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Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) exhibits extensive oxidative stress throughout the body, being detected peripherally as well as associated with the vulnerable regions of the brain affected in disease. Abundant evidence not only demonstrates the full spectrum of oxidative damage to neuronal macromolecules, but also reveals the occurrence of oxidative events early in the course of the disease and prior to the formation of the pathology, which support an important role of oxidative stress in AD. As a disease of abnormal aging, AD demonstrats oxidative damage at levels that significantly surpass that of elderly controls, which suggests the involvement of additional factor(s). Structurally and functionally damaged mitochondria, which are more proficient at producing reactive oxygen species but less so in ATP, are also an early and prominent feature of the disease. Since mitochondria are also vulnerable to oxidative stress, it is likely that a vicious downward spiral involving the interactions between mitochondrial dysfunction and oxidative stress contributes to the initiation and/or amplification of reactive oxygen species that is critical to the pathogenesis of AD.

Keywords

Alzheimer disease; oxidative stress; mitochondrial dysfunction; mitochondrial fission; mitochondrial fusion; DLP1

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia that predominantly affects the elderly populations and is characterized by selective neuronal death and two pathologic hallmarks, i.e., senile plaques formed by extracellular deposits of amyloid-β (Aβ) peptides and neurofibrillary tangles (NFTs) composed of intracellular aggregations of

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hyperphosphorylated tau protein [1]. The majority of AD cases are sporadic. Less than 10% of AD cases are caused by genetic mutations in three genes including amyloid-β protein precursor (APP), presenilin 1, and presenilin 2, which are involved in the production of Aβ peptide. Down's syndrome (DS) patients, who carry an extra copy of chromosome 21, develop AD-type dementia with pathological hallmarks in the brain, likely due to the extra copy of the APP gene located on this chromosome. A vast research effort has been made to study Aβ overproduction and/or tau hyperphosphorylation. However, their contribution to the onset and pathogenesis of this devastating disease are still controversial.

There were 26.6 million cases of AD in the world in 2006 and it was projected that the worldwide prevalence of AD will grow four fold to 106.8 million with 1 in 86 people living with AD by the year 2050 [2]. The increase is a result of the aging population worldwide which signifies the fact that AD is a disease of aging and aging represents the single biggest risk factor for AD. Increased oxidative stress has been implicated in the aging process. Oxidative stress is the redox state resulting from an imbalance between the generation and detoxification of reactive oxygen species (ROS). ROS are unavoidable physiological byproducts which act as a double-edged sword in the biological system [3]: they can serve crucial functions such as signaling molecules under carefully controlled situations, but can do damage to biological system when present in excess amount since they are capable of oxidizing all major biomolecules including nucleic acid (DNA, RNA), protein, and lipids. The brain is highly susceptible to oxidative imbalance due to its high energy demand, high oxygen consumption, rich abundance of easily peroxidizable polyunsaturated fatty acids, high level of potent ROS catalyst iron, and relative paucity of antioxidants and related enzymes. It is no wonder that oxidative imbalance and subsequent oxidative stress mediated damage to biomolecules is extensively reported in AD and increasing evidence suggest that oxidative imbalance plays a critical role in the disease [4]. As the main source of ROS generation and also a major target of oxidative damage, progressive impairment of mitochondrial function has also been implicated in aging and AD [5]. The interaction between oxidative stress and mitochondrial dysfunction likely forms a vicious downward spiral that amplifies the deficits and likely plays an important role in the pathogenesis of AD.

2. Evidence of Oxidative Stress in Alzheimer's Disease

ROS are generated under normal conditions and their levels are kept relatively low by the delicate balance between the rate of their production and the rate of their clearance by antioxidant and related enzymes. Thus, either enhanced ROS production or impaired antioxidant system will tip the cellular redox balance to oxidative imbalance and cause ROS overproduction. ROS are usually highly reactive, unstable and have a very short half-life, thus making them difficult to measure directly. Oxidized biomolecule products generated by ROS are much more stable and commonly used as ROS markers. In addition, ROS could also be assessed indirectly by measuring antioxidant levels or antioxidant enzyme activity. In fact, oxidative imbalance and significant increase of its by-products have been consistently reported in AD.

