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REVIEW ARTICLE **OPEN ACCESS**

Molecular cascade of Alzheimer's disease

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ABSTRACT
Alzheimer disease (AD) is a most commonly recognized neurodegenerative disorder. The incidence of this disease is progressively rising every year due to sedentary in life style. There is no current therapy available in the market to treat however; they can only relive the symptoms of AD. It is characterized with severe irreversible loss in cognition in most of the all age people incurable to till now. The cognitive dysfunction manifestation is considered because of excessive production of Amyloid beta (Aβ) inside the neurons, impaired cholinergic functions and calcium homeostasis, neuroinflammation and generation of free radicals. Therefore, these diverse pathways in the pathophysiology of AD make it more multifactorial and complex neurodegenerative disorder. A wide range of mitochondrial abnormality correlated with brains of AD patients including DNA defects, impaired electron transport chain activity resulting in increase in oxidative stress, decrease in the level of mitochondrial enzymes activities and initiation of apoptotic death in cholinergic neurons. This review focused on the molecular mechanism of AD to understand the pathophysiology of Aβ induced toxicity in various brain regions to provide the better therapeutic and preventable strategies to work against the AD.
Key words: *Alzheimer's disease, cholinergic functions, neurodegenerative disorder.*

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INTRODUCTION

Alzheimer's disease (AD)is described by Alios Alzheimer's in 1906 at a conference in Germany [1]. AD is a most common and irreversible form of dementia that is mostly prevalent in more than 50 million population worldwide [2].Recently, AD is observed to be a chronic disorder with the manifestations of impaired cognition that affects the memory, thinking, orientation, comprehension, learning, language, and judgmental capacity [3]. AD is mainly divided into two categories named as familial Alzheimer's disease (FAD) and sporadic (SAD) leads to cognitive dysfunction and neuronal loss in the central nervous system (CNS) [4, 5]. At the sub cellular level, the presence of specific cytoskeletal abnormalities, including the presence of variety of long chain amino acid (40 and 42)of amyloid beta (Aβ), is reported in the pathophysiology of AD [6].Genetic manifestation has become one of the attribute to the pathogenesis of AD and mutations in amyloid precursor protein (APP) in early onset of FAD[7], presenilin (PS-1) and PS-2are reported in this context[8]. On the other hand, SAD is another model of AD to which both genetic and epigenetic factors contribute in neurodegeneration [9]. It has been observed that cellular metabolic disruption i.e. increased brain insulin resistance [10], decreased glucose consumption and energy metabolism [11], energy deficit, reactive oxygen species induced oxidative stress[12] and inflammation [13],excessive production of Amyloid beta (Aβ) inside the neurons [14], impaired cholinergic functions and calcium homeostasis [15,16] in neuron which further leads to neurodegeneration in SAD. The pathophysiology of AD in terms of Amyloid beta deposition, disruptive cholinergic functions, oxidative stress (OS) and calcium homeostasis is important to discuss to understand the disease progress in an individual.

ALZHEIMER'S DISEASE ASSOCIATED ALTERATION

Cholinergic dysfunction: Cholinergic hypothesis is mostly accepted in the AD pathophysiology. It has been documented that neurodegeneration of cholinergic neuron in memory sensitive brain regions such as hippocampus and prefrontal cortex, play promising role in cognitive like functions[17]. This is

supported by our laboratory work through by measuring the downregulation of the choline acetyl transferase (ChAT) and acetylcholine (ACh) and up regulation of acetyl cholinesterase (AChE) that associated with cognitive impairment [18]. The cholinergic hypothesis is widely accepted in considering several therapeutic approach to treat cognitive dysfunction.

Amyloid beta deposition and mitochondrial dysfunction: Amyloid beta derived from the Amyloid precursor protein (APPs) via amyloidogenic pathway [19]. Through this pathway APPs can be cleaved by the β secretase in initial phase into soluble APPsβ and the β-C-terminal fragment further the β-C-terminal fragmentis cleaved by γ secretase complex to synthesize Aβ on the mitochondrial surface[19] where it can form complex with mitochondrial membrane and transported into mitochondria [20,21]. The mitochondrial hypothesis determine the mitochondrial efficiency of electron transport chain in terms of higher rate of production of reactive oxygen species (ROS) that leads to production of Aβ [22]. Although amyloid beta is natural product of metabolism, it is present in cells in precise range so its concentration is controlledthrough a balance between its synthesis and its clearance [19]. Different cellular proteases such as neprilysin, insulin degrading enzyme, cathepsin and presequence protease (PreP) have been found in a cell to increase the clearance of Amyloid beta [23, 24]. This fact has been proved that these protease have lowered activity in AD [25, 26, 27]which leads to an impairment in the clearance of Aβ. Therefore, the impaired clearance of Aβ is better way to ameliorate the cognitive dysfunction.

Calcium homeostasis: Although the calcium regulation is necessary for the neuron to maintain normal function [28] therefore dysregulation of calcium leads to impaired cognitive function.Several ideas postulate that Aβincreased the calcium level in cytoplasm as well as in mitochondria [29,30,31]. Increased calcium level in cytoplasm of cell is taken up by the mitochondria through mitochondrial calcium uniporter (MCU) [32,33].Endoplasmic reticulum (ER)-mitochondria calcium transfer is the process of the communication between the two cellular organellesthat potentially regulate mitochondrial respiration, ATP production and normal functioning of bioenergetics [34]. Mitochondrial associated endoplasmic reticulum membrane (MAM) that regulate calcium level, glucose, phospholipid- cholesterol metabolism and maintain of membrane-lipid composition [35,36]. Aggregation of Aβ is responsible for the MAM alterations and its associated calcium dysregulation [34].

CONCLUSION

The genetic background, dyshomeostasis and aging are considered to make the pathophysiology of AD a bit more complex. The precise molecular mechanism of AD is obscure. There are many therapeutic approaches that are available in market to control but none of them provides a potential therapeutic solution to AD. A better understanding in the pathogenesis of AD and its management is a prerequisite need for current era.

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