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Mitochondria and Alzheimer's disease

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ABSTRACT

Reductions in cerebral metabolism sufficient to impair cognition in normal individuals also occur in Alzheimer's disease (AD). FDG PET studies have shown that decreased glucose metabolism in AD precedes clinical diagnosis and the degree of clinical disability in AD correlates closely to the magnitude of the reduction in brain metabolism. This suggests that the clinical deterioration and metabolic impairment in AD are related closely. Diminished metabolism can lead to the hyperphosphorylation of tau and increased production of amyloid beta peptide, hallmarks of AD. These observations suggest also that early mitochondrially therapeutic interventions may be an important target in delaying AD progression in elderly individuals and in treating AD patients.

Alzheimer's disease (AD) is the most common age-related progressive neurodegenerative disorder with an estimated prevalence of 24 million people worldwide [1]. AD is characterized by a complex etiology due to multiple genetic and environmental risk factors.

Several penetrant autosomal dominant mutations have been identified (http://www.molgen.ua.ac.be AD/FTD mutation database) in three genes (amyloid precursor protein, APP; presenilin 1, PSEN1; presenilin 2, PSEN2) connected with early-onset familial AD (EOFAD), while the presence of the apolipoprotein E allele ε4 (ApoE4) is the only confirmed genetic risk factor for late onset sporadic AD (LOAD) cases [2].

Despite many years of research and great progress in the knowledge of the molecular pathogenesis of AD, a full understanding of the etiology of the sporadic form is still out of reach [3]. The pathological features of AD include extracellular amyloid beta peptide (Aβ) accumulation, intracellular neurofibrillary tangles of hyper-phosphorylated tau, which are also accompanied by oxidative stress or mitochondrial dysfunction and synaptic damage [4]. Mitochondria generate cellular energy (ATP) and are also implicated in several cellular processes essential for cell life and death, including the regulation of second messenger levels, such as the calcium ion (Ca^{2+}) and reactive oxygen species (ROS) [5].

Neuronal activity is extremely energy dependent and neurons are particularly sensitive to changes in mitochondrial function [6]. Furthermore, the maintenance of calcium homeostasis is critical for neuronal synaptic function [7]. Dysfunction of mitochondrial energy metabolism leads to reduced ATP production, impaired calcium buffering and the generation of ROS. Positron emission tomography (PET) studies have shown reduced cerebral metabolism in temporo-parietal cortices in the onset of both familial and sporadic forms of AD correlated to decreased glucose metabolism [8,9]. The cerebral metabolic abnormalities precede the onset of symptoms and the degree of clinical disability correlates closely to the magnitude of the reduction in brain metabolism [10].

Since 1983, studies in animal models have demonstrated abnormalities of mitochondrial enzymes in Huntington and Alzheimer brain, suggesting that the alterations leading to AD may be related to mitochondrial oxidative metabolism [11,12]. Several decades of research have firmly established that ROS production is inherent to mitochondrial oxidative metabolism, and mitochondria are believed to be the major intracellular source of ROS [13]. Recent studies suggest that ROS are involved in physiological signaling cascades and regulate important cellular and organ functions [14,15]; however, excessive increase may lead to oxidative stress and be a primary or aggravating factor in aging and neurodegenerative diseases.

For the past 20 years, the amyloid cascade hypothesis has dominated scientific research but increasing evidence also indicates a possible mitochondrial cascade hypothesis [16]. The mitochondrial activities associated with metabolic dyshomeostasis and reduced ATP synthesis, involved in AD, are also closely related to aging.

By using *in vivo* and in *vitro* approaches, many studies demonstrated that Aβ may interact with the mitochondria, showing co-localization of Aβ with complex II of the respiratory chain, and it may be responsible for mitochondrial dysfunction [17–25].

Mitochondrial dysfunction primarily involves the Aβ mitochondrial transporter (ABAD), mitochondrial DNA (MtDNA) and ROS production, in particular pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase (KHD) and cytochrome c oxidase (C-IV) [26].