2.1 Lipid peroxidation

A large body of research has demonstrated that lipid peroxidation is greatly enhanced in AD. Lipid peroxidation refers to the process in which lipids are attacked by ROS through a free radical chain reaction mechanism to generate lipid peroxidation products. By far, the most extensive lipid peroxidation products studied in AD are reactive aldehydes including 4-hydroxynonal, malondialdehyde (MDA), and 2-propenal (acrolein), and chemically and metabolically stable isoprostanoids including F2-isoprostanes and F4-neuroprostanes. It was reported that the 4-hydroxynonal levels are significantly elevated in hippocampus [6–8], entorhinal cortex [8], temporal cortex [8], amygdala [6, 7], parahippocampal gyrus [9], ventricular fluid [10], and plasma [11] in AD patients compared with age-matched control subjects. Significant increase of MDA was also reported in hippocampus [6], pyriform cortex [6], temporal cortex [12, 13], occipital cortices [14], and erythrocytes [15] from AD patients. Several studies found no change of basal MDA [16–20] but significant higher stimulated MDA production in various AD brain regions [16, 19]. In addition, acrolein, the most reactive of the α,β-unsaturated aldehydes, was found to be elevated in AD hippocampus/parahippocampal gyrus [21–23], amygdala [22], superior and middle temporal gyrus [23], and cerebellum [23]. F2-isoprostanes and F4-neuroprostanes are stable products generated from peroxidation of arachidonic acids and docosahexaenoic acid, respectively. Their levels were found to be significantly increased in frontal/temporal poles [24], cerebrospinal fluid [25–27], urine [27], and plasma [27] of AD patients.

2.2 Protein oxidation

Oxidative modifications of proteins, resulting either from direct ROS attack, or from the reaction with glycation, glycoxidation, and lipid peroxidation products binding, have also been extensively reported in AD. The most widely studied markers of protein oxidation are protein carbonyls and 3-nitrotyrosine. A significant increase of protein carbonyl content was reported in hippocampus [28, 29], parietal lobe [30], and superior middle temporal gyrus in AD patients [29]. However, it still remains controversial whether there is elevation of overall brain carbonyl levels in AD [17, 30, 31]. Significant increase of the carbonyl level of specific proteins such as creatine kinase, glutamine synthase, and ubiquitin carboxy-terminal hydrolase L-1 was detected in different AD brain regions including hippocampus, frontal and temporal lobes, inferior parietal lobe, and cerebellum [29, 32–34]. The other major protein oxidative modification, 3-nitrotyrosine, is the end product of the interaction of peroxynitrite with tyrosine residues and was found to be significantly increased in AD in various brain regions [34–40] and cerebrospinal fluid [37].

2.3 DNA/RNA oxidation

Numerous studies have provided evidence that oxidative damage of DNA/RNA was increased in AD. Oxidative damage of DNA can cause DNA double strand breaks, DNA/DNA or DNA/protein crosslinking, and base modification. High levels of DNA breaks were found in both AD hippocampus [41] and AD cerebral cortex [42]. The most widely used DNA oxidative markers in AD are 8-hydroxydeoxyguanosine (8-OHdG) and 8-hydroxyguanosine (8-OHG), which is the product of guanine oxidation. Guanine is the base most readily attacked by oxidative stress due to its low oxidation potential compared with

the other three DNA bases. AD brains demonstrated significant increase of 8OHdG and 8-OHG in both mitochondrial DNA and nuclear DNA compared with age-matched controls [30, 35, 43]. RNA is largely single stranded and is usually subjected to similar oxidative damage/modifications as DNA. Predominant oxidation of cytoplasmic RNA rather than nuclear DNA was reported in AD [44]. Significant higher levels of oxidized rRNA or mRNAs were also documented in AD [45–47].

