

Mitochondrial Dysfunction and Alzheimer's Disease

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ABSTRACT

There are many links between Alzheimer's disease and mitochondrial dysfunction. Glucose utilization defects in the brain of Alzheimer's Disease (**AD**) patients suggest possible abnormalities in mitochondrial function in AD. There are many links between Alzheimer's disease and mitochondrial dysfunction. A glucose utilization defect in the brain of AD patients suggests possible abnormalities in mitochondrial function in AD. Biochemical and morphological alterations of mitochondria play an important role in the pathogenesis of AD. A β induced neuronal toxicity seen in Alzheimer's disease is due to mitochondrial dysfunction. Both APP and A β block the transport of mitochondrial proteins by interacting with mitochondrial proteins causes disturbances of electron transport chain and produce Reactive Oxygen Species (**ROS**). By these processes they cause the damage to mitochondria and neuronal dysfunction. Basing on the different mechanisms of the mitochondrial dysfunction causing Alzheimer's disease, various possible therapeutic targets for Alzheimer's disease is discussed.

Key words: Mitochondria dysfunction, Alzheimer's disease, Tau proteins, Szeto schiller (**Ss**) peptides, Mito Q, Hprep.

Abbreviations: **AD**- Alzheimer's Disease; **APP** – Amyloid Precursor Protein; **A β** - Amyloid Beta; **BACE** - Beta-site Amyloid Precursor Protein Cleaving Enzyme; **HPreP**-- Human Presequence Protease

Alzheimer's disease is characterized by selective neuronal loss, synaptic alterations, mitochondrial abnormalities, and tau pathology, resulting in neurofibrillary degeneration, inflammatory responses and extracellular deposits of A β peptide in the form of neuritic plaques. The histological hallmark of AD is senile plaques and cerebro vascular deposits. The extra cellular amyloid plaques are composed of amyloid beta and neurofibrillary tangles built up of hyper phosphorylated tau. This A β is derived from Amyloid Precursor Protein (**APP**). Through an initial beta cleavage followed by an intra membranous cut of Presenilin 1 (**PSI**) dependent gamma secretase complex.

There are many links between Alzheimer's disease and mitochondrial dysfunction. Glucose utilization defects in the brain of AD patients suggests possible abnormalities in mitochondrial function in AD [1,2]. There is evidence that the reductions in the availability of both glucose/energy and insulin contribute to the formation of amyloidogenic derivatives and hyper phosphorylated tau protein [1].

Mitochondria play an important role in cell survival and death. It regulates both energy metabolism and apoptotic pathways. They regulate intracellular calcium homeostasis, cellular Oxidation and reduction potential, cell cycle regulation and synaptic plasticity [3]. They are the power house of cells, providing energy to cells through oxidative phosphorylation. Mitochondria are also source of reactive oxygen species and are also targets of ROS toxicity. Dysfunction of mitochondria leads to synaptic stress, dysfunction of synaptic transmission, apoptosis and neuro degeneration [4,5]. Dysfunction in Mitochondrial electronic transport proteins has been associated with the pathophysiology of AD [6]. It is seen that mitochondrial function at the cellular level, through cytochrome oxidase activity measurements, has consistently shown activity deficits consistent with mitochondrial compromise [7].

Furthermore, cytoplasmic hybrid cells in which mitochondria from sporadic cases of AD were fused with other cells also indicate a defect in mitochondrial function in AD [8,9]. In a number of studies it was seen that oxidative stress is involved not only in damage to proteins of NFT and senile plaques but also there is extensive damage to the cytoplasm of neurons vulnerable to death during AD [10,11]. In a study to find out the mitochondrial abnormalities in AD, using cytological in situ hybridization, immune cytochemistry and morphometry found out that major abnormalities were associated with vulnerable neurons, suggesting an intimate relationship between mitochondria and oxidative damage in AD [12]. Altered mitochondrial fluidity and the activity of mitochondrial cytochrome C oxidase, have been to be lo in AD brains [13]. Furthermore,

a correlation was reported between cytochrome oxidase activity and deficit in cognitive abilities [14,15]. It was reported that accumulation of APP across the mitochondrial import channels, inhibited the entry of nuclear encoded cytochrome C oxidase subunits IV and Vb proteins, which was associated with decreased cytochrome C oxidase activity and increased H_2O_2 . Mitochondrial accumulation of APP as also observed in the cholinergic, GABAergic and glutamergic neurons in AD. Apolipoprotein genotype analysis revealed that AD patients with the $\epsilon 3/\epsilon 4$ alleles had the highest content of mitochondrial APP. All these suggest that abnormal accumulation of APP across mitochondrial import channels is a hall mark of human AD pathology [16].