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Aβ is able to pass through the cell membrane and mitochondrial membranes using the amyloid channel and Aβ transporter systems, in particular, [25] the translocase of the outer membrane (TOM40) and the translocase of inner membrane (TIM22) [27,28]. The Aβ cytotoxic mechanism affects the membranes leading to invaginations, budding, vesicle formation and permeabilization in mitochondria. Moreover, Aβ binds to the basement membrane and induces an up-regulation of the biosynthesis of membrane components, such as laminin or collagen IV, that promote Aβ pathological deposits. Aβ interaction with several proteins of the membrane permeability transition pore (MPTP), involved in many mitochondrial functions, modifies the permeability of the mitochondrial membrane [28].

In cortical neurons, Aβ is also involved in the release of calcium from the endoplasmic reticulum (ER), leading to an increase in cytosolic calcium levels. The calcium is taken up by mitochondria and mitochondrial functions are impaired. This massive influx may contribute to opening the MPTP, bringing about the collapse of the mitochondrial membrane potential and the generation of pro-apoptotic signals and ROS [29]. Furthermore, the massive increase in intracellular calcium can initiate both necrotic and apoptotic cell death [28].

Moreover, Aβ may inhibit mitochondrial respiration affecting several proteins involved in these processes [25]. Two studies have reported that the α-chain of ATP synthase is altered in degenerating neurons in AD and that the interaction between Aβ and ATP synthase results in ATP depletion [30,31]. Furthermore, a subsequent study reported that Aβ decreases cytochrome c oxidase activity, but the mechanism is still unclear [32]. In contrast, the activity of ROS production sites, in particular cytochrome c reductase (complex III), results increased [33], highlighting that inhibition of mitochondrial respiration and ATP depletion may be associated with the deleterious effects of ROS [34].

ROS can damage macromolecules directly, causing protein and lipid peroxidation. The oxidation of specific cellular proteins, such as enzymes, calmodulin, the Aβ peptide and tau-protein, represents a critical determinant of brain function [35]. Moreover, ROS may induce spontaneous DNA oxidation among the normal bases [36].

Many studies have demonstrated that Aβ is able to induce apoptosis with both *in vitro* and *in vivo* approaches. The exact mechanism is still unclear, although several hypotheses have been proposed; [37,38] one possible pathway is the involvement of Aβ in the mitochondrial release of the apoptosis-inducing factor (AIF), responsible for initiating caspase-independent apoptosis by causing DNA fragmentation and chromatine condensation [22]. Recently, a study reported that the apoptosis pathway may involve activation of caspase-3, the c-Jun transcription factor or p53 [28].

In summary, Aβ may have many effects on mitochondria through different mechanisms including modification of membranes, reduced respiratory function, the generation of ROS, increased vulnerability to other toxic substances and induction of apoptosis disorders involving calcium. Moreover, Aβ may induce mutations in MtDNA and RNA.

To date, the role of mitochondria in the development of AD is still very controversial, but there is no doubt that mitochondrial dysfunction, abnormal mitochondria dynamics and degradation by mitophagy occurring during the disease process, contribute to its onset and progression. A study in cultured fibroblasts from sporadic and familial AD patients has shown an alteration in mitochondrial activities by a reduction in CO2 production. The study has particularly demonstrated the occurrence of change in mitochondrial metabolism in the fibroblasts of AD patients carrying the PS1 mutation [39].

Studies in fibroblasts from patients carrying the PS1 M146L mutation show the reduction in alpha-ketoglutarate dehydrogenase complex (KGDHC) activity in response to exposure to mild stress [40]. Moreover, MTT (3–4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide), which represents a general marker of cellular dehydrogenase activity, appears decreased in the presence of mutated fibroblast Aβ deposits [40]. This suggests that KGDHC activities may have a clinically relevant role in the pathophysiology of AD [40].

