Chapter

# Mitochondria in the Cerebral and Cerebellar Cortex in Alzheimer's Disease, Target for a Therapeutic Approach

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## Abstract

Alzheimer's disease remains the main cause of dementia in advanced age worldwide. Among the etiopathological background of the disease mitochondrial alterations may play a crucial role, given that they are closely related to metabolic and energy deficiency in neurons, glia, and endothelial cells in Alzheimer's disease and other neurodegenerative disorders. In a series of morphological and morphometric studies of mitochondria in the cerebrum and the cerebellar cortex in Alzheimer's disease, by electron microscopy, we described marked morphological and morphometric alterations. The most frequent ultrastructural alterations of the mitochondria consist of disruption of the cristae, accumulation of osmiophilic material, and marked changes of shape and size in comparison with the normal controls. Mitochondrial alterations were particularly prominent in dendritic profiles and dendritic spines. The ultrastructural study of a substantial number of neurons in the cerebellum revealed that mitochondrial alterations do not coexist, as a rule, with the typical Alzheimer's pathology, such as cytoskeletal alterations, amyloid deposits, and tau pathology, though they are frequently observed coexisting with alterations of the cisternae of the Golgi apparatus. Therapeutical regimes targeting mitochondria may be beneficial in early cases of Alzheimer's disease.

**Keywords:** Alzheimer's disease, Mitochondria, Electron microscopy, Oxidative stress Treatment, cerebrum, cerebellum

## 1. Introduction

Alzheimer's disease is the main causative factor of presenile and senile dementia [1] involving a large number of potential pathogenetic mechanisms, which for years was extinguishing the mental capacities, affecting seriously the cognition of the patients and leading to a tragic epilogue of the life with many social, economic and humanitarian consequences.

The phenomenology of familial or sporadic Alzheimer's disease is the final act of a drama, which gradually was causing selective and progressive neuronal loss [2], extensive synaptic alterations [3, 4], progressive neurofibrillary degeneration [5] resulting in intracellular accumulation of hyperphosphorylated tau protein [6], in the form of neurofibrillary tangles, with a parallel accumulation of extracellular

deposits of Aβ peptide forming neuritic plaques with an obvious microglial involvement [7]. The accumulation of the Aβ peptide as the main causative factor in Alzheimer's disease has been the core of the amyloid cascade hypothesis, which gained a considerable reputation, attempting to interpret all the pathological phenomena in the stream of the morphological and functional disintegration in Alzheimer's disease [8].

However, a substantial body of evidence underlines the increasing differentiation from the amyloid hypothesis [9] and emphasizes the crucial role that mitochondrial alterations and dysfunction may play in the pathogenesis of Alzheimer's disease and other neurodegenerative disorders [10–14].

Mitochondria are double membraned organelles, which are the cardinal energy suppliers of the eukaryotic cells by generating ATP, via oxidative phosphorylation. Mitochondria have their circular, double-stranded DNA (mtDNA), encoding thirteen proteins essential for oxidative phosphorylation [15], which is continuously processed by five protein complexes of the respiratory chain (complexes I-V).

Mitochondrial DNA plays reasonably a crucial role in the homeostatic mechanisms of the cell, by providing the essential energetic background for most of the cellular procedures. Moreover, mitochondrial DNA is also involved in a significant number of functional pathways, concerning cellular signaling by generating reactive oxygen species (ROS) synthesis of neurotransmitters at the presynaptic terminals. It is reasonable, that based on their multidimensional activity, mitochondria would be versatile structures, continuously renewed by fusion and fission [16] and frail to degradation thru mitophagy [17, 18].

Mitochondrial morphology is mainly modulated by the neurofilaments and microtubules, given that mitochondria are mostly transported along the microtubules [19], expressing at the same time an immediate adaptation to energetic needs and immune responses of the cells [20]. The fact that mitochondria have an antiviral signaling protein (MAVS), in connection to the outer membrane, emphasizes their importance in activating immune reactions [21] and participating in antiviral responses [22].

In Alzheimer's disease, the mitochondrial alterations, are responsible for the reduced energy production, oxidative stress, and the inflammatory reactions [23], which are among the early phenomena of the disease [24, 25], in the broad spectrum of the functional and morphological alterations [26, 27], which occur affecting progressively the neuronal and synaptic integrity.

Mitochondrial alterations resulting in substantial oxidative stress have been described in a considerable number of neurodegenerative diseases [28–30], a fact which emphasizes the importance of mitochondria morphological and functional integrity in the normal life and long survival of neurons and glial cells. Oxidative stress triggers also the initiation of a real cascade of pathological phenomena, including the modulation of innate immunity, which provokes a further mitochondrial dysfunction, given that mitochondria and mtDNA are very sensitive to oxidative stress [31, 32]. Besides, the association of oxidative stress with the increased accumulation of calcium ions [33], would also be considered among the principal causes of apoptosis [34].

