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The Role of Mitochondria in Alzheimer's Disease and its Potential Therapies

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Abstract

Alzheimer's disease (AD) is a common form of dementia, affecting millions of people worldwide, mostly the elderly population. The gradual decline in cognitive functions, loss of memory, and sleep disorder are the most frequently reported in AD patients. Multiple studies have been carried out to find a potential therapeutic approach to prevent the progression of Alzheimer's disease and increase the performance of cognitive abilities. Mitochondrial dysfunction leading to oxidative stress and other environmental factors, diet and lifestyle are the major risk factors. Mitochondria play an essential role and are a potential therapeutic target for treating and preventing AD progression. Various biochemical molecules involved in mitochondrial metabolic pathways are tested as directly acting on mitochondria. Numerous antioxidants are considered as a potential treatment for AD. Here, we highlighted the emerging mitochondrial base therapies and potent antioxidants that can be used in Alzheimer's disease treatments.

Keywords: Alzheimer's Disease, Mitochondria, Therapies, Antioxidants

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CONTENTS

1. INTRODUCTION

Alzheimer is a disease first discovered by Alois Alzheimer in 1901. It is s mental complex mostly affecting aged people accompanied by the loss of memory and cognitive abilities. It is an irreversible defect and millions of people are currently affected. It is supposed to be more than 40 million diseased individuals worldwide and it is expected that the number will be double after two decades [1]. There are about one million people with dementia in Pakistan. Among these people, 70% are of age 65 or above and 15% of age 75 or above. Every one out of ten of age 65 is living with AD in the United States. AD was the 8th leading cause of death in 2001 but now it becomes the 5th leading cause of death in the US. More than 4.6 and 6.4 million people are living with dementia in Japan and China respectively. Various factors have been marked as significant for the onset of AD, some of the factors contributing to the disorder are autophagy defect, genetic factor, stimulation of receptor on myeloid cells, alteration in microflora, way of life, coronary and traumatic brain damage. Factors like hypertension, depression, smoking, obesity, biochemical and physical impairment are considered at an alarming rate in the onset of Alzheimer's [2]. Almost 70% of affected cases have lost their ability to problem-solving and memory which is due to the onset of Alzheimer's disease [3]. Under clinical investigation in most of the cases people effected with AD have memory dysfunction, demise in cognitive abilities, fail to maintain daily life activities [4]. This review article will provide brief knowledge to AD and reviews some of the emerging antioxidants that can be used to treat Alzheimer's disease.

Alzheimer's disease is a gradual process of losing the ability to manage things properly from mild to severe problems of dementia. It is recorded as the prominent cause of death with an average survival of at least 8 years if diagnosed at the age of 65 [5]. It is important to understand the biology and genetic factors of this disorder. To find treatment in this regard, the basic nature and neuropathology must be analyzed. It can be sporadic or inherited in nature in aged individuals. Age mark as the most significant risk factor for AD, disorder at the elderly age mostly termed as sporadic with most cases encounter after the age of 65 and termed as the late-onset or sporadic AD while in other individuals reported at an early age are called early-onset AD. Most of the early-onset AD case has a family history of dementia. Familial Alzheimer cases are usually caused due to mutations in the gene for amyloid precursor protein (APP), PSEN1, or PSEN2 [6–8]. Mutated APP affects Aβ cleavage while PSEN1 and PSEN2 help γ secretase to cleave APP. The duplication of amyloid precursor protein is also considered as a source of familial Alzheimer's as reported by Kasuga and Shea *et al*, in 2009 and 2016 respectively [9,10]. Other genes linked to AD are shown in Figure 1.

2. NEUROPATHOLOGY OF ALZHEIMER'S DISEASE

Several features about the neuropathology can be demonstrated, under microscopic study affected individuals have brain shrinkage and cortical damage and atrophy. A microscopic study suggested the inclusion of plaques of amyloid and neurofibrillary tangles. The product of APP extension and the accumulation and deposition in the extracellular spaces. In normal physiological condition, APP is cleaved by α-secretase and γ-secretase to form the nontoxic fragment while in AD, the APP is cleaved by γ-secretase and β-site of Amyloid precursor Cleaving Enzyme 1 (BACE1) to form toxic Amyloid β peptides which oligomerize and leads to deposition of β amyloid plaques [11]. The deposition of amyloid occurs in various stages, firstly it accumulates in the frontal, temporal, and occipital areas of the brain except for the hippocampus. At the next stages, amyloid resides in all portions with medium density. Finally, the deposition accumulates the whole part of the hippocampus with some areas of subcortical regions and cerebellum [12].