ROLE OF MITOCHONDRIA IN NEURODEGENERATIVE DISEASES

AD is associated with neurofibrillary tangles and senile plaques, in association with a deficiency of cytochrome c oxidase and mitochondrial defect. In some cases of AD, disease progression is associated with mt DNA and tRNA mutations. A partial mitochondrial defects known to produce ROS generation(33).These findings suggests that certain AD cases result from a chronic electron transfer chain deficiency that generates ROS and somatic DNA damage, leading to cortical dysfunction. These modifications are often detrimental, affecting proteins, nucleic acids, carbohydrates and lipids. Cells have a number of defense mechanism against this damage, like mechanisms to detoxify ROS, repair damage and remove the damaged elements.

The brain is vulnerable to oxidative stress due to its high lipid content, high oxygen requirement, and its low antioxidant defenses [17]. It is seen that before the onset of amyloid pathology, mitochondrial oxidative stress occurs early in AD progression [16,18]. Oxidative stress mostly associated with $A\beta$ accumulation in neocortex (7,44,45),thereby playing an important role in pathogenesis of AD [19]. Due to lack of his tones, mitochondrial DNA are vulnerable for oxidative damage. The morphological alteration of the mitochondria seen in subcortical centers like thalamus, globus pallidum, red nucleus, and in locus ceruleus, suggests a generalized mitochondrial dysfunction in AD, which may be associated with neuronal loss and synaptic alteration and consequently mental faculties [20]. In Alzheimer's disease the amyloid precursor protein has been localized to mitochondria as has the toxic amyloid beta peptide. Many morphological alterations in AD could very well be linked to mitochondrial changes since blockage of mitochondrial energy production shifts amyloid precursor protein metabolism to the production of more amyloidogenic forms of amyloid [21].

Proteins are essential in mitochondrial function, structural integrity and also in binding to the cytoskeleton. Porin an outer membrane protein of mitochondria, are important for binding of neurofilaments and microtubules [22]. Normally a limited number of dendritic spines contain mitochondria, been increased in number inside the dendritic branches during synaptogenesis. A decrease in energy metabolism and altered cytochrome C oxidase activity are among the earliest detectable defects in AD [23]. Mitochondrial dysfunction and synaptic damage are early features of AD. It was found that amyloid beta oligomers in synaptosomal mitochondrial fractions and

decreased energy metabolism in AD transgenic mice [24]. Accumulation of amyloid beta in synapses directly disturbs mitochondrial function resulting in oxidative stress, decreased ATP, and increased Ca⁺⁺ influx; in addition interaction of mitochondrial amyloid beta with its binding proteins induced neuronal stress and mal function [25].

Mitochondria are the principal site for the ATP production Oxidative Phosphorylation System (**OXPPOS**). The mitochondrial OXPPOS system consists of five subunit complexes (complex 1-V). Studies have shown that direct exposure to A β significantly impairs mitochondrial Electron Transport System (**ETC**), which is essential for ATP production and its enzymes are the major source of ROS production [26,27].

Synaptic terminals require more ATP for neuro transmitter release. Studies have shown that in AD there is a synaptic mitochondrial dysfunction. However whether amyloid beta accumulates predominantly in synaptic mitochondria or synaptic mitochondria rich in amyloid beta is more vulnerable is not clear. However it is known that oxidative damage is responsible for defective neurotransmission and synaptic damage and loss might be responsible for cognitive dysfunction in AD. There is evidence that amyloid beta enter the mitochondria and disrupts mitochondrial functions in brains of AD patients and transgenic mouse models. In a study to find out whether the Beta cleaved C – terminal fragment (C99), another neurotoxic fragment of APP, accumulate in mitochondria of neurons affected by AD, it was seen that mitochondrial accumulation of C99 and full length APP might occur through BACE1 dependent mechanisms and contribute to inducing mitochondrial dysfunction and cognitive impairments associated with AD [28].