Oxidative stress in Alzheimer's disease is mostly related to amyloid β (Aβ) accumulation in the neocortex [35, 36], which is a phenomenon playing a crucial role in the pathogenetic process of Alzheimer's disease [37]. The mitochondrial dysfunction has culminated with the existent beta-Amyloid toxicity in connection with the decreased rate of glycolysis [38] and the inhibition of the mitochondrial cytochrome c oxidase by a dimeric conformer of Aβ42 [39, 40]. Besides, the increasingly synthesized reactive oxygen species (ROS), aggravate the mitochondrial dysfunction, increase the mitochondrial Ca load [41], initiating mitophagy eventually [42].

However, mitochondrial ROS in low levels may play a positive role acting as second messengers and controlling several physiological processes [43]. Also, ROS are considered as being responsible for NLRP3 inflammasome activation [44, 45].

In excessive ROS synthesis the endogenous antioxidant defense system, such as superoxide dismutase, glutathione peroxidase, superoxide reductase, catalase, are unable to counteract the ROS's vulnerability. It is also significant, that cytosolic mtDNA may activate the NLRP3 inflammasome increasing, even more, the inflammatory reactions [46].

Also, the hyperphosphorylated tau protein interacts with the voltage-dependent anion channel 1 (VDAC1) protein, affecting mitochondrial pores and deteriorating mitochondrial activity [47]. In a parallel way, caspase-cleaved tau impairs mitochondrial dynamics in Alzheimer's disease [48]. Therefore, it seems that the convergence of amyloid and tau pathology on mitochondria impair synergistically the mitochondrial function and exacerbate oxidative stress [49].

From the morphological point of view, the shape and the size of mitochondria are highly variable depending upon the fusion and fission processes, which are regulated by mitofusins (Mfn-1 and Mfn- 2) and optic atrophy protein- 1 (OPA- 1) [50]. From the morphometric point of view, the number of the mitochondria varies in the soma and neuronal processes, according to the energy state of the cell, given that they are transported and accumulated to regions where energy demands and ATP consumption are particularly high [51].

In Alzheimer's disease, morphological alterations of the mitochondria have been described [11, 52, 53] even in the early cases of the disease [11] coinciding with dendritic and synaptic pathology [54]. Some evidence suggests that the interaction of mitochondrial fission protein DRP- 1 with the Aβ peptide and the hyperphosphorylated tau protein results in mitochondrial fragmentation increasing therefore the mitochondrial damage [55].

Mitochondrial trafficking in Alzheimer's disease plays also an important role in abnormal mitochondrial positioning and accumulation. Mitochondrial motility is controlled normally by kinesin and dynein which are powered by ATP hydrolysis, whereas the immobilization of mitochondria in places of high energy consumption is controlled by syntaphilin [56]. In Alzheimer's disease, the hyperphosphorylated tau protein at AT8 sites (ROS), as by-products of the respiration chain, aggravates the mitochondrial dysfunction, increases the mitochondrial Ca load and the neuronal oxidative stress [41], initiating mitophagy eventually [42].

However, mitochondrial ROS in low levels may play a positive role acting as second messengers and controlling several physiological processes [43]. I addition, ROS are considered as being responsible for NLRP3 inflammasome activation [44, 45].

On the contrary, in excessive ROS synthesis the endogenous antioxidant defense system, is unable to counteract the ROS's vulnerability. It is also significant the fact, that cytosolic mtDNA may activate the NLRP3 inflammasome increasing, even more, the inflammatory reactions [46].

Besides the hyperphosphorylated tau protein interacts with the voltage-dependent anion channel 1 (VDAC1) protein, affecting mitochondrial pores and deteriorating mitochondrial function [47]. In a parallel way, caspase-cleaved tau impairs mitochondrial dynamics in Alzheimer's disease [48]. Therefore, it seems that the convergence of amyloid and tau pathology on mitochondria impair synergistically the mitochondrial activity and exacerbate oxidative stress [49].

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In Alzheimer's disease, the hyperphosphorylated tau protein at AT8 sites [57] may impede the mitochondrial transport via microtubules, leading to improper distribution of mitochondria in giant spines and abnormal synapses [58, 59]. In parallel, oligomers of Ab peptide impair mostly the anterograde movement of mitochondria [60], increasing the number of stationary mitochondria in the neuronal soma.

The observation that mitochondrial abnormalities occur as an early phenomenon in Alzheimer's disease [11], supports the hypothesis that mitochondrial degeneration plays a primal role in Alzheimer's disease pathogenetic procedure, inducing a chain of pathological alterations involving tau and amyloid pathology. Morphological alteration of mitochondria, as well as abnormal interconnections of mitochondria with neurofilaments and microtubules, have been described at the level of electron microscopy in dendrites, axons, and synaptic components, a fact which emphasizes the close association of mitochondrial pathology with the broad pattern of the morphological changes in Alzheimer's disease [61, 62].

In this study, which is an extensive observation on electron microscopy, we attempted to describe the morphological alterations of mitochondria in early cases of Alzheimer's disease in neurons from various areas of the cerebral and cerebellar cortex, proposing also therapeutic approaches in the initial stages of Alzheimer's disease, based on the existing mitochondrial pathology.