Tau proteins are neuron-specific microtubule-associated proteins (MAPs) that are produced from a single MAPT (microtubule-associated protein tau) gene by alternative splicing exons 2, 3, and 10 which exist as six isoforms. MAPs play important role in maintaining neuronal structure, microtubules stability, axonal transport, axonal outgrowth, and synaptic plasticity. The longest tau isoform has 79 potential Serine and Threonine phosphorylation sites which are regulated by kinases and phosphatases. In AD, there is an imbalance in the kinases and phosphatases as a result tau is hyperphosphorylated and becomes defective. The tau lost its microtubule-binding ability and dissociates from microtubules which dimerize into paired helical filaments (PHFs) and neurofibrillary tangles (NFTs) in neurons, as a result, microtubule loses their stability and axon collapse. Instead of clearing plaque deposition activated microglia release certain cytokines and cause neuroinflammation that contributes to neuron death in AD [13].

Transgenic animal models have been particularly useful in the study of AD in all aspects, from the understanding of its molecular etiology to the development of potential drug treatments. But using animal models for the demonstration of Alzheimer's disease has many problems. Different transgenic animals are used as models for AD, but they did not reflect the disease state. Multiple rat studies show no relation to human characteristics. AD can be induced in monkeys by intracerebroventricular injection of Streptozotocin [14]. Many cell-based models are also used to study AD.

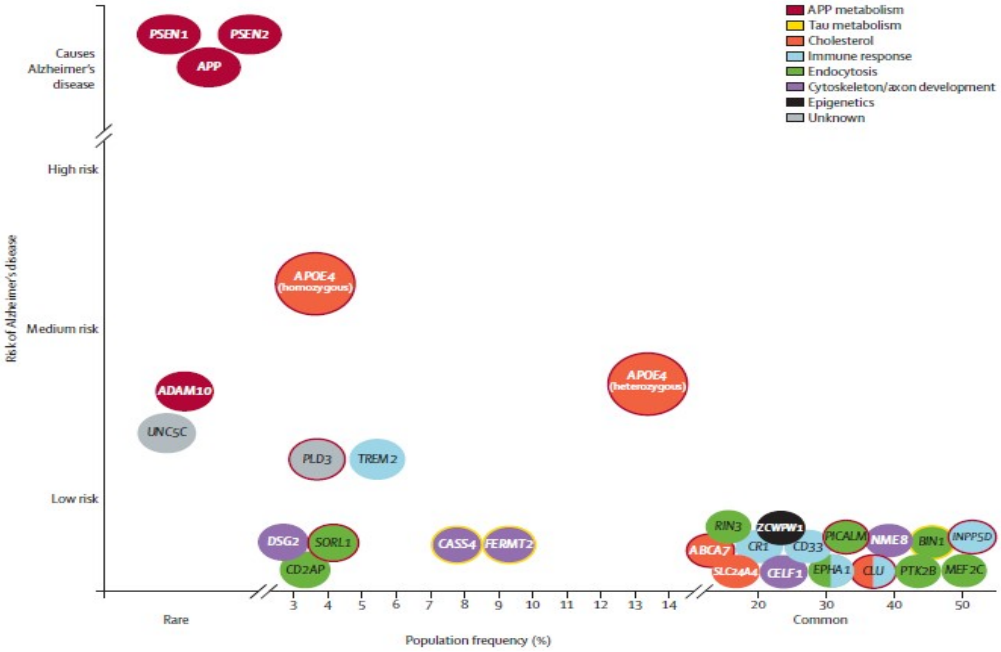

Fig. 1. Genes associated with Alzheimer's disease [4].

