AKT pathway with insulin, because doing so is essential for the brain at times of high metabolic demand. Hence, it is logical to assume that insulin-dependent glucose transportation helps prevent cognitive impairment[21]. This claim is supported by a study done on rat hippocampus, where they found that glycolysis and an improved spatial memory followed after insulin triggered glucose transportation to the plasma cell membrane. To add on, GLUT 8 also promotes glucose homeostasis in neurons.

Since insulin is found in high concentrations in regions of the brain associated with learning and memory, such as the hippocampus, entorhinal cortex, and the frontal cortex, insulin may be essential to cognition. Researchers have even found that the insulin receptors in both animal and human hippocampus alter after spatial learning. It has also been suggested that insulin signaling enhances neuronal plasticity, which is the ability of neurons to adapt and react to changes in stimuli. Insulin resistance in the brain can be due to the suppressant of insulin receptors or dysfunction of the insulin cascade[22]. This resistance can cause dysregulation of metabolism or impaired cognition and mood in both the periphery (outside the central nervous system) and the brain. In addition, similarities between peripheral metabolic disorders in type 2 diabetes and AD have been discovered.

The accumulation of Tau proteins is an established biomarker in the pathogenesis of AD. Moreover, in patients with AD, Tau protein is three times more hydrophosphorylated [4]. Many types of kinase, which are enzymes that carry out phosphorylation, have been found to play a role in insulin resistance[23]. Thus, the correlation between an increased amount of kinase and hydrophosphorylated tau protein suggests the role insulin resistance may have on development of AD. In mice that had the Tau protein in their brains removed, the hypothalamus was damaged. A damaged hypothalamus can potentially initiate changes in energy metabolism[24]. Thus, having dysfunctional Tau protein could lead to insulin resistance in the brain, which is something that may be relevant when looking at AD patients.

There are two pathways in which APP substrate is processed to create amyloid beta. APP can be cleaved differently through the different pathways. 90% of it is processed in the non-amyloidogenic pathway, while the remaining 10% is processed in the amyloidogenic pathway, which is the pathway that leads to the accumulation of harmful AB plaques[25]. Through phosphorylation, insulin plays a role in triggering the non-amyloidogenic pathway, meaning insulin may be able to prevent AB accumulation. The cleavage of APP in the amyloidogenic pathway starts with beta-secretase cleaving APP into N-terminal (sAPPβ) fragments and a longer C-terminal fragment, which contains the precursor proteins CTFβ and C99. Then, y-secretase cleaves CTFβ to produce AICD and AB strands that will eventually

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leave the cell and form neurofibrillary tangles in the brain. Thus, insulin resistance may play a role in increasing AB accumulation and thus worsening AD pathology.

Although many have collected data that can support the insulin resistance hypothesis of AD, the validity of some of this data heavily relies on the amyloid-beta hypothesis being true. For instance, even though researchers have found that insulin resistance can produce more harmful AB strands, it is not certain that insulin resistance undeniably causes AD, because it is not fully established that AB plaques cause AD. Another limitation of this hypothesis is that it cannot be applied to all individuals with AD. This is because not all AD patients have insulin resistance. Therefore, although the results of studies related to the insulin resistance hypothesis can be helpful in the search for treatment, the possibly that it will create a big impact is low.

5. Evaluation of the Hypotheses

After thorough evaluation of each hypothesis, it is concluded that the presenilin hypothesis is comparatively the most reliable and valid hypothesis. This is due to the fact that both the AB hypothesis and the insulin hypothesis heavily rely on the claim that AB plaques are the main cause of AD, despite the fact that AB-inhibiting drugs have been proven to be ineffective in eliminating AD symptoms. Another reason why the AB hypothesis is not fully recognized is because there has been no evidence to support the fact that the accumulation of AB directly causes the onset of AD symptoms. Rather, a correlation is all that has been uncovered. Furthermore, as mentioned earlier in the review, researchers have found that the increase in the ratio of AB40/42 does not produce more AB42 peptides; instead, the increase of this ratio is mostly due to a decrease in AB40. Although extensive research has been done to support the insulin resistance hypothesis, it cannot apply to all patients with AD, because not all AD patients have insulin resistance. All in all, the presenilin hypothesis is the most applicable and valid hypothesis when compared to the other two. With further research, it has the potential to generate positive outcomes in the search for AD treatments and therapies.

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