## 2. Material and methods

### 2.1 Material

For describing the morphological alterations of neuron's organelles in early cases of Alzheimer's disease by electron microscopy we focused our observation mostly on the mitochondria in twenty-two cases, fourteen men and eight women, aged 52–87 years, who fulfilled all the clinical, neuropsychological [63] and laboratory diagnostic criteria of Alzheimer's disease.

The brains were derived from patients, who died accidentally 24 to 46 months following the clinical diagnosis of Alzheimer's disease. Additional 15 brains, macroscopically intact derived from apparently healthy persons of parallel age with the patients, were used as normal controls.

Multiple samples from many areas of the brain, namely from the prefrontal area of the frontal lobe, the frontal pole, the acoustic cortex, the visual cortex, the parietal lobe, the insula, the vermis of the cerebellum, and the cerebellar hemispheres were taken in a room temperature of $4^0$ C., 4 to 5 hours after death. Samples

also from the hippocampus, the hypothalamus, the mammillary bodies, the locus coeruleus, the red nucleus, the globus pallidus were excised under the same conditions, processed for electron microscopy, and the findings were described and in previous reports.

### 2.2 Method

All the specimens were immediately immersed in Sotelo [64] fixing solution, for three hours, then post-fixed in osmium tetroxide for 30 min. and dehydrated in graded alcohol solutions and propylene oxide. Thin sections were cut in a Reichert ultratome, contrasted, with uranyl acetate and lead citrate, and studied in electron microscopes Elmiscope 1 and Zeiss 9As. All the methodological and technical details of the preparation of the specimens for electron microscopy have been described extensively in our previous reports [65, 66].

Following the morphological description of the mitochondria, we proceeded also to morphometric estimations on micrographs of a standard magnification of 56.000X.

The methodology of the morphometric estimation of the mitochondria and the statistical analysis of the data have been extensively described in our previous reports [11, 65].

## 3. Results

The mitochondria in cases of Alzheimer's disease demonstrate a wide variation of size and shape in comparison with the mitochondria of normal control brains (**Figure 1**). We noticed that numerous mitochondria were small round or elongated, particularly those which were inside the dendritic profiles or the synaptic terminals (**Figure 2**).

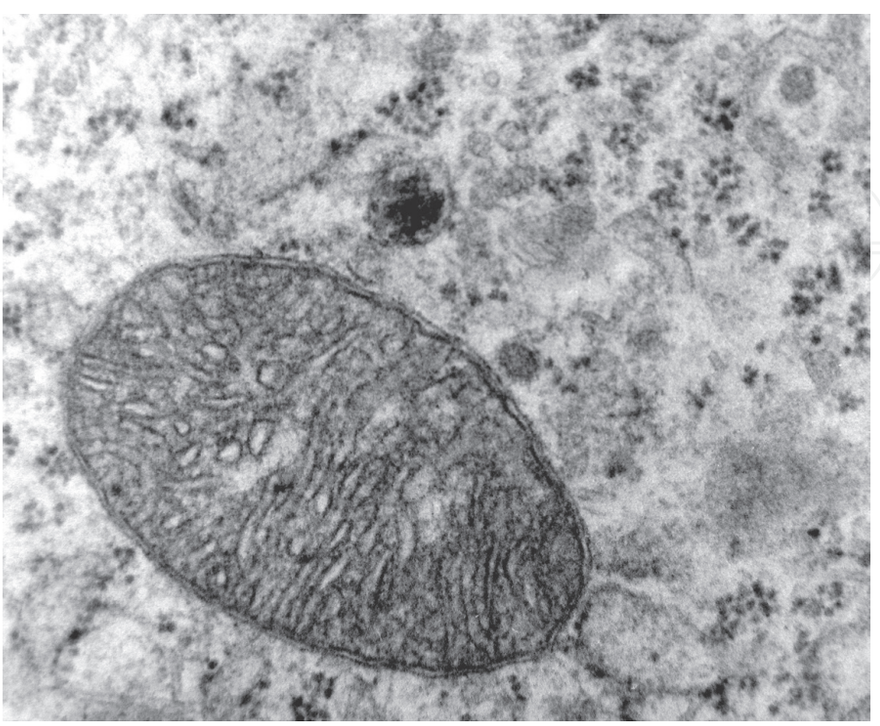

**Figure 1.**
*Mitochondrion of a Purkinje cell of the cerebellum of 75 years old man unremarkable neurologically. (Mag. 72,000 X).*

