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Review Article

Mitochondrial Dysfunction in Alzheimer's Disease and Possible Therapeutic Targets to Prevent Progression of Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is the most frequent cause of dementia in aged population. Till now, there is no effective treatment for AD. Now various studies have kinked AD to mitochondrial dysfunction, due to accumulation of Aβaggregates, neurofibrillary tangles, cholinergic transmission, oxidative stress and neuroinflammation causing neurodegeneration and cognitive decline seen in AD. Here in this article, how the mitochondrial dysfunction/dynamics are involved in the pathogenesis of cognitive decline seen in cases of AD and various therapeutics targeted against mitochondrial dysfunctions are described, thereby causing a ray of hope for preventing progression of AD.

Keywords: Mitochondria dysfunction; Mitochondria therapy AD; Mitochondria and AD

Introduction

AD is the most common form of dementia. Affecting millions of people worldwide (Alzheimer's Association 2020). AD is characterized by the deposition of extracellular senile plaques neurofibrillary tangles and ultimately neuronal degeneration, causing memory impairment and dementia. Since the exact mechanism and pathogenesis is little understood, only symptomatic treatment is available presently.

It is postulated that in AD, Aβ and phosphorylated tauaffect the neuronal functions due to dysfunction of mitochondria and synapses. It is seen that in the early stages of AD metabolic changes in the cells occur much earlier than the development of amyloid plaques and NFT (Neuro Fibrillary Tangles) [1,2]. It is suggested that mitochondrial dysfunction specifically oxidative phosphorylation is the most important for the development and progression of AD [3].

Recently in a study it was seen that in the bioenergetics of mitochondria in AD and the role of mitochondrial cascade hypothesis, a mitochondrial cascade hypothesis was proposed [4]. This hypothesis states that Aβ is not the primary pathology in AD, consistent with the findings of early mitochondrial dysfunction can lead to cognitive impairment, increased Aβ aggregation and AD pathogenesis [5].This mitochondrial cascade may be primary or secondary in AD. Neurons possess a higher number of mitochondria near synapses, and below a certain number of mitochondria causes' impaired neuronal function and intracellular signaling. It has been seen due to dysfunction of mitochondrial damage, mutations or impaired transport of metabolites may lead to Aβ oligomeric or fibrillary formation and phosphorylated tau function [6]. Thus, mitochondrial damage due to insults like oxidative stress and accumulation of Aβ oligomers act synergistically to further damage and drive AD pathology [4]. Accumulation of Aβ in synapses directly disturbs mitochondrial function resulting in oxidative stress, decreased ATP, and increased CA++ influx, in addition interaction of mitochondrial Aβ with its binding proteins induced neuronal stress and dysfunction [7].

Factors Causing Dysfunction of Mitochondria in AD

Age: Old age is the most important risk factors for neurodegenerative diseases, like AD, in advanced age there is marked changes in mitochondrial structure and decreased function. Due to these changes, there is both metabolic failure and apoptosis. Impaired mitochondrial hemostasis is associated with imbalance between fusion and fission, with the predominance of the later, thereby accelerating deterioration [8]. It is also seen accumulation synaptic mitochondria due to advanced age, interfere with synaptic activities like ATP production and calcium homeostasis, required for efficient neurotransmitter release, plasticity, thereby causing impaired cognition and memory [9]. In advanced age, there is also free radicle damage in addition to metabolic failure. Mitochondria are the principal source of free radicals, oxidative damage would be more severe in mitochondrial DNA [10]. Accumulations of free radicals is associated with anti-oxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase and reductase in the AD brain [11]. So increased free radical production, energy failure, reduced regenerating power and repairs of DNA will all contribute to misfolded protein aggregation augmenting APP amyloidogenic process leading to Aβ plaque formation, ultimately to cognitive decline and AD [10]. It is also suggested that aging related reduction in proteasome activity further promote Aβ and tau accumulation [12].

