

Review Article

Mitochondria, Amyloid β , and Alzheimer's Disease

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Hypometabolism is a hallmark of Alzheimer's disease (AD) and implicates a mitochondrial role in the neuropathology associated with AD. Mitochondrial amyloid-beta ($A\beta$) accumulation precedes extracellular $A\beta$ deposition. In addition to increasing oxidative stress, $A\beta$ has been shown to directly inhibit mitochondrial enzymes. Inhibition of mitochondrial enzymes as a result of oxidative damage or $A\beta$ interaction perpetuates oxidative stress and leads to a hypometabolic state. Additionally, $A\beta$ has also been shown to interact with cyclophilin D, a component of the mitochondrial permeability transition pore, which may promote cell death. Therefore, ample evidence exists indicating that the mitochondrion plays a vital role in the pathophysiology observed in AD.

1. Introduction

The incidence of Alzheimer's disease (AD) in the US is expected to increase to as many as 13.2 million by 2050 [1]. AD pathology is characterized by the progressive accumulation of senile plaques (consisting of amyloid β -peptide, $A\beta$) and neurofibrillary tangles (consisting of aggregates of the microtubule-associated protein tau). Oxidative damage has been implicated to play an early role in the pathogenesis of AD [2]. In AD patients a significant decrease in energy metabolism is observed in the frontal and temporal lobes as indicated by *in vivo* positron emission tomography (PET) [3]. Correlated with this increase in oxidative damage and decrease in energy metabolism is a decrease in mitochondrial enzyme (cytochrome *c* oxidase, pyruvate dehydrogenase, α -ketoglutarate dehydrogenase) activity in AD patients [4–6].

Mitochondrial dysfunction has been shown to play a key role in age-related neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [7]. Mitochondria produce the majority of ATP in cells and function to maintain Ca^{2+} homeostasis. Mitochondria produce ATP by coupling electron transfer to the pumping of protons across the inner mitochondrial membrane. However, electrons can escape the electron transport chain and reduce oxygen to form reactive oxygen species (ROS). Oxidative damage results from a disturbance in the ROS-antioxidant balance

that favors oxidation. Oxidative damage to mitochondria may be especially relevant in neurodegenerative disease since mitochondria are regulators of both cellular metabolism and apoptosis [8].

2. Mitochondrial Enzyme Oxidative Damage and ROS Production

A hallmark of AD is hypometabolism which, importantly, precedes the clinical presentation of the disease [9, 10]. Early studies utilizing PET indicated that brain metabolism throughout the cortex in AD patients is significantly lower than cortical metabolism in normal subjects [11, 12]. Clinical data from PET studies have shown which areas of the brain are mostly affected by mild and moderate AD, such as the posterior cingulate cortex, parietotemporal cortex, and prefrontal association cortices [13]. Also decreased metabolism and synaptic loss have been shown to overlap in the frontal and middle temporal gyri [14–17].

Mitochondria sustain the activity of neurons by producing ATP via the electron transport system (ETC) (Figure 1). Complex I (NADH dehydrogenase) catalyzes the transfer of two electrons from NADH to coenzyme Q [18]. Complex III (ubiquinol-cytochrome *c* oxidoreductase) catalyzes the transfer of electrons from coenzyme Q to cytochrome *c*.

Complex IV (cytochrome *c* oxidase) reduces oxygen to water. As electrons are transported through complexes I, III, and IV, protons are pumped into the inner membrane space, generating an electrochemical gradient. This store of energy is used to generate ATP via the ATP synthase. ROS production is linked to membrane potential ($\Delta\psi$) such that a high $\Delta\psi$ promotes increased ROS production [9]. High $\Delta\psi$ results in altered redox potential of ETC carriers and an increase in the half-life time of ubisemiquinone leading to increased ROS production. Also, any damage to components of the ETC could lead to a stalling of reduced intermediates of the ETC which would increase the probability of an electron slipping and reducing O_2 to form ROS.

Postmortem assessment of human AD brains has revealed increased levels of oxidative damage which coincides with impairments in metabolism and $A\beta$ processing [19]. Since mitochondria are the primary source of cellular ROS production, it is at least conceivable that as an organism ages mitochondrial enzymes would be especially vulnerable to oxidative damage. Damage to mitochondrial enzymes would cause defects in electron transport and promote ROS production. Redox proteomic analysis has revealed that a number of mitochondrial proteins are oxidatively modified including VDAC, aconitase, GAPDH, and lactate dehydrogenase in AD patients [20].