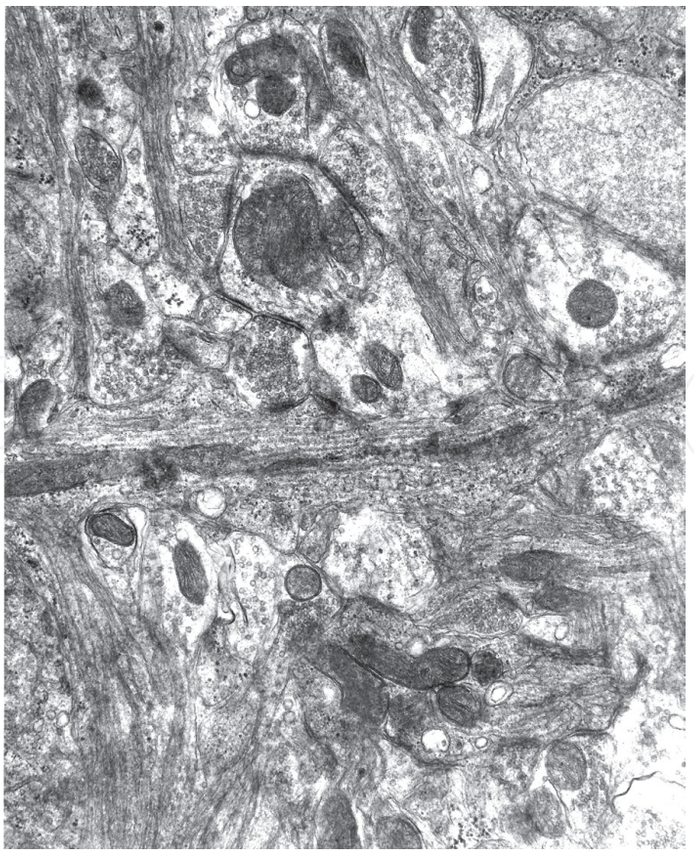

**Figure 2.**
*Mitochondrial alterations in synaptic terminals and dendritic profiles in the molecular layer of the cerebellum of a male patient aged 75 years, suffered from Alzheimer's disease. The disruption of the mitochondrial cristae is obvious. Electron micrograph (Mag.68,000 X).*

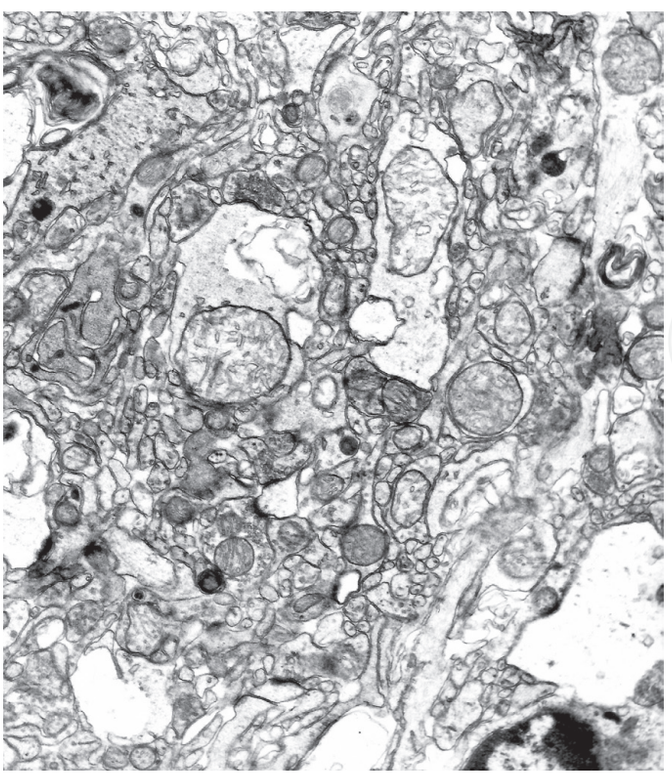

**Figure 3.**
*In the majority of the synaptic profiles the mitochondria are elongated demonstrating an impressive polymorphism, concerning the arrangement of the cristae. Mitochondria in a synaptic profile in the molecular layer of the cerebellum of a male patient aged 68, who suffered from Alzheimer's disease. Electron micrograph (Mag. 68,000X).*

A substantial number of mitochondria show disruption of the cristae, though others include osmiophilic material [10, 11, 13]. In the majority of the synaptic profiles, the mitochondria showed an impressive polymorphism, concerning the pattern and the arrangement of the cristae (**Figure 3**). That polymorphism was particularly obvious in dendritic profiles in acoustic and visual cortices, where morphological alterations of the mitochondria coexisted frequently with the fragmentation of the Golgi apparatus (**Figure 4**).

The ultrastructural study of the cerebellar cortex, in the vermis and the hemispheres, revealed impressive mitochondrial polymorphism in the soma of the neurons, the dendritic profiles (**Figure 5**), as well as in the axons and the synaptic terminals (**Figure 6**) [66, 67].

Besides, the electron microscopy study revealed that morphological alterations are frequently seen in neurons of the prefrontal cortex, which included mostly small round mitochondria, with an abnormal arrangement of the cristae (**Figure 7**). Abnormal polymorphic mitochondria in association with the fragmentation of the Golgi apparatus were also observed in the Purkinje cells of the cerebellar cortex in the vermis and the hemispheres [68], in the stellate cells of the molecular layer of the cerebellar cortex (**Figure 8**), as well as in a substantial number of neurons of the prefrontal cortex [69].

By the morphological analysis of the mitochondria in the cortex of the brain hemispheres in Alzheimer's disease, it was realized that mitochondrial pathology was associated as a rule with dendritic and spinal pathology [70].