EFFECTS OF TAU ON MITOCHONDRIA

Tau proteins are a group of neuronal microtubule associated proteins. Phosphorylation of tau proteins negatively regulates its ability to stimulate microtubule assembly. Tau is the major component of paired helical filaments in AD. The pathological diagnosis of AD is by finding of NFT. It was reported that microtubule assembly in brain extract of AD cases is impaired and hyper phosphorylation of tau may contribute to this deficit [29]. It is reported that hyperphosphorylated tau and or neurofibrillary tangles cause mitochondrial dysfunction, and inhibition of axonal transport in AD [30,31]. In a study it was evident that there as interplay between phosphorylation of tau and neuronal oxidative stress-induced pathology is important in the formation of neurofibrillary tangles. In a study to find out the aberrant behavior of tau in axonal transport in the neurons and non neuronal cells, it was found that tau was capable of reducing the net anterograde transport of vesicles and cell organelles by blocking the micro tubule tracks [32]. Thus a misregulation of tau could cause the starvation of synapses and oxidative damage, long before tau detaches from microtubules and aggregates in to neurofibrillary tangles.

Cell culture data links tau over expression to mitochondrial trafficking deficits, which have been associated with negative consequences to mitochondrial distribution and function. Regulation of mitochondrial distribution and function is essential in neurons. Deregulation of these function

has been shown to be associated with impaired synaptic function and and synapse loss, [33] and proposed to be an early event in AD [34]. In a study it was seen that tau mis localization to the somatodendritic compartment, and subsequent aggregation, in intact brain of both a mouse model of taupathy and human AD would affect mitochondrial distribution [35]. In addition in the same study it was seen that soluble fibrillar tau would be important for these changes. In the same studies it was also seen that soluble tau over expression is detrimental to the axonal transport and mitochondrial distribution and function. Suggested mechanism for tau over expression causing transport deficits are (1) inhibiting progress of kinesin 1, by forming a road block on the microtubule where excessive tau is bound [36,37] (2) Destabilization of microtubules due to hyperphosphorylated tau losing its affinity for the microtubule [38,39] (3) Tau may interfere with the signaling pathways, or molecules such as GSK3B kinase, thereby exerting more indirect control over transport process [40,41] (4) Increasing evidence suggests that abnormal mitochondrial dynamics like increased fission and decreased fusion are early key factors found in AD [42]. These process allow exchange of materials between mitochondria [43]. Even brief contact can involve fusion and extensive exchange of proteins in each compartment of mitochondria. It was demonstrated that APP over expression causes mitochondrial fragmentation in neurons [44]. By interfering and with fission and fusion dynamics. Changes to this equilibrium can result in mitochondrial and neuronal dysfunction and synaptic loss or neuronal death [45-47]. It has been shown that manipulation of primary mammalian fission GTPase, Dynamin Related Protein 1 (**DRP1**) has been shown to result in mitochondrial distribution deficits and perineuronal clumping [33,45,46,48]. It is known that abnormal proteins like tau, may directly interact with mitochondria and/or Dynamin Related Protein1 (**Drp1**), a protein that maintains and remodels mammalian mitochondria, and initiate mitochondrial fragmentation, dysfunction, impaired axonal transport of mitochondria and neuronal death and cognitive decline [46,49,50]. All these studies indicates that tau mis localization and aggregation is associated with mitochondrial dysfunction, and by suppressing soluble tau species recovery of mitochondrial distribution to near normal levels, suggesting that soluble tau species play a more significant role in mitochondrial distribution than aggregated forms [51-54] Tau also mediates the neurotoxic effects of AB which can promote the mis-localization of tau to the dendrites [55] and mitochondria [56]. In contrast, Tau reduction has been shown to ameliorate the behavioral and neurodegenerative pathology in models of AD [57]. Impaired mitochondrial biogenesis also contributes to mitochondrial dysfunction in AD. Expression levels of PGC1alpha, NRF1, NRF2, and TFAM were significantly decreased in both AD hippocampal tissue and APPs us M17 cells suggesting, mitochondrial biogenesis was affected during neurodegeneration [58].