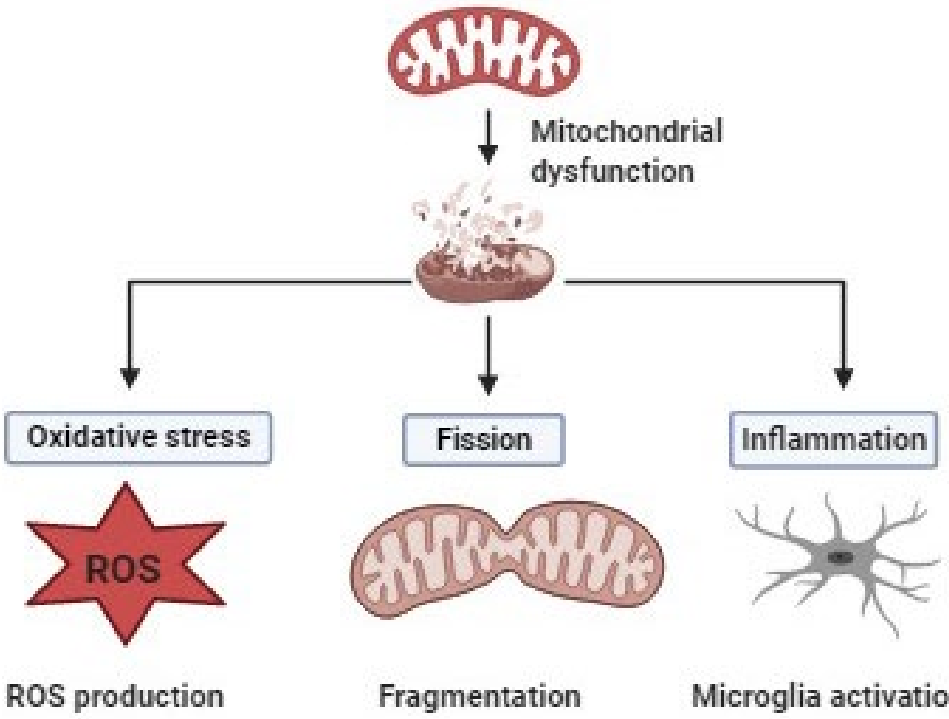

Fig. 2 Mitochondrial dysfunction cause oxidative stress, mitochondrial fission process and neuroinflammation.

3. ROLE OF MITOCHONDRIA IN ALZHEMEIR'S DISEASE

Mitochondria is a double membrane cellular organelle with unique structural and functional characteristics. The matrix of the organelle occupies the inner side of both membranes. Mitochondria are referred to as the power generator of the cell due to their diverse function of providing energy to perform various activities in the cell. The energy production is the result of certain biochemical reactions such as oxidation and phosphorylation in the inner mitochondrial membrane with the help of a respiratory chain reaction complex. As a result, the inner membrane potential is generated and is utilized by the ATP enzyme complex [15].

Mitochondria have its own DNA which encodes 13 mitochondrial protein units. While other required components are synthesized in the nucleus and transported to the organelle through the ribosomal process in the cytosol. The whole process requires a coordinated sequence of reactions [15]. Neurons act as a passage for the transmission of sensory messages and depend on the mitochondrial concentration in the synaptic terminals. These organelles generate ATP and a buffer concentration of Ca^{2+} to maintain the neurotransmission and generation of membrane potentials along the axon [16–18].

Many mitochondria are required in the synaptic areas for sustainable transmission and efficient information transport. Mitochondria synthesis takes place in the neuronal body and is transported to the synaptic site through transportation proteins kinesin, dynein, and microtubules along the axon. The metabolic reactions and concentration of calcium ions in the synaptic terminals are responsible for mitochondrial transportation [19–22]. The enzymatic impact of mitochondria has two side effects firstly the inner membrane potential which is required for the importation of nuclear protein which reflects the health of mitochondrial cells [23]. Secondly, the electronic release from the respiratory chain complex contributes to the release of reactive oxygen that in turn is considered as a byproduct of bioenergetics sequences [24].

In the normal biochemical functions, reactive oxygen species (ROS) are at the optimal amount due to the availability of antioxidant system the cellular injury is contained. While in aging and neural dysfunctions the equilibrium is disrupted. The high concentration of ROS results in damage to the important parts of the brain due to generated oxidative stress. All the biomolecules like proteins, lipids, and carbohydrates are targeted [24]. All major parts of the brain, the hippocampus, and the cortex are at great risk due to oxidative stress due to increased consumption of oxygen and mitochondrial energy dependence [25]. It has been observed that amyloid-beta aggregates are present in mitochondria before the formation of extracellular amyloid plaques [26]. Amyloid-beta also cause an increase in the cytoplasmic Ca^{+2} which is uptake by mitochondria through Mitochondrial Calcium Uniporter (MCU) to decrease cytoplasmic Ca^{2+} overload. High mitochondrial Ca^{2+} level can cause neuronal death. Mitochondrial Ca^{2+} influx related genes were downregulated in the human brain of AD while mitochondrial efflux related genes were upregulated to regulated mitochondrial Ca^{2+} overload [27].