From the morphometric point of view, the ellipsoid mitochondria in normal controls appear to have an average diameter of 650 ± 250 nm and a mean axial ratio of 1.9 ± 0.2. The round or global mitochondria in normal controls appeared to have a mean mitochondrial radius of 350 nm.

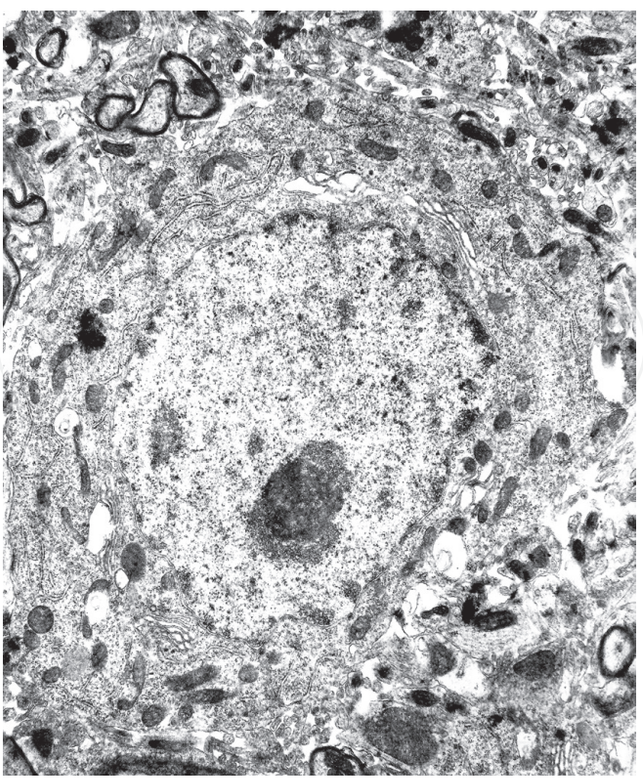

**Figure 4.**
*Mitochondrial polymorphism is obvious in neurons of the acoustic cortex, where morphological alterations of the mitochondria coexist frequently with the fragmentation of the Golgi apparatus. Electron micrograph of a neuron from the acoustic cortex of a female patient, who suffered from Alzheimer's disease at the age of 73 years, (Mag. 28, 000 X).*

In the brains of patients who suffered from Alzheimer's disease, the ellipsoid mitochondria of the neurons appeared to have an average diameter of 510 ± 250 nm and a mean axial ratio of 1.7 ± 0.2. The round mitochondria have had a mean radius of 280 nm. Also, the round mitochondria appeared to have a mean radius of 350 nm.

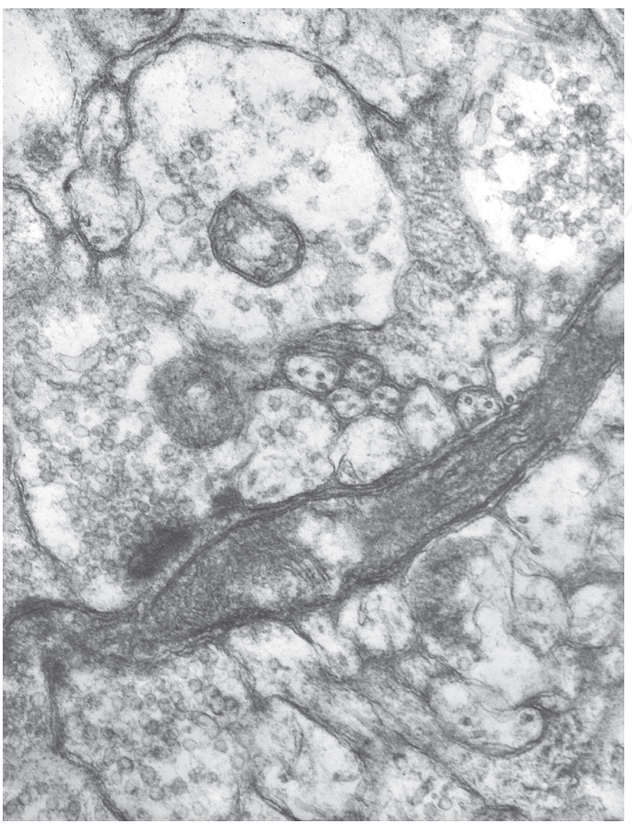

**Figure 5.**
*Very elongated mitochondrion in a dendritic profile in the mocelular layer of the vermis of a male patient aged 63 years, who suffered from Alzheimer's disease in the early stages. Electron micrograph (Mag. 128,000 X).*