2.4 Antioxidants

In addition to the widespread increase of oxidative biomolecule products, significant decrease of antioxidant levels or antioxidant enzyme activity has been repetitively reported. The plasma levels of antioxidants such as albumin, bilirubin, uric acid, lycopene, vitamin A, vitamin C, and vitamin E were found to be decreased in AD patients [48, 49]. Significant decrease in the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase were also reported in different AD brain areas including frontal and temporal cortex, although the expression levels of some of them were increased [13, 50–52].

3. Oxidative Stress as an Early Event in Alzheimer's Disease

It is known that AD has a long latent period before symptoms appear and a diagnosis can be made. Recent studies demonstrated that the onset of AD is commonly preceded by an interim phase known as mild cognitive impairment (MCI), when there is no significant increase of senile plaques and NFTs [53–55]. Indeed, MCI subjects exhibited significant oxidative imbalance compared with age-matched controls. For example, the levels of the isoprostane 8,12-*iso*-iPF$_{2\alpha}$-VI were significantly increased in cerebrospinal fluid, plasma, and urine of MCI subjects compared with age-matched control subjects, whereas the levels of AD cerebrospinal fluid markers such as Aβ or tau remained unchanged [56]. Enhanced overall protein peroxidation as well as oxidative modification of specific proteins was also found in hippocampus and superior and middle temporal gyri from MCI subjects [57, 58]. Previous and more recent studies showed significant decreased levels of non-enzymatic antioxidants such as uric acid, vitamin C, vitamin E, vitamin A, lutein, zeaxanthin, β-cryptoxanthin, and α-carotene, and reduced activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione reductase in MCI patients [59, 60]. Since MCI subjects are at high risk to progress to early AD and the widespread oxidative damage in MCI could precede the pronounced AD neuropathological alterations, these facts strongly suggest that oxidative imbalance appears at the very early stage of AD and is probably a central feature of the pathogenesis of AD. In fact, it was also reported that lipid peroxidation product, isoprostane 8,12-iso-iPF2alpha-VI, is increased in the urine, blood, and cerebrospinal fluid of AD patients and correlated with the severity of the disease [27], further suggesting that oxidative stress also plays an important role in the progression of the disease.

Patients with DS, caused by trisomy of chromosome 21 and characterized by enhanced Aβ production in the brain and increased incidence of developing AD in middle ages [61], demonstrated predictable progression of AD-type pathology with age. Significant oxidative stress occurs in young DS patients in the absence of significant AD pathologic hallmarks

such as senile plaques and NFTs [62–65]. *In vitro* cultured DS neurons derived from fetal DS also demonstrated higher levels of ROS and significant oxidative damage [66]. The results that ROS overproduction preceded neuronal death, and that antioxidants could greatly enhance neuronal viability, strongly suggested that DS neurons had a preset oxidative imbalance, which was probably responsible for neuronal deficits and subsequent pathological changes during the progression of DS.

Depending on the stability of oxidation modification products, two distinct distribution patterns of oxidative modification were revealed by detailed *in situ* studies: Products of lipid peroxidation or protein glycation often cause crosslinked molecules which are resistant to degradation at the site of generation. These modifications likely represent cumulative oxidative damage during the course of the disease. *In situ* detection of these modifications indicates that they were widely present in neurons with and without associated pathology [36, 67, 68]. On the contrary, oxidized DNA/RNAs are rapidly turned over, the levels of which likely reflect steady state oxidative stress. However, RNA oxidation is prominent in cells without pathology but less abundant in neurons with pathology in AD brain [69–72]. These data suggest that oxidative stress occurs earlier than, and likely contributes to the formation of AD-associated pathology and furthermore, AD-associated pathology may play a protective role in quenching ROS production. Such a notion is also supported by studies in DS patients where oxidative stress gradually decreased when amyloid pathology increased with age [73]. Nevertheless, one most recent live imaging study demonstrated active ROS production followed by neuronal death in the proximity to amyloid plaques in the brain of APP/PS1 transgenic mice [74]. Whether this observation can be directly translated into the human situation is unclear since many therapeutics effective in AD mouse models failed to have any clinical benefit in human patients. Overall, these studies suggest that oxidative stress is not only an early event during the course of the disease, but also precedes the AD pathology which suggests a central role of oxidative stress in the pathogenesis of AD.