3.1. Alzheimer Mitochondrial Dysfunction

In a diseased person deviation in bioenergetics, pathways are also linked with reduced glucose consumption and are considered an essential feature of Alzheimer's disease. Glucose level can be demonstrated using positron emission tomography (PET) technique which has demonstrated a consistently low rate of glucose breakdown approximately 25 to 30 percent lower than healthy men [28]. Regions of the brain involved in memory processing are the most vulnerable to a reduced rate of metabolism [29]. The disrupted rate of metabolism can easily be related to mitochondrial defects [30]. Several hypotheses have been put forward regarding the neuropathology of AD disease concerning mitochondrial dysfunction. The "amyloid cascade hypothesis" had been on the upper hand in AD in the past three decades. The above hypothesis speculates about the formation of amyloid plaque and APP mutation which finally triggers the early onset of AD [31]. In 2004 another hypothesis was proposed regarding the onset of sporadic AD and was called the "mitochondrial cascade hypothesis" it states that every human being carries his own heritage of mitochondrial functions which influences the risks of an onset of AD. Simply it can be said that mitochondrial dysfunctions can trigger another biochemical reaction cascade which may lead to the late onset of AD [32,33]. To the validation of this hypothesis, it has been reported that some of the mitochondrial functions such as

mitochondrial morphology, its number, oxidation and phosphorylation, membrane potential, calcium buffering, ROS, mtDNA oxidation, and mutation were strongly affected. Many others like neuronal mitochondrial protein transport and mitophagy were also affected. Regarding neuronal transmission dysfunction in any of these could lead to disruption in the synaptic passage and eventually could collapse the whole network of the brain reported by Cai and Tammineni in 2017 [34].

Mitochondria dynamics play important role in the normal functioning of the cells and it is disrupted in pathological conditions. Abnormal mitochondrial fusion and fission are associated with an increase in ROS production [35]. In AD, mitochondrial fission takes place more than mitochondrial fusion [36]. Various attributes related to metabolisms such as high blood pressure, diabetes, and a higher level of cholesterol are associated with AD. Aged people with obesity are at risk of AD more than normal individuals. Various studies have been carried out to investigate the metabolic deficiency of N-acetyl-aspartate (NAA) and neuron degeneration. No role of NAA in brain functioning is identified. Other physiological and biochemical processes like lipid metabolism and maintenance are compromised in AD. In the compensation of disease glucose metabolism, the amino acid metabolism is altered which leads to toxicities that contribute to AD progression [13]. Reports have been obtained about the accumulation of ceramide in certain parts of the brain [37]. Amyloid-beta accumulation in mitochondria induces mitochondrial dysfunction which leads to apoptosis [38–40].

Mitochondrial dysfunction is a contributing factor in sleep disorder in AD patients. It is a common sign that can be investigated which is correlated with memory loss and cognitive degradation. Various studies have stated about the factor of sleep disorder related to mitochondrial dysfunction [41].

3.2. Mitochondrial Unfolded Protein Response in Alzheimer's Disease

Numerous studies show ER stress or ER unfold protein response role in Alzheimer's disease pathogenesis, but little was known about the mitochondrial unfolded protein response in AD. Mitochondrial unfolded protein response (mtUPR) ensures proper functioning of mitochondria which results in the activation of mitochondrial chaperones and proteases that facilitate proper protein folding and degrade misfolded proteins. Recently, *in vivo* and *in vitro* studies show that amyloid-beta plaques in AD trigger mtUPR [42]. It has been observed that inhibition of the mevalonate pathway or sphingolipid biogenetic pathway decreases mtUPR resulting in a change in cell morphology, increased ROS production and decreased cell viability.

4. MITOCHINDRIAL THERAPIES IN ALZHEIMER'S DISEASE

Being a potential precursor for the onset of Alzheimer's mitochondria is considered as an active site for potential therapy. AD still has no cure and prevails a lack of information about a significant stimulating event for the disease. Although improvement has been made for the better understanding and treatment of disorder not only to heal but to prevent the onset and symptoms in the affected person. Different antibodies and inhibitors are used to treat AD. In 1990, the first antibody was used to reduce the amyloid levels in the brain. Currently, there have been traditional treatments for AD individuals, the cholinesterase inhibitors i.e. donepezil, rivastigmine, galantamine, and memantine which blocks the N-methyl-D-aspartate receptor and the excess of glutamate functioning.

NMDA along with acetylcholine are essential for maintaining learning and memory, its concentration is strongly contained in AD [43]. The said treatment however enhanced memory and cognitive abilities without having inhibition for the reduction in the progression of the disease. There are two main dimensions of AD pathology, mitochondrial dysfunction, and the demise of energetic metabolism that's why mitochondria can be a potential therapeutic target. In past times various compounds have been tested against AD targeting mitochondria without having any significant outcomes. With time studies showed mitochondria being a potential therapeutic target along with other recommended treatments. There are two approaches to targeting mitochondria.