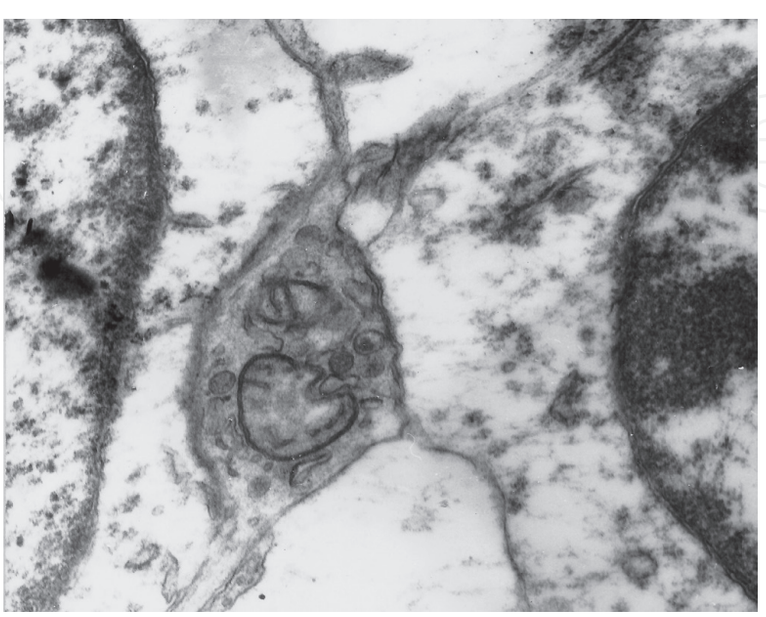

**Figure 6.**
*Fragmentation of the cristae and impressive polymorphism of mitochondria in dendritic spines in the cortex of the cerebellar hemispheres of a male patient who suffered from Alzheimer's disease at the age of 75 years. Electron micrograph. Mag.135.000X).*

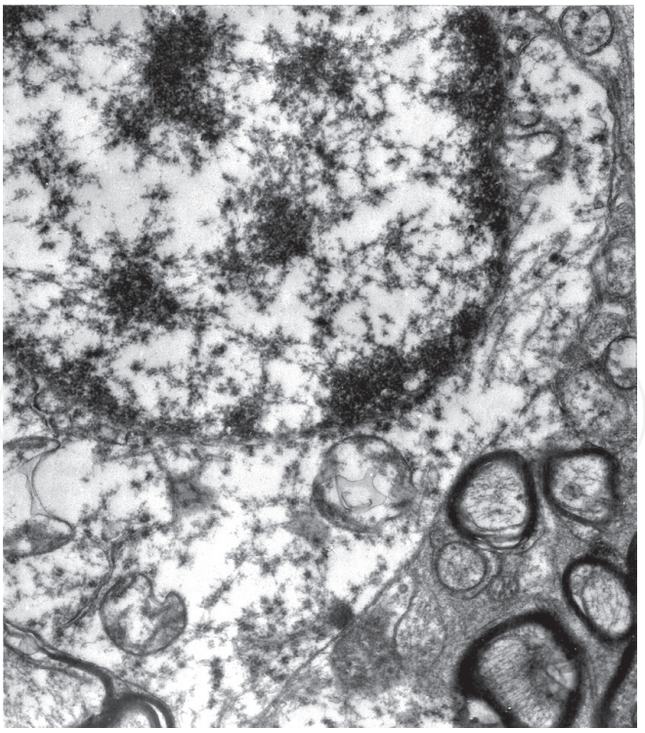

**Figure 7.**
*Small mitochondria with abnormal arrangement of the cristae in a neuron from the prefrontal cortex of a male patient aged 75 years, who suffered from Alzheimer's disease in the early stages. Electron microgram (Mag. 28,000 X).*

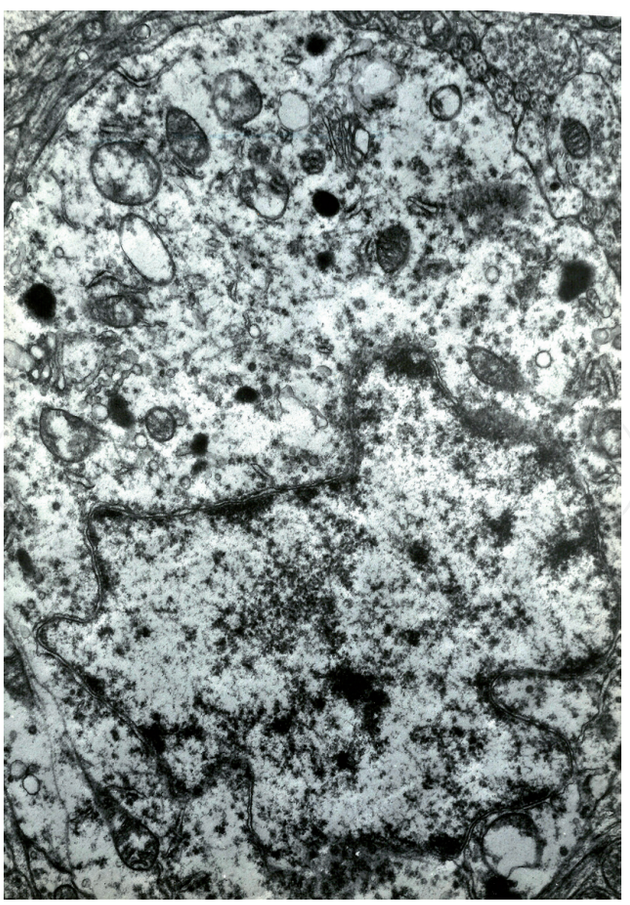

**Figure 8.**
*Morphological alterations of mitochondria, coexist frequently with fragmentation of Golgi apparatus. Small compact mitochondria and fragmented cisternae of Golgi apparatus in the soma of an interneuron (stellate cell) of the molecular layer of the cerebellum of a male patient aged 63 years, who suffered from Alzheimer's disease in the early stages. Electron micrograph (Mag. 28,000 X).*

## 4. Discussion

The morphological alteration of the mitochondria, which was extensively observed in the cortex of the brain hemispheres, the vermis and the hemispheres of the cerebellum pleads in favor of a generalized mitochondrial dysfunction in Alzheimer's disease, which would be associated with wide neuronal loss, impaired axoplasmic flow, dendritic pathology, and marked synaptic and spinal alterations, which would be seriously affecting the mental faculties of the patients [71].