THERAPEUTIC TARGETS AGAINST MITOCHONDRIAL DYSFUNCTION

Since mitochondria are the major source of ROS and are vulnerable to oxidative stress. It is presumed that, use of antioxidant therapy specially the development of specifically designed

mitochondrial antioxidants. The Szeto Schiller (**SS**) peptides, a family of small mitochondria targeted antioxidant molecules were developed as a potential treatment for AD [59]. These SS peptides display mitochondrial accumulation having a sequence motif that allows them to target mitochondria. The antioxidant action can be attributed to the tyrosine, or dimethyl tyrosine that plays a role in scavenging mitochondrial ROS, in particular SS31. Similarly a patent developed Mito Q, a mitochondrial targeted antioxidant is undergoing phase III trial for the diseases associated with mitochondrial oxidative diseases like neurodegenerative diseases [60]. Since Mito Q enters the mitochondria through mitochondria several folds more than natural antioxidants, it rapidly neutralizes free radicals, before they reach their targets, thus showing better therapeutic potential [61]. By using cytoplasm hybrid neurons from AD and age matched non AD humans, it was found that treatment with antioxidant probucol protects against AD induced mitochondria induced Extracellular Signal Regulated Kinase (**ERK**) activation and mitochondrial fission fusion imbalances. Inhibition of ERK activation reestablishes the mitochondrial fission and fusion balances [62]. In a study to investigate whether Soy Isoflavone (**SIF**), reduces oxidative stress and improves the antioxidant ability in mitochondria of rat brain damaged by injection of beta amyloid peptide 1-42, indicated that SIF could alleviate the oxidative damage and maintain the redox imbalance in brain mitochondria damaged by AB 1-42. This study suggests that SIF induces expression of neuro protectant proteins [63,64]. This may have a therapeutic potential. However further studies are needed to explore the exact mechanism by which SIF protects mitochondria from AB induced dysfunction. Similarly in a study it was found that Genistein, a major Soybean Isoflavone (**sif**), could alleviate A β 25-35 induced cell apoptosis and prevent A β 25-35 induced TNF alpha and IL-1B release from c6 glial cells (rat glioma cell lines). In addition, GEN prevented A β 25-35 induced up regulation of the gene and protein expression of TRL 4 and GEN significantly up regulated the expression of 1Kb alpha IN c6 cells damaged by A β 2535. This suggests that GEN can alleviate the inflammatory stress caused by A β 25-35 treatment, which might be associated with the neuroprotective effect of GEN regulating the TRL4/NFkB signaling pathway [65]. It is known that structural and functional mitochondrial alterations play an early part in synaptic failure of AD pathogenesis and an aggravated mitochondrial impairment have been described in triple APP/PS/tau transgenic mice carrying both the plaques and tangled in comparison to mice over expressing tau or amyloid precursor protein alone. It was seen that a neurotoxic amino terminal NH₂ derived from tau fragment mapping between 2626-230 amino acid of the human tau 40 isoforms interacts with A β peptides in human AD synapses in association with mitochondrial Adenine Nucleotide Translocator -1 (**ANT-1**) and cyclophilin D. This study provides a common, direct and synergistic toxicity of pathological APP and tau products on synaptic mitochondria. The pathological convergence between tau and A β and mitochondrial may help to explain why the diseased A β or tau modifying strategies have not given promising result individually, and suggest potential, new pathways and targets for a more efficient combined therapeutic intervention of early dysfunction in AD [66]. Similarly in a study a molecular mechanism is proposed in which the pathological A β -NH₂h tau interplay on ANT1 in Alzheimer's neurons involves the thiol redox state of ANT1

and A β 1-42 induced ROS increase [67]. This study is an important innovation as it suggests the possibility of using various strategies to protect the cells at the mitochondria level, by stabilizing or restoring mitochondrial function or by interfering with the energy metabolism providing a promising tool for treating or preventing AD. In a study involving the efficacy of cerebrolysin in a transgenic model of tauopathy, it was found that cerebrolysin treatment normalized the level of Drp 1 (a protein that hydrolyzes GTP and required for mitochondrial division) and restores mitochondrial structure, suggesting the ability of cerebrolysin to ameliorate the neuropathology in the tauopathy model by reducing the accumulation of hyperphosphorylated tau and reducing alteration in mitochondrial biogenesis associated with tau [68]. This indicates that cerebrolysin may be a therapeutic target in AD therapy.