1) Directly acting on mitochondria pharmacologically

2) Acting indirectly on the organelle through changes in lifestyle

4.1. Antioxidants

The increased oxidative stress followed by a reduction in antioxidant potential reported in the brain and cerebrospinal fluid (CSF) from the AD individuals. Antioxidants can reduce the production of ROS and oxidative stress to protect cells from oxidative damage. It also decreases the inflammation process such as coenzyme Q and glutathione. Prominent antioxidants such as vitamins E and C were tested to counter this oxidative impairment and reduce AD symptoms. Studies show vitamin E and other indicators of peroxidation found reduced in AD patients and with no major demise in cognition [44,45]. Its certain level of prescription in addition to selenium was found harmful and having an oxidative effect along with neuron necrosis and ganglia activation [46]. Targeting mitochondria directly through antioxidant compounds were considered one of the significant therapeutic approach for treating Alzheimer. Coenzyme Q10 and antioxidants were directly used having quinone structure and fragments of mitochondrial RCC. CoQ10 revealed to have prevented cognitive demise [47]. Although having no positive effect in human administration, to counter this problem mitoquinone mesylate (MitoQ) an oxidant targeting mitochondria helps to penetrate lipid bilayers on another side of the membrane [48,49]. Beta-carotene and phytochemicals found in fruits and vegetables show antioxidant and anti-inflammatory activities that can protect against cell damage. Curcumin is considered a safe medicinal drug from history to treat many diseases. It has antioxidant and anti-inflammatory potential. It reduced oxidative stress and inflammation in mice receiving amyloid-beta dose [50]. However, no significant results were achieved.

Melatonin, N-Acetyl-Cysteine (NAC), and Ginkgo Biloba:

4.1.1. Melatonin

A neural hormone secreted by a pineal gland having neural protection capability in Alzheimer's pathology [51]. Melatonin performs the activity against amyloid-beta. It inhibits the amyloidogenic process by triggering α-secretases to cleave APP and stimulates the non-amyloidogenic processes by downregulation of β-secretase and γ-secretase [51]. It also acts as a scavenger for reactive oxygen species [52]. It blocks the production of ROS at the mitochondrial level, restores the Ca^{2+} balance [53].

4.1.2. N-Acetyl-Cysteine (NAC)

It is a key biomolecule maintaining mitochondrial performance and act as an initiator for the internal production of antioxidant glutathione which counteracts oxidative damage [54]. It showed improvement in cognitive activity and memory recovery [55].

4.1.3 Ginkgo Biloba

Shows antioxidant activity which is normally used as Chinese traditional medicine and acts as an effective medicine in mitochondrial functions. Trials were carried for the prevention of memory loss in adults with AD disorder [56].

5. OTHER MITOCHONDRIAL-BASED AD THERAPIES

Oxaloacetate, NAD, Pioglitazone, and Dimebon are potential therapeutic molecules and can be used directly targeting mitochondria for the treatment of AD. Oxaloacetate a byproduct of the mitochondrial metabolic cycle and is proposed for the treatment of AD [57]. Nicotinamide adenine dinucleotide (NAD), coenzyme significant in glycolysis and oxidative phosphorylation. Various studies show that it affects mitochondria directly and have positive results. Oral administration for the treatment of AD subjects was also tested in the past to enhance brain functioning and cellular bioenergetic generation and was found with no further degradation of cognitive abilities [58]. Inhibiting MCU which will decrease mitochondrial Ca^{2+} can be used to prevent neuronal death. Mitochondrial UPR related proteins can be used as a potential therapeutic target for the treatment of AD.

6. CONCLUSIONS

Oxaloacetate, NAD, Pioglitazone, and Dimebon are potential therapeutic molecules and can be used directly targeting mitochondria for the treatment of AD. Oxaloacetate a byproduct of the mitochondrial metabolic cycle and is proposed for the treatment of AD [57]. Nicotinamide adenine dinucleotide (NAD), coenzyme significant in glycolysis and oxidative phosphorylation. Various studies show that it affects mitochondria directly and have positive results. Oral administration for the treatment of AD subjects was also tested in the past to enhance brain functioning and cellular bioenergetic generation and was found with no further degradation of cognitive abilities [58]. Inhibiting MCU which will decrease mitochondrial Ca^{2+} can be used to prevent neuronal death. Mitochondrial UPR related proteins can be used as a potential therapeutic target for the treatment of AD.

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CONFLICT OF INTEREST

The authors have no conflict of interest regarding the publication of this review article.

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