The defective mitochondria in Alzheimer's neurons may not supply adequate levels of Adenosine Triphosphate (ATP), which is very important at the synaptic level for normal neural communication. It is expectable that the low levels of cellular ATP at nerve terminals may lead to extensive loss of synapses or cause defective function in the majority of them [72]. Besides, oxidative stress decreases the rate of choline recycling at the synapses, leading to Ach deficiency [73].

Many morphological alterations of AD could be linked to mitochondria changes since blockage of mitochondrial energy production shifts amyloid-protein precursor metabolism to the production of more amyloidogenic forms of amyloid [74]. Thus it induces the production of A68 antigen [75, 76], and activates the mitogen-activated protein kinase pathway [77–79].

Also, inadequate energy production impairs the mitochondrial motility in the soma, the axons, and the dendritic branches of neurons, resulting in trafficking jams aggravating even farther the mitochondrial function [80].

Accumulation also of transmembrane-arrested AβPP may block protein translocation, affecting, even more, the mitochondrial function. In a parallel way, the accumulated Aβ peptide in the mitochondrial membrane may be transported from the cytosol via mitochondrial translocases, which are located either in the outer or the inner mitochondrial membranes. Moreover, the Aβ peptide interacts with an Aβ-binding dehydrogenase (ABAD) in the mitochondria of patients suffering from Alzheimer's disease as well as in transgenic mice, suggesting that ABAD is closely related, to mitochondrial toxicity [81]. Overexpression of ABAD can increase oxidative stress, accelerating, therefore, neuronal death. However, ABAD may play an important role in the oxidation of alcohols, facilitating the reduction of aldehydes and ketones, and decreasing subsequently the metabolic stress [82].

The Aβ-peptide may interact with cyclophilin D (CypD), a component of the mitochondrial transition pore, inducing cytotoxicity [83]. Moreover, morphological alterations of mitochondria in AD may be related to the increased mitophagy, which is proved by the accumulation of mitochondrial autophagic elements in neurons of AD patients [84]. In AD the PINK1-Parkin-dependent mitophagy pathway may also be involved in mitochondrial pathology [85]. The prompt clearance of damaged mitochondria may result in increasing the density of normal mitochondria in dendrites and synaptic terminals, which is a fact ameliorating the synaptic function [86].

## 5. Suggestions on the treatment of Alzheimer's disease on the basis of mitochondrial pathology

Concerning the treatment of Alzheimer's disease, we would underline that the preclinical stage is frequently overlooked, because it might be characterized as mild cognitive impairment, with considerable consequences on the course and the treatment of the disease.

Following the clinical manifestation of the disease and the diagnostic documentation, many therapeutic regimes have been applied without any substantial beneficial effect. In the decade 2002–2012 more than 240 drugs, mostly cholinesterase inhibitors, and NMDA receptor antagonists, have been tried for the treatment or even the amelioration of the quality of life in patients suffered from AD [87, 88], without any obvious effectiveness. Besides, any strategy attempting to reduce the amyloid aggregations in the brain, despite the numerous trials, was not fruitful [89].

Based on mitochondrial pathology, in the limits of the broad pathogenetic spectrum of Alzheimer's disease, the mitochondria may be considered as the potential therapeutic targets, which might inhibit the stream of the neuropathological alterations and impede the clinical deterioration of the patients.

Strategists protecting the mitochondria in Alzheimer's disease would include the administration of efficient antioxidant factors, which might counteract the oxidative stress, and decrease ROS production [90].

Natural antioxidants that could penetrate the blood–brain barrier may be effective in the initial stage of Alzheimer's disease. The administration of Vitamins C, E, beta carotene, glutathione, Coenzyme Q10, epigallocatechin gallate, curcumin, lipoic acid, *Ginkgo biloba*, resveratrol, pramipexole, N-acetylcysteine, latrepirdine, idebenone, ubiquinone may reduce the production of ROS, suppressing the oxidative stress.

The tetracyclin Minocycline prevents also oxidative stress and controls the release of cytochrome c from mitochondria, inhibiting the activation of caspase-3 and the subsequent apoptosis [91], being therefore quite effective in the treatment of AD [92].

In a parallel way, the adaptation of the Cretic or Mediterranean diet, combined with frequent proper physical exercise, in the early stages of the disease, may stabilize the mental capacities of the patients for a non-limited period and postpone the tragic epilogue of the disease. Besides, prolonged administration of pyruvate may improve the working memory in the preclinical stage AD [93].