Evidence further supporting the causative role of oxidative imbalance in the pathogenesis of AD comes from studies showing that antioxidant vitamin deficiency alone is sufficient to induce neurological deficits similar to those in AD. For example, it has been extensively reported that the deficiency of vitamin E, one of the most important fat-soluble antioxidants, caused dementia and other neurological symptoms with an increased risk of developing AD [75, 76], and the addition of vitamin E could reverse the neurologic dysfunction [76]. In addition to vitamin E, the deficiencies of other vitamins that have antioxidant activity were also reported to impair brain function. The lack of folate, a water-soluble vitamin B9 that is important for the development and normal function of the central nervous system [77], resulted in cognitive decline, dementia, depression and other neurological symptoms [78, 79]. And, the treatment with folic acid could significantly alleviate neurological deficits in those folic acid deficiency patients [80]. Dementia, cognitive impairment and other AD like neurological symptoms have also been found in subjects with vitamin B12 [81] and vitamin D deficiency [82]. Taken together, these findings suggest that oxidative imbalance is an early event and likely plays an important role in the pathogenesis of AD.

4. Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease

Mitochondria are the major source of oxidative stress because the unavoidable electron leakage during electron transfer leads to the constant production of superoxide anion which, despite the presence of an efficient mitochondrial/cellular antioxidant system, is responsible for 90% of the endogenous ROS. It is suggested that dysfunctional mitochondria are less efficient producers of ATP but more efficient producers of ROS, which could represent a major source of oxidative imbalance observed in AD [83, 84]. Indeed, mitochondrial dysfunction is a prominent and early feature of AD [85], and almost all aspects of mitochondrial function have been reported to be impaired in AD.

4.1 Reduced energy metabolism

Reduced energy metabolism in the diseased brain is one of the best documented abnormalities in AD. In fact, low glucose metabolism at baseline and longitudinal glucose metabolism decline is viewed as a sensitive measure useful for monitoring change in cognition and functionality in AD and MCI, and is being increasingly adopted to assist diagnosis and used to predict future cognitive decline [86–88].

4.2 Alterations in the key enzymes in oxidative phosphorylation

A genome-wide transcriptomic study suggests that cerebral glucose metabolic decline in AD is associated with reduced neuronal expression of nuclear genes encoding subunits of the mitochondrial electron transport chain. Indeed, several key enzymes of oxidative metabolism including α-ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex, and cytochrome oxidase all demonstrated reduced expression and/or activity in AD [84, 89–94], alteration of which significantly correlated with clinical state and plaque counts [95]. Increased oxidative stress likely caused further reduction in activity of some of these enzymes such as that of α-ketoglutarate dehydrogenase complex.

4.3 Calcium dyshomeostasis

Dysfunctional mitochondria contribute to calcium dyshomeostasis through impaired buffering capacity or direct impact on the endoplasmic reticulum calcium channels [96]. Indeed, calcium mishandling was reported in peripheral cells from AD patients such that endoplasmic reticulum (ER) develops calcium overload and calcium uptake is diminished [97, 98]. Indirect evidence suggests elevated intracellular calcium in AD brain since calmodulin-dependent kinase and calpain are elevated in vulnerable neurons early in the disease process [99–102]. Most recently, it was demonstrated that the function of mitochondria-associated ER membranes and ER-mitochondrial communication are increased significantly in fibroblasts from patients with both the familial and sporadic forms of AD [103]. Consistently, increased expression of several ER-mitochondria interface proteins were also reported in early stage of AD [104]. These suggest that altered MAM will likely contribute to calcium dyshomeostasis and mitochondrial dysfunction.