Several mitochondrial genetic mutations lead to early degeneration of specific human tissues, mitochondrial mutations may cause degeneration at a later point in life. The first mutation reported in MtDNA was 4336 G, which occurs more frequently in individuals with AD [41]. Human MtDNA is a circular molecule of 16,569 base pairs encoding 13 polypeptide components in the respiratory chain, two ribosomal RNA genes and 22 transfer RNA genes, necessary to support intramitochondrial protein synthesis. This type of DNA is maternally transmitted and does not undergo recombination. Mitochondrial DNA presents a high mutation rate due to the lack of histone proteins, inefficient DNA repair and close proximity to ROS produced during oxidative phosphorylation [28]. Based on the instability and irreparability of the mitochondrial genome, due to the absence of histones and enzymatic repair systems, it is possible that during aging the accumulation of oxidative stress induces MtDNA damage and subsequent mitochondrial dysfunction. A study has demonstrated the presence of increased oxidation in both mitochondrial and nuclear DNA bases in the frontal, parietal and especially in the temporal lobes of AD cases, and MtDNA oxidation was approximately 10-fold higher than nuclear DNA oxidation [42].

There is evidence suggesting that tissues from both AD patients and individuals with mild cognitive impairment have elevated levels of oxidative DNA damage. Aβ peptides are directly involved in free radical/ROS formation, cellular dysfunction and subsequent neuronal death. Further mitochondria are thought to be the central target for oxidative stress-induced damage [13]. Several studies on the influence of MtDNA mutations have shown different and contrasting results which may be due to ethnicity variability in the MtDNA [43–45]. In Caucasian populations there are 9 mitochondrial haplogroups. Polymorphisms in MtDNA may cause changes in enzyme activities through changes in the mitochondrial respiratory chain and free radical overproduction. Specific sets of polymorphisms define groups of mitochondrial DNA evolved from the same ancestor [46,47].

Carrieri and colleagues analyzed MtDNA haplogroups and APOE polymorphisms in sporadic AD patients, finding that ApoE and MtDNA polymorphisms are statistically dependent variables in AD, while they are independent in groups of healthy subjects [48]. In this study, the odds ratio analyses were in agreement with the hypothesis of an interaction between ApoE4 and MtDNA haplogroups in sporadic AD [48]. In another study, an analysis regarding the subhaplogroups of MtDNA showed that within the H haplogroup the H5 subtype showed the highest and most significant difference between AD patients and controls [49]. Other studies also reported differences in mitochondrial haplogroups in AD and many other studies are in progress on DNA and cells from different groups [50].

To date, there is evidence that mitochondrial dysfunction and oxidative damage have an important role in several neurodegenerative diseases in which the mitochondrial contribution may be the primary cause (eg, Parkinson's disease), or a consequence of biochemical dysfunctions (eg, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis) (Table 1).

The varied mitochondria functions may explain the cell subpopulations susceptibility to cellular aging, stress and genetic modifications leading to the heterogeneous spectrum of pathological phenotypes. Transgenic mouse models of human neurodegenerative diseases are showing the possible mechanisms correlating the mitochondrial deficit and the different pathological phenotypes [51]. However, although several theories do exist, none of them have ever equivocally demonstrated how the mitochondrial abnormalities contribute to the diseases pathogenesis thus, the connection between mitochondrial deficit and the development of neurological diseases remains partially unknown [52].

Due to the strong evidence of a possible important and early role of mitochondria in AD and other neurodegenerative disorders,

Table 1
Key mitochondrial dysfunctions in the most studied neurodegenerative diseases.