Genetic cause of mitochondrial dysfunction

Several studies have shown that a higher occurrence of mutation of both nuclear and mitochondrial DNA in AD patients. Genetic mutation of presenilin1, presenilin2, APP, Tau and APOE4 genes are strongly associated with Aβ aggregating and AD development. IN addition other susceptible genes are believed to increase AD risk or cause disease through interactions with environmental factors.

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Environmental Toxins

Mitochondrial dysfunction is aggravated by toxins, like pesticides, organic pollutants and heavy metals and industrial waste products, Exposure associated with these toxins produce mitochondrial dysfunctions, leading to features like AD. Metabolic syndrome and mitochondrial function. Studies have indicated a close relationship between metabolic syndrome and AD [13]. In metabolic syndrome there is insulin resistance, a closely related event to mitochondrial dysfunction. Middle aged obesity is correlated with cognitive impairment and ultimately to AD. Metabolic syndrome also results in accumulation of advanced glycation product that can lead to free radical generation oxidative stress and Aggregation of AB fibrils in neuron and microglia [14].

Etiological hypothesis of relationship between AD and mitochondrial dysfunction

The brain tissue is very sensitive to any reduction of ATP generation by OXPHOS. During this process it involves five mitochondrial protein complexes. (Complex 1 to 5) During this process the proton gradient generated by complex 1, III and IV which helps in phosphorylation of ADP to ATP [15].This energy stored in ATP is then utilized for synthesis of neuro transmitters, and complex phosphorylation mediated signaling pathways. There is deficiency and impaired mitochondrial complex (I-V) are seen in AD brain and AD models [16]. It has been reported that a substantial decrease in ATP synthase in MCI patients [17].

It is seen that the cognitive and synaptic plasticity impairments in AD are associated with a decrease in extracellular ATP [18].The inner membrane potential generated by OXPHOS is important for protein transport and regulating molecular changes of mitochondrial responses to other insults, leading to AD [19]. These ultimately lead to cognitive impairments

Mitochondrial dynamics, mitochondrial fission and fusion

Mitochondria are dynamics undergo frequent changes in size, shape, number and location these processes are called mitochondrial dynamics. These are two unique, closely controlled adverse process namely fission and fusion [20],

Imbalance between fission and fusion, motility and turnover may lead to defects in neurons. It is known that mitochondrial fusion is neuro protective whereas fission seems a sign of apoptosis and fragmentation [21].

I t was seen that there is defective fission /and or fusion process is found in various neurodegenerative diseases [22].

It is seen that mitochondrial ubiquitin ligase MITOL/MARCH5 is down regulated in pts with AD. It was seen in a study that if there is a disturbances in the dynamics of mitochondria by deleting MITOL, it can trigger cognitive decline in a mouse model of AD. MITOL deletion in the brain enhanced the seedling effects of Aβ fibrils. It has been also suggested alteration of mitochondrial morphology might be a major factor in AD due to directing the production of AB form, oligomers orplaques, responsible for disease development [23].

Mitochondrial Transport

The proper distribution of mitochondria is achieved by the mitochondrial transport mechanism. This mitochondrial motility is powered by various GTPase. This movement is essential for neuronal functions, neuro transmission and synaptic plasticity. Obstructions to mitochondrial transport markedly disrupt synaptic functions [24]. Multiple kinesin and cytoplasmic dyenin have been implicated anterograde and retrograde mitochondrial transport respectively [25]. Mitochondrial axonal anterograde transport requires action of Mfin2 (fusion protein), and Milton/Miro complexes [26]. These Milton/Miro proteins are regulated by cellular signaling like Ca++, ROS, Oxygen levels, and ATP, and determines mitochondrial movements. Impaired mitochondrial transport is associated with various neurodegenerative diseases. It is known that in AD, axonal pathology, and synaptic dysfunctions occur before the detectable AB and tau aggregation and mitochondrial dysfunction results in synaptic failure [27]. Axonal degeneration due to abnormal accumulation of mitochondria appears to be available strategy to maintain synaptic strength and plasticity, thereby delaying cognitive decline in AD patients [27]. It has been reported that Ca++ dysregulation and changes in microtubule associated proteins like tau, which causes rapid delivery of mitochondria to sites of high energy demand Increased Ca++ has been suggested to arrest mitochondrial transport, causing energy deficits Further Ca+ elevation may trigger overexpression and hyper phosphorylation of tau via activation of kinases or microsomal prostaglandin E synthase1, thereby disrupting mitochondrial distribution and cause axonal dysfunction and synaptic loss seen in AD mouse models [28].