4.4 Mitochondrial DNA (mtDNA)

Elevated levels of sporadic mutations in the mtDNA including the most common 5-kb deletion were demonstrated in the brain of AD patients [105, 106]. In fact, several of the

mutations in the mtDNA control regions were unique to AD [107–110]. Due to the absence of protective proteins such as histone, the relative paucity of efficient DNA repair system and the close proximity to site of ROS generation, mtDNA is vulnerable to ROS attack. Analysis of oxidized nucleoside revealed three-fold increase in oxidative damage in the mtDNA in AD brain [111], which probably is the cause of the increased mutations. Consistent with the systemic increase of oxidative stress, mutations in mtDNA were also found in blood samples from AD and lymphoblastoid lines derived from AD blood samples. Many of these mutations occur at sites of known mtDNA transcription and replication regulatory element and thus cause reduced transcript levels of crucial mitochondrial proteins that is deleterious to mitochondrial function [107, 112]. A causal role of mtDNA alterations in some of AD-related deficits such as oxidative stress and biochemical deficits in cytochrome oxidase activity and calcium handling were demonstrated in cybrids where mtDNA from AD patients were transferred into cell lines devoid of mtDNA [113].

4.5 Apoptotic pathway

Mitochondria lie in the center of the intrinsic apoptotic pathway. Although it remains controversial whether apoptosis plays a major role in neurodegeneration in AD [114], it is clear that many components of the intrinsic apoptotic pathway are activated or altered in AD brain [115]. It is of interest to note that the activation of these molecules may not necessarily lead to apoptosis. For example, it appears that caspase 3 is cleaved and activated in AD which is linked to tau cleavage and NFT formation [116].

5. Abnormal Mitochondrial Dynamics and Oxidative Stress in Alzheimer's Disease

The normal function of mitochondria is dependent upon their intact structure to keep the proper electrochemical gradient. Structurally damaged mitochondria, as evidenced by broken cristae and partial or near complete loss of the internal structure, were abundant and represent a prominent feature in vulnerable neurons in biopsied AD brain as revealed by electron microscopy [105], which is likely the structural basis of the significant mitochondrial dysfunction in AD. A slight but significant increase in mitochondrial size along with a significant decrease in mitochondrial number in these neurons was noted [105]. The size and number of mitochondria are regulated by the dynamic process of mitochondrial fission and fusion [117], therefore, this study was the first that implicated the involvement of abnormal mitochondrial dynamics in AD.

Mitochondria are highly dynamic organelles that undergo continual fission and fusion events which regulate the morphology and distribution of mitochondria [118]. Mitochondrial fission and fusion are regulated by mitochondrial fission proteins such as dynamin-like protein 1 protein (DLP1, also referred to as DRP1), Fis1 [119, 120], and Mff [121], and mitochondrial fusion proteins such as Mitofusin 1 (Mfn1), Mitofusin 2 (Mfn2), and optic atrophy protein 1 (OPA1) [119, 120]. The majority of DLP1 resides in the cytoplasm. However, during fission, DLP1 is recruited to the mitochondrial surface and appears as punctate spots. Fis1, Mff, Mfn1, and Mfn2 are mitochondrial transmembrane proteins localized to the outer mitochondrial membrane [122, 123], while OPA1 is localized to the

inner mitochondrial membrane. In support of the involvement of altered mitochondrial dynamics in AD, recent studies demonstrated significant changes in the expression of almost all mitochondrial fission and fusion proteins including DLP1, OPA1, Mfn1/2, and Fis1 in the brain from AD patients [124–128]. Mitochondrial DLP1, the fraction critical for mitochondrial fission, is increased in AD brain [124]. Consistently, DLP1 phosphorylation at Ser616 and S-nitrosylation of DLP1, which either facilitate DLP1 translocation to mitochondria or activate the GTPase activity of DLP1 and thus facilitate mitochondrial fission, are also increased in AD [124, 129]. Interestingly, DLP1 interacts with Aβ monomer and oligomers and phosphorylated tau in AD brain tissues [126, 130], although it remains to be determined how such interactions may impact mitochondrial dynamics. More detailed analysis revealed significantly reduced mitochondrial length but increased mitochondrial width with a significant increase in overall size that resulted in a rounder and fatter (i.e., swollen) morphology of mitochondria in vulnerable neurons from biopsied AD brains [131]. Although larger mitochondria are normally the result of inhibited fission or enhanced fusion, similarly swollen mitochondria were abundant in the brain of fusion-deficient Mfn2 knockout mice [132].