The most documented reduction of mitochondrial enzyme activity in AD is the activity of complex IV [5, 21–23]. Since peroxidative damage of cardiolipin in mitochondrial membranes has been shown to affect the activity of complex IV; ROS-mediated damage of membranes is postulated to partly be responsible for $A\beta$ inhibition of complex IV [24]. However, since antioxidants fail to fully protect mitochondria from amyloid beta toxicity, it has been hypothesized that $A\beta$ itself directly inhibits mitochondrial enzymes [24]. The $A\beta_{25-35}$ fragment has been shown to selectively inhibit complex IV [25]. The $A\beta_{25-35}$ fragment retains the residues required for aggregation and undergoes aggregation more rapidly than full-length $A\beta$. In another study, both the full-length $A\beta_{1-42}$ and $A\beta_{25-35}$ fragment resulted in inhibition of complex IV, and $A\beta_{25-35}$ raised the K_m of complex IV for reduced cytochrome *c* [26]. The authors concluded that $A\beta$ may act as an inhibitor of one of the cytochrome *c* binding sites of complex IV.

Additionally, α -ketoglutarate dehydrogenase has been shown to have reduced activity in AD [27]. Recently we reported an age-dependent decrease in NADH-linked, complex I- driven respiration rate and an increase in mitochondrial ROS production in aged dogs [28]. Therefore, it is evident that cumulative oxidative damage over the lifespan of an organism can affect mitochondrial efficiency and leave neurons susceptible to cell death.

3. Oxidation of Mitochondrial DNA

It has been hypothesized that ongoing oxidative damage to mitochondrial DNA (mtDNA) may be the underlying mechanism for cellular senescence [29]. Since mtDNA repair mechanisms are limited and because mtDNA is situated in

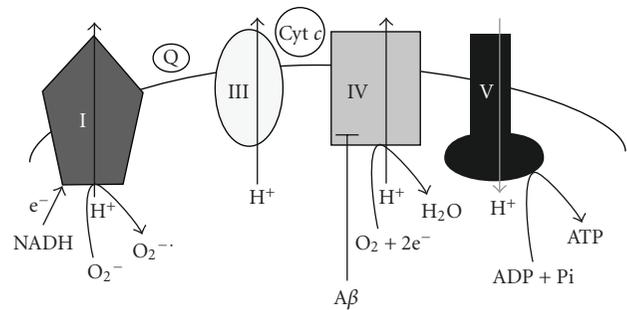


FIGURE 1: The relationship between amyloid- β ($A\beta$), mitochondrial electron transport chain (ETC), and superoxide ($O_2^{\bullet-}$) formation. As electrons are transferred through complexes I, III, and IV, protons are pumped into the inner membrane space, generating an electrochemical gradient. The energy stored is used to generate ATP via complex V (ATP synthase). Damage to components of the ETC can lead to a stalling of reduced intermediates which increases the probability of electrons slipping and reducing O_2 to form superoxide. $A\beta$ has been shown to directly inhibit complex IV which would lead to bioenergetic impairment and increased formation of reactive oxygen species.

close proximity to the site of ROS production, mtDNA is more vulnerable to oxidative damage than nuclear DNA [30]. With age, oxidation of mtDNA increases compared to nuclear DNA leading to an age-dependent accumulation of mtDNA mutations [31]. One recent study found that somatic mtDNA control region mutations are elevated in AD patients [32]. These mutations would lead to an overall reduction in mtDNA copy number which would result in a decrease in oxidative phosphorylation. In addition, a mutation that affects L-strand transcription was also discovered. This mutation inhibits complex I respiration which leads to increased ROS production, decreased membrane potential, and subsequent Ca^{2+} deregulation. The effects of these mutations may lead to opening of the mitochondrial permeability transition pore and subsequent neuronal death. Other evidence that oxidative damage to mtDNA could contribute to AD pathology is the observation that a risk factor for late-onset AD is a maternal history of AD [33]. This observation could be related to the fact that mitochondrial DNA is maternally inherited.