Mitochondrial Ca++ disturbance in AD

Mitochondrial dysfunction markedly impairs calcium hemostasis as mitochondria acts as a calcium buffer and as a source of energy for ca pumps and exchanger in in plasma membrane and endoplasmic retinaculum [29]. When excessive Ca is absorbed in to mitochondria, there is consequent increase in the production of ROS, inhibition of ATP synthesis, release of cytochrome c and activation of caspases and apoptosis recent study suggested that Aβ accumulation induces in vivo mitochondrial Ca overload leading to neuronal death, suggesting that MCU complex inhibition and blocking the activation of Mptp might represent novel therapeutic approaches for AD [30]. Is like AD. It is known that mitochondrial calcium overload and the resulting dysfunctions area a cause of apoptosis in multiple neurodegenerative disease [31]. It needs further studies to have a clear understating the role of mitochondrial calcium dysregulation in AD pathogenesis.

Free radical generation and mitochondrial dysfunction

Free radicals that can form under conditions like hydrogen peroxide, during mitochondrial electron transport and other reactions, Superoxide radicals are formed primarily by complex1. III and TCA cycles. These free radicals generated can enter the cytoplasm. These excessive free radicals generated will cause alterations of biomolecules to cause oxidative stress. Free radicals promote the expression and activity of B and gamma secretases, leading to form excessive Aβ production, thereby causing more mitochondrial dysfunction [32,33]. The oxidative stress can create a self-sustaining cycle, which further exacerbates mitochondrial dysfunction, calcium deregulation, oxidative stress and Aβformation, thus aggravating neuronal dysfunction and neurodegeneration and cognitive impairment [34]. Indeed, the degree of cognitive impairment and synaptic loss in AD has been related to the amount

of Aβ accumulation in mitochondria [34].

Therapeutic Strategy

Exercise and diet

Studies have shown the beneficial effect of caloric restriction and exercise in slowing the process of aging and improving mitochondrial functions in humans and rodent models [35,36]. It has been shown that there are many beneficial effects of exercise in AD, like better blood flow to the brain, enhanced thickness of hippocampus, enhanced neurogenesis, cognitive performance [37,38]. It is seen that physical exercise can mitigate inflammation and oxidative stress [39]. This attenuation might be one of the mechanisms of cellular aging and clinical benefit [40].

Sufficient consumption of vitamins, minerals and natural foods rich in antioxidants is an ideal way to maintain antioxidants status.

Therapies targeting mitochondrial dysfunction maybe slow or halt the progression of AD. Therapies are mainly directed towards mitochondrial antioxidants, and modulators of mitochondrial dynamics. Studies have mainly targeted towards decrease in free radical generation, microglial activation, and excessive fragmentation, to minimize the mitochondrial dysfunction thereby protecting from neuronal injury and cognitive impairments in AD [41].

In a transgenic mouse model of AD it was shown that MitoQ prevented cognitive decline in these mice as well as oxidative stress, Aβ accumulation, astrogliosis, synaptic loss, and caspase activation in their brains. The work presented herein suggests a central role for mitochondria in neurodegeneration and provides evidence supporting the use of mitochondria-targeted therapeutics in diseases involving oxidative stress and metabolic failure [42].

It was seen that in ethanol induced intracellular accumulation of oxidants, Mito VitE maintains the glutathione peroxidase/glutathione reductase functions, protein expression of gamma-glutamylcysteine synthetase and total cellular glutathione levels. This suggests that ethanol induced toxicity is ameliorated by Mito VitE Overall, Mito VitE by a toxicity through modulations of endogenous cellular proteins-and antioxidant means [43]. More studies are required to explore Mito VitE applications to elderly humans and humans with neurodegenerative diseases.