While admittedly non-conclusive due to the “snap-shot” nature of the morphometric study based on electron microscopy micrographs, considering the biochemical data, these studies collectively suggested that there is likely enhanced fission which leads to structurally damaged and swollen mitochondria in vulnerable neurons in the AD brain. Such a notion is supported by *in vitro* and animal models of AD [133]. For example, neurons treated with oligomeric Aβ or overexpressing familial AD-causing mutant APP demonstrate mitochondrial fragmentation and structural damages [124, 131, 134]. Feany’s group demonstrated that tau overexpression causes mitochondrial elongation in *Drosophila* through actin-stabilization mediated DLP1 mislocalization [135], however, overexpression of caspase cleaved tau or tau hyperphosphorylation (i.e., cardinal features of human tauopathies including AD) causes mitochondrial fragmentation in mammalian cells [136–140]. Damaged and swollen mitochondria are also documented in the brain of Tg2576 and APP/PS1 mice [141]. Interestingly, the 3-dimension reconstruction of consecutive electron micrographs revealed the presence of swollen mitochondria connected by very narrow membrane segments resembling “beads-on-the-string” pattern in these AD mouse models [141]. This peculiar “beads-on-the-string” pattern may reflect enhanced fission caught in action before the final scission or enhanced fission with arrested final scission, the distinction of which requires techniques that can overcome the snap-shot nature of an electron microscopy study such as *in vivo* imaging on live animals.

While it remains to be determined whether and how excessive fission causes structural damage to mitochondria in AD, it is clear that excessive fission is sufficient to cause many deleterious consequences seen in AD including increased oxidative stress [142]. It was reported that ROS was overproduced along with mitochondrial fragmentation when neuronal cells were exposed to high glucose concentrations [142]. The inhibition of mitochondrial pyruvate uptake, an effective means to stop ROS increase, did not prevent mitochondrial fragmentation while genetic inhibition of mitochondrial fission by dominant negative mutant form of DLP1 prevented ROS production in high glucose conditions,

suggesting that mitochondrial fragmentation plays a critical role in ROS overproduction and oxidative imbalance [142]. More recently, we and others demonstrated that mitochondrial electron-transport-chain complex inhibitors such as rotenone, 1-methyl-4-phenylpyridinium, and 3-nitropropionic acid cause fragmentation of the mitochondrial network along with increased ROS production [143–145]. Antioxidants could only partially alleviate electron-transport-chain complex inhibitors induced mitochondrial fragmentation [144, 145], while inhibition of mitochondrial fission could significantly reduce ROS overproduction and block mitochondrial/cellular dysfunction [145], further suggesting that mitochondrial function and dynamics are intimately related, and mitochondrial morphological dynamics are essential for the maintenance of ROS balance. Indeed, ROS overproduction in AD models could be efficiently prevented or rescued by the inhibition of mitochondrial fission or the promotion of mitochondrial fusion, demonstrating the contribution of abnormal mitochondrial dynamics to oxidative imbalance in AD [124, 127, 131, 146]. Defects in mitochondrial fission and fusion can also increase ROS indirectly through negative impact on bioenergetics, calcium handling, and mtDNA integrity. For example, mitochondrial fission plays crucial role in the assembly of electron transport complexes and controls the dynamic features of mitochondrial nucleoids [147, 148]. Unopposed fission leads to rapid accumulation of mtDNA mutations and decreased calcium buffering capacity [149, 150]. The balance of mitochondria fission and fusion is also sensitive to oxidative imbalance. Most recent studies demonstrated that, through regulation of mitochondrial fission and fusion proteins such as DLP1 and Mfn2, both endogenous [151] and exogenous [152] application of ROS might directly impair mitochondrial fission and fusion balance, induce mitochondrial fragmentation and further cause subsequent mitochondrial dysfunction including ROS overproduction and thus form a vicious cycle that amplifies oxidative stress which perhaps plays an important role in the oxidative imbalance in AD.