4. Amyloid- β : Cause or Effect of Mitochondrial Dysfunction

$A\beta$ has been shown to accumulate in mitochondria from AD patients [34]. Altered processing of amyloid precursor protein (APP) which results in deposition of neurotoxic forms of $A\beta$, known as the amyloid hypothesis of AD, is believed to play a central role in the development of AD [35]. This hypothesis is supported by studies which show that immunization against $A\beta$ decreases amyloid levels and improves cognition in APP transgenic mice [36–38].

Intracellular and mitochondrial accumulation of $A\beta$ likely precedes extracellular $A\beta$ deposition [34, 39, 40]. Recently $A\beta$ has been shown to accumulate early (as young

as 4 mo) and specifically in synaptic mitochondria [40]. We have shown that synaptic mitochondria have high levels of cyclophilin D (CypD) which makes them more susceptible to changes in synaptic Ca^{2+} [41]. Importantly, synaptic Ca^{2+} homeostasis is regulated by synaptic mitochondria, and susceptibility to Ca^{2+} would disrupt synaptic function [42]. CypD is a peptidyl-prolyl *cis-trans* isomerase located in the matrix and is a component of the mitochondrial permeability transition pore (mPTP). CypD translocates from the matrix to the mPTP and interacts with the adenine nucleotide translocase of the inner membrane to promote pore formation. Opening of the mPTP leads to a collapse in $\Delta\psi$ and release of proapoptotic molecules (i.e., cytochrome C, Smac/Diablo, and apoptosis-inducing factor). A reduction in $\Delta\psi$ would lead to bioenergetic failure and subsequent synaptic failure ending in neuronal death. In fact, mitochondrial $\text{A}\beta$ has been shown to interact with CypD, and CypD deficiency attenuates $\text{A}\beta$ -induced mitochondrial stress [43]. This may indicate that because synaptic mitochondria have increased levels of, (i) cyclophilin D and (ii) $\text{A}\beta$, they are important in the pathogenesis of AD.

Mitochondrial dynamics are altered in AD patients, and mitochondrial fission has been shown to be more prevalent than fusion in AD [44]. This observation is supported by evidence indicating that the number of mitochondria is decreased in AD which corresponds with an increase in mitochondrial size [45]. APP overexpression, through $\text{A}\beta$ production, was shown to increase protein levels of proteins associated with fission (Fis1) and decreased protein levels of those involved in fusion (dynamamin-like protein and OPA1) [46]. In addition $\text{A}\beta$ has been shown to cause oxidative damage to Drp1 which resulted in mitochondrial fission [47]. Altered mitochondrial dynamics may result in decreased mtDNA copy number which would result in defects in mitochondrial electron transport activity.

While the exact mechanism underlying APP mismetabolism is unclear, it appears that $\text{A}\beta$ production itself is least partially induced by oxidative stress [48]. $\text{A}\beta$ can function both as an antioxidant and pro-oxidant [49]. At low concentrations (low-nanomolar) $\text{A}\beta$ remains monomeric and can function as an antioxidant. However, at higher concentrations, aggregation of $\text{A}\beta$ produces H_2O_2 . $\text{A}\beta$ -induced oxidative stress and mitochondrial dysfunction has been demonstrated in AD models [50, 51]. In APP mutant mice that display increased levels of $\text{A}\beta$, cognition-related brain regions have altered glucose metabolism [52]. Furthermore, mitochondria-targeted antioxidants have been shown to attenuate $\text{A}\beta$ -induced mitochondrial dysfunction [53]. Taken together, mitochondrial-induced oxidative stress may induce the production of $\text{A}\beta$, which itself increases oxidative stress and impairs mitochondrial function and may provide a feed-forward loop that increases $\text{A}\beta$ levels.

5. Conclusion

In summary, since cerebral hypometabolism and inhibition of mitochondrial function have been demonstrated in AD, mitochondria likely play a role in AD neuropathology. $\text{A}\beta$

has been shown to both directly and indirectly impair mitochondrial function. Impairment of mitochondrial function increases ROS production which may further damage mitochondrial enzymes and mtDNA. Likely, mitochondrial dysfunction exacerbates the production of ROS and $\text{A}\beta$, which provides a feed-forward mechanism ultimately leading to AD pathology.

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