

Impaired Beta Amyloid Synthesis in Alzheimer's Disease

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Abstract: *Alzheimer's disease (AD) is neurodegenerative disease. It is clinically categorized by progressive deterioration of memory, and pathologically by histopathological changes including extracellular deposits of amyloid-beta (A β) peptides forming senile plaques (SP) and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain. The cause of the disease is still uncertain. However, there are various hypotheses suggesting the pathogenesis of this disease and "The Amyloid Hypothesis" which postulates that the deposition of beta-amyloid causing AD is widely accepted. The impaired synthesis of the (A β) has significant implications on the pathogenesis of the disease.*

Keywords: alzheimers, beta amyloid

1. Introduction

Alzheimer's Disease (AD) was first described by a German psychiatrist and neuropathologist Alois Alzheimer in 1906 thus was named after him. AD is a common neurodegenerative disease and it is increasing rapidly worldwide. Symptoms include memory loss, progressive cognitive impairment, and behavioral deficits. There is no cure for the disease as treatment available now is only to reduce the symptoms of the disease. Aging is the main risk factor for developing AD. Based on studies, it was estimated that the age-associated prevalence rate of AD would be doubled every 5 years in patients above 65 years. In addition to aging, interaction of other factors such as genetic alterations and polymorphisms, abnormal immune or inflammatory responses, traumatic injury, oxidative stress, drugs, and hormone replacement therapy can also lead to AD.

Main pathological evidence in this disease is the presence of senile plaques. The core of the plaque is made up of beta-amyloid protein. Besides, there is also a concomitant loss of the cholinergic marker enzyme, choline acetyltransferase (ChAT). The accumulation of amyloid- β (A β) in the brain is claimed to be the reason for the pathological features of AD.

To prove this hypothesis, the location of the gene for the (APP) is on chromosome 21 is taken into consideration, and the fact that people with Down Syndrome where they have an extra gene copy of the ADD gene on the chromosome 21 almost universally get AD by the age of 40. Familial AD families with a duplicated APP gene locus, exhibit total A β overproduction and all develop early-onset AD. In addition to that, a specific isoform of apolipoprotein, APOE4 allele, is a major genetic risk factor for AD as it leads to excessive buildup of amyloid in the brain although generally apolipoproteins enhance the breakdown of beta amyloid.

2. Beta Amyloid Synthesis And Impairment Leading to Alzheimer's Disease

Amyloid beta (A β) is a peptide of 36–43 amino acids. The physiological function of A β is unclear although some studies have shown that the absence of A β does not lead to

any loss of physiological function. However, studies show A β is a highly multifunctional peptide with significant non-pathological activity and it is associated with the activation of enzymes, functioning as a transcription factor, regulation of transport of cholesterol, protection against oxidative stress, and anti-microbial activity (associated with A β 's pro-inflammatory activity). A β is formed from the (APP) which is a, it can penetrate through the neuron's membrane. APP is significantly important in the growth of neurons, survival and post-injury repair of the neurons. A β is formed by the sequential cleavage of APP by the enzymes α -, β - and γ -secretase. The γ secretase, cleaves within the transmembrane region of APP produces the C-terminal end of A β peptide and produces various of isoforms of 36-43 amino acid residues in length. The most common isoforms are A β 40 and A β 42. The A β 40 form is the more common than A β 42. However, the A β 42 is more fibrillogenic which is associated with AD. Studies also show there is an increase of A β 42 production in cases of mutations in APP associated with early-onset Alzheimer's.

Majority of Alzheimer's disease are sporadic, which means that it not genetically inherited though certain genes can be risk factor. However, approximately 0.1% of AD cases are familial forms of dominant (not sex-linked) inheritance, whereby there is onset of the disease before 65 years of age. It is also known as early onset familial Alzheimer's disease. Majority of autosomal dominant familial AD could be associated with mutations in one of three genes namely the (APP) and presenilins 1 and 2. Mutations in the APP and presenilin genes mostly increase the production A β 42, which is the main component of senile plaques. However, some of the mutations just changes the ratio between A β 42 and other forms like A β 42 without increasing A β 42 levels. According to this, it can be said that presenilin mutations can lead to the disease even if they lower the total amount of A β produced and may point to other roles of presenilin or a role for alterations in the function of APP and/or its fragments other than A β .

Thus, Alzheimer is associated with the failures in regulating A β production and clearance, leading to increased levels of A β and leading to neurotoxicity. Neurotoxic A β is at first released as a monomer, then molecular interactions will

cause aggregation into oligomers, fibrils, and plaques in the brains of patients with AD. The disturbances in the synthesis and aggregation of the beta-amyloid peptide which leads to the pathology of AD is still unknown. The buildup of aggregated amyloid, which are toxic form of the protein disturbs the cell's calcium ion homeostasis, triggering programmed cell death (apoptosis). Moreover, utilization of glucose by the neurons is disturbed and functions of some enzymes are inhibited as A β selectively accumulates in the mitochondria in the cells of brains of Alzheimer patients

Therefore, compounds that block A β aggregation could be clinically useful for treating AD such as peptides have designed to bind and inhibit A β based on the sequences and structures related to the self-assembling property of A β . However numerous researches are yet to be done to find the cure for Alzheimer's disease. Currently, there are no definitive measures to prevent Alzheimer's disease however, diet, pharmaceuticals and intellectual activities may help delay the process.

References

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