6. Conclusion

The importance of oxidative stress in the pathogenesis of AD is supported by the early occurrence and the widespread nature of oxidative damages in AD. Increased oxidative stress also characterizes the aging process. However, that oxidative stress is significantly increased in the AD brain compared to age-matched elderly controls indicates that AD is not a normal part of aging which thus suggests that additional factors must be involved in initiating and/or amplifying oxidative stress during the onset and progression of the disease. Among many potential initiators/sources, mitochondria likely play a critical, if not central, role because of their primacy in energy metabolism and redox homeostasis. Defects in mitochondrial dynamics, either due to the response to genetic deficits or metabolic or environmental alterations, will make mitochondria less versatile in responding to the changing needs of cells which likely have particularly debilitating effects on neurons. The resultant mitochondrial dysfunction and ensuing oxidative stress and their interactions have the potential to form a vicious downward spiral that becomes a ubiquitous causative feature of cell malfunction and degeneration (Figure 1). Clearly, more studies are needed to understand the initiation of oxidative stress and the critical contribution of mitochondrial dysfunction in AD.

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Abbreviations

AD	Alzheimer's disease
Aβ	amyloid-β
APP	amyloid-β protein precursor
DS	Down's syndrome
DLP1	dynamin-like protein 1 protein
ER	endoplasmic reticulum
8-OHdG	8-hydroxydeoxyguanosine
8-OHG	8-hydroxyguanosine
MDA	malondialdehyde
MCI	mild cognitive impairment
mtDNA	mitochondrial DNA
Mfn1	Mitofusin 1
Mfn2	Mitofusin 2
NFTs	neurofibrillary tangles
OPA1	optic atrophy protein 1
ROS	reactive oxygen species

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Highlights

Oxidative stress is an early and prominent feature of AD.

Structurally and functionally damaged mitochondria are characteristics of AD.

Mitochondrial fragmentation contributes to mitochondrial damage and dysfunction in AD.

A vicious downward spiral involving ROS and mitochondrial deficits is critical to AD pathogenesis.

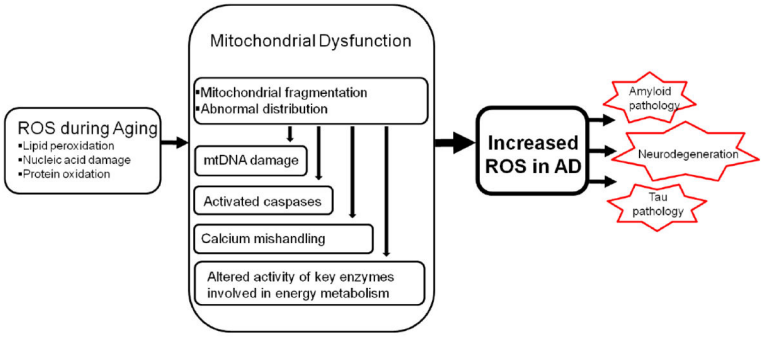

Figure 1.

Mitochondrial dysfunction is likely involved in the initiation and/or amplification of oxidative stress during the onset and progression of Alzheimer disease. Oxidative stress can negatively impact mitochondrial integrity and function. Defects in mitochondrial dynamics, either due to the response to genetic deficits or metabolic or environmental alterations, will make mitochondria less versatile in responding to the changing needs of neurons which will exacerbate mitochondrial dysfunction in chronic condition. The resultant mitochondrial dysfunction and ensuing greater oxidative stress and their interactions have the potential to form a vicious downward spiral that becomes a ubiquitous causative feature of cell malfunction, insufficient compensation and degeneration in AD.