Phenotype	Mitochondrial dysfunctions
Alzheimer's disease	Increased mtDNA defects in brain tissue Decreased levels of cytochrome oxidase, pyruvate dehydrogenase, and α-ketodehydrogenase activity Abnormal mitochondrial gene expressions Aβ binds ABAD and increases ROS production leading to mitochondrial dysfunction Aβ increases expressions of mitochondrial fission genes and decreases expressions of fusion genes causing abnormal mitochondrial dynamics in neurons Abnormal mitochondrial trafficking leading to an insufficient levels of ATP at synapses Aβ interacts with mitochondrial proteins and causes structural damage to mitochondria
Huntington's disease	Reduced mitochondrial enzyme activities of complexes I, II, III, and IV Increased mtDNA defects in brain and peripheral tissues Abnormal mitochondrial dynamics due to mutant Htt which increases mitochondrial fission and decreases mitochondrial fusion Mutant Htt interacts with mitochondria and microtubules and impairs the axonal transport of mitochondria to nerve terminals Mutant Htt reduces mithocondrial calcium uptake capacity
Parkinson's disease	Germ-line and somatic mtDNA defects in substantia nigra. PINK1 and parkin mutations reduces mitochondrial fission leading to the loss of mitochondrial and tissue integrity Significant accumulation of mutant α-synuclein and decreased complex I activity in substantia nigra and striatum The lack of DJ-1 shows an impaired protection from oxidative damage caused by mitochondrial toxins.
Amyotrophic lateral sclerosis	Mitochondria are targets of toxicity in motor neuron Mutant SOD1 in spinal cord and brain mitochondria causes neuronal toxicity under metabolic and oxidative stress conditions

Aβ = amyloid beta, ATP = adenosine triphosphate, ABAD = Aβ mitochondrial transporter, mtDNA = mitochondrial DNA, ROS = reactive oxygen species, Htt = Huntingtin; PINK1 = PTEN-induced kinase 1, mtDNA, SOD1 = superoxide dismutase 1.

mitochondria are now considered a possible target for therapy [53]. Several different therapeutical approaches have been proposed to protect or repair mitochondria: mitochondria antioxidants, MtDNA repair enzymes, overexpression of sirtuins, overexpression of nuclear transcription factor, overexpression of insulin-like growth factor 1 [13].

Agents targeting mitochondrial dysfunction have shown positive effect in some neurodegenerative diseases for which there is no effective symptomatic or disease-modifying therapy available to date, such as in progressive supranuclear palsy and AD [54].

Very recently it has been shown that deoxyglucose treatment induces ketogenesis, sustains mitochondrial function and reduces pathological changes in the brain of an AD mouse model [55]. This treatment reduces the amount of Aβ and the negative effect of oxidative stress and lipid peroxidation, both in the hippocampus and cortex, but has no effect on the other AD principal hallmarks, such as phosphorylated tau levels. Recently, it has been shown in an AD mouse model that long-term diazoxide (ATP channel activator) treatment reduces Aβ and tau pathologies and improves cognitive function. Diazoxide activates K+ channels (KATP) in both plasma membrane and mitochondrial inner membrane, which are fundamental for the activity of this molecule in suppressing the AD-like disease process. Diazoxide, through hyperpolarization of the plasma membrane, may reduce Aβ production and N-methyl-D-aspartic acid (NMDA) receptor-mediated cellular Ca2+ overload. Simultaneously, activation of mitoKATP channels may preserve cellular energy substrates and reduce mitochondrial free radical production. Collectively, these actions of diazoxide likely contribute to delaying the AD process and to improving cognitive function [56].

Finally, studies have demonstrated that the mother's AD status has a key role in the individual's risk of developing LOAD [57–59]. A recent study shows reduced platelet mitochondrial cytochrome oxidase (COX) activity in cognitively healthy subjects with a maternal AD history compared to those subjects with a paternal history of AD. This suggests that COX abnormalities reflect the maternal inheritance-dependent LOAD endophenotype and possibly reflect mitochondrial DNA involvement. Moreover, it has been demonstrated that decreased COX and citrate synthase activities are independent of ApoE status, suggesting that other factors may contribute to the AD etiology [60].

In conclusion, evidence indicates that mitochondrial abnormalities are plausible risk factors in the spectrum of chronic oxidative stress in AD, eventually contributing to synaptic failure and neuronal degeneration. Mitochondria seem to be affected early on in both sporadic and familial AD and the changes in these organelles are inherited through a maternal pathway. Preliminary evidence suggests that early mitochondrially therapeutic investigations may be an important target in delaying AD progression and in treating AD patients.

Conflict of interest

All authors declare the absence of conflict of interest.

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