It was seen that Mitotempo suppresses Aβ-induced mitochondrial and neuronal oxidative stress. Mito tempo protects mitochondrial bioenergetics from Aβ toxicity. Mito tempo preserves mtDNA abundance from Aβ toxicity. Mito tempo has the potential to protect mitochondrial and neuronal function in AD [44].

In the neurotoxicity due to of glutamate and β-amyloid (Aβ), the loss of ATP occurs first. It was supposed that supplementing the cells, with the precursor creatine make more phosphocreatine (PCr) and create large energy reserves with consequent neuroprotection against stressors. In a study it was seen that isolated neurons from hippocampus are also protected from Aβ toxicity by Cr, if sufficient Cr is available, healthy neurons may be able to maintain PCr levels that would rapidly decline without exogenous Cr [45]. The oral availability of Cr, its ability to increase brain PCr levels [46], and its apparent lack of side effects provide further reason for optimism to establish Cr supplementation as an adjuvant or preventive therapeutic for several neurodegenerative and age-related diseases.

Several recent studies demonstrated that increased glutathione levels protect neurons against protein oxidation, loss of mitochondrial function, and DNA fragmentation induced by Aβ, by using glutathione or glutathione inducer in neurons expressing mutant APP [47]. These mitochondrial targeted antioxidants enter the mitochondria and they neutralize free radicals and decrease oxidative damage, and thereby protect neurons. Further research is needed to determine whether these mitochondrial targeted molecules can be used in mouse models of aging and neurodegenerative diseases [48].

In a study it was seen that resveratrol significantly reversed motor and cognitive impairment, and that the beneficial effects of resveratrol might be due to its antioxidant activity. Sirtuins (silent information regulators) are members of the NAD^+-dependent histone deacetylase family of proteins in yeast, and its homologousare required in a variety of cellular processes, including mitochondrial functions, cellular metabolism, energy metabolism, gluconeogenesis, cell survival, and aging [49]. Activation of sirtuins improves mitochondrial function, extends life span, and promotes longevity in various species, including yeast, suggesting that sirtuins may, therefore, potentially delay the onset of age-related neurodegenerative disorders.

Increased intracellular NAD^+ concentration activates SIRT1 in brain following caloric restriction, and this results in a reduction in amyloid pathology in a mouse model of AD [50]. Increased SIRT1 protected against hippocampal degeneration in another mouse model of AD [49].

CoQ10 is an essential biological cofactor of the electron transport chain. CoQ10, also known as ubiquinone, serves as an important antioxidant in mitochondrial and lipid membranes [51]. Idebenone, a synthetic analogue of CoQ10, has been studied in several neurodegenerative disorders for neuroprotection. Idebenone protects neuronal cells against β-amyloid-induced toxicity [52]. Another randomized, double-blind, placebo-controlled, multicenter study, 300 patients with Alzheimer-type dementia were treated for 2 years with 30 or 90 mg/day idebenone or placebo [53]. There was no significant improvement in a small trial in HD [54]. These results are controversial since another large trial showed no benefits [55].

Conclusions

Various studies have shown that mitochondrial dysfunction causes AD through complex interaction with other mechanism of pathogenesis. Mitochondrial dysfunctions occur early and cause progression of AD. Abnormalities seen in mitochondrial dysfunctions like ATP generation, hemostasis, ROS production, biogenesis and mitophagy. These changes are seen due to changes in mitochondrial dynamics in AD, but also due to accumulation of Aβin synaptic terminals, causing impairment of functions, impaired neurotransmission, ultimately cognitive dysfunction., Again this mitochondrial dysfunction cellular exposure to tau, thereby causes AD. Therefore, mitochondrial dysfunction trigger or aggravates energy deficiency, oxidative stress, calcium deregulation, protein aggregates, excitotoxicity, leading to disruption of mitochondrial membrane potential, neuronal apoptosis and ultimately leads to cognitive decline. However, these mitochondrial dysfunctions can be targeted at every level; thereby can prevent the progression of AD.

Anyway, there needs to be further studies to find out the various targets aiming at dysfunction/dynamics of mitochondria, to have an effective therapy for AD prevention without having many side effects.

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