It is known that there is accumulation of A β in mitochondria in aged and AD brain. A β enters the mitochondria through the protein Translocase of the Outer Membrane (**TOM**) machinery [69]. The Receptor for Advanced Glycation Product (**RAGE**) also aids in localization and transport of mitochondrial A β . Neurons lacking RAGE exhibit lowered mitochondrial A β accumulation and are protected from A β induced mitochondrial dysfunction [70]. Thus accumulation of amyloid beta within the mitochondria perpetuates increased free radical formation and activation of the apoptotic pathway. It is seen that Human Presequence Protease (**hPreP**) is responsible for the degradation of mitochondrial amyloid beta peptide in neuronal cells, and thus seems to be an attractive agent to increase the proteolysis of A β , thereby offering a potential target for Alzheimer's drug design by identifying potential activators of hPreP. Basing on these it was found that compounds 3c and 4c enhanced hPreP mediated proteolysis of A β (1-42) Pf1 B (2-54) and fluoregenic substrate V, suggesting that activation of hPreP by small benzimidazole derivatives provides a promising avenue for AD treatment [71]. However further studies are required on the effects of small benzimidazole derivatives on hPreP agonist activity in order to develop a new therapeutic agent for the treatment of Alzheimer's disease. Similarly in a mouse model of AD, it was seen that ANAVEX2, AE37 (a mixed muscarinic receptor ligand and a Sigma 1 Receptor (**α R**) agonist, prevented A β 25-35 induced increases in lipid peroxidation levels, Bax/Bcl ratio and cytochrome C release in to cytosol. All these are indicators of increased toxicity. ANAVEX2-73 and PRE-084 efficiently prevented the mitochondrial respiratory dysfunction and resulting oxidative stress and apoptosis. The alpha1 R targeted selectively or non-selectively therefore appears as a valuable target for protection against mitochondrial damages in AD [72].

CONCLUSION

Basing on various studies, it has been proposed that amyloid beta has a significant role in synaptic dysfunction and in memory impairment in AD. It is known that A β enters at the synaptic terminals and enters the mitochondria, and mitochondria are responsible for neurodegeneration. Studies have shown that oxidative damage induces amyloid beta and it provides a direct link between mitochondrial dysfunction in AD and pathogenic A β . A β and APP are localized to mitochondrial membrane. They block the transport of mitochondrial proteins, disrupt the electron

transport, and produce ROS thereby causing mitochondrial damage and dysfunction since the lack of histones in mitochondria renders them to a vulnerable target for oxidative damage. A β accumulates at synaptic terminals and causes impairment function and also enters the synaptic mitochondria and damage, and leads impairment of neurotransmission, thereby causing cognitive dysfunction.

There is a strong evidence that mitochondrial dysfunction occurs early and acts in disease progression. Mutations in mitochondrial DNA and oxidative stress are a strong background for the neurodegenerative diseases. It is associated with energy crisis of the cells and excitotoxic cell death, and is important in the process of apoptosis.

Therapies' targeting the process of mitochondrial energy metabolism, free radical generation, or interactions with various proteins with mitochondria seems attractive. So newer therapies directed towards protection to mitochondria by administration of antioxidant could be introduced in early stages of AD. There is tremendous development has been made in strategies to lower A β production and toxicities, for the development of an effective drug for treatment of AD. However further studies are needed to test the efficacy of antioxidants and also agents that focus on the functional association of mitochondria with APP and A β might be useful for developing an ideal drug directing towards various pathogenetic mechanism for treatment of AD, so as to lessen the burden in the society.

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