We have realized, by a detailed clinical and neuropsychological evaluation of a considerable number of patients, who suffered from Alzheimer's disease in the initial stages, that the quotidian administration of Riboflavin (Vit.B2) in a dose of 100–200 mg per day would play a positive role in inhibiting the course of the disease and stabilizing the mental faculties of the patients (Baloyannis, unpublished data). It is known that riboflavin serves as a flavoprotein precursor in the synthesis of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) [94, 95], which are electrochemically-active factors involved in regulatory pathways of mitochondria. Riboflavin serves also as a cofactor in fatty acid β-oxidation. Riboflavin deficiency may be involved in the pathogenetic mechanism of several neurodegenerative disorders [96, 97]. Thus, riboflavin supplementation may be enriching the therapeutical regime in some non-uncommon neurological conditions [98, 99] including Alzheimer's disease [100].

At the experimental level, mitochondrial-targeted molecules, such as MitoQ and Szeto- Schiller (SS) peptides have been used for increasing the concentration of antioxidants into mitochondria [101]. MitoQ exerts direct antioxidant action by scavenging superoxide, peroxyl, and peroxynitrite ROS. It seems also to contribute effectively, enhancing the mitochondrial biogenesis in a transgenic mouse model of Alzheimer's disease [102, 103].

The fact that the interaction of ABAD with the Aβ peptide may increase the toxic effects upon the mitochondria, suggests that ABAD inhibitors such as AG18051 [104] and RM-532-46, might be applied as therapeutic factors in the treatment of patients who suffer from AD.

Also, a decrease of the CypD in AD relieves the toxic effect that Aβ imposes on the mitochondria and may ameliorate the mental condition of the patients [83] improving the synaptic function by the restoration of mitochondrial activity [105]. Also, Oligomycin-sensitivity conferring protein (OSCP) is a crucial subunit of mitochondrial F1Fo ATP synthase, essential for its structural stability [106]. In Alzheimer's disease, deregulation of mitochondrial F1FO-ATP synthase was described [107]. It is reasonable to be hypothesized that OSCP would be a positive factor in the treatment of early cases of Alzheimer's disease.

The administration of factors that may regulate mitophagy, and cardiolipin-induced mitophagy [108] such as NAD+ precursors, actinonin (AC), spermidine, urolithin A (UA), rapamycin, and doxycycline may also control the mitochondrial unfolded protein response (UPRmt), reducing the Aβ accumulation and proteotoxicity [109].

The administration of metformin can increase also the resistance of the mitochondria to oxidative stress [110]. The supplementation with nicotinamide may be beneficial in the early stages of Alzheimer's disease improving the cognition of the patients [111].

The administration of mitochondrial uncoupling factors such as 2, 4-dinitrophenol (DNP) may be effective too, protecting mitochondria and stabilizing neuronal function in animal models of AD [112, 113]. Besides, the administration of galanthamine hydrochloride may control autophagy [114], as was noticed by the decrease of autophagosome formation.

Recently it was found that vacuole membrane protein 1 (VMP1), which is located in the endoplasmic reticulum (ER), may play a crucial role in mediating autophagy [115] and controlling mitochondrial morphology, given that numerous mitochondria are damaged upon VMP1 deficiency [116]. It must be underlined that autophagy is an important mechanism for maintaining cell homeostasis by liberating the cell from the accumulation of misfolded proteins and other undesired elements [117].

Erythropoietin (EPO) [118], is a cytokine essential for erythroid development and maturation, playing a beneficial role in progressive degenerative diseases [119] exercising among others a protective effect on mitochondrial morphology, facilitating the activity of cellular bioenergetics [120].

Furthermore, the relation between mitochondria and endoplasmic reticulum (ER) referred to as the MAMs [121, 122], which are enriched in presenilin proteins [123], may play an important role in the pathogenetic cascade of Alzheimer's disease, given that they are involved in the production of intracellular Aβ [124], and play also a substantial role in cellular Calcium homeostasis [125, 126] and lipid transport between the endoplasmic reticulum and the mitochondria [127]. A deep understanding of MAMs involvement in the pathogenesis of AD may provide new ways of therapeutic approach in the early stages of AD.

The protection of mitochondria by the Szeto-Schiller (SS) peptides, particularly the SS31 tetra-peptide [128, 129], which is targeted to the inner mitochondrial membrane, revealed that it may have protective effects against mitochondrial and synaptic toxicities in APP transgenic mice [130], reducing also mitochondrial fragmentation and increasing mitochondrial transport in AD neurons [131].

Mitochondrial biogenesis is decreased in AD [132] due to the decrease of the rate of mitochondrial division, a fact that aggravates substantially the mitochondrial dysfunction [133]. Supporting mitochondrial biogenesis may contribute to the therapeutic confrontation of AD [134]. Therefore, the administration of Nicotinamide riboside [135, 136], as well as of pioglitazone or rosiglitazone may improve the mental condition of the patients [137, 138].

In experimental models, the administration of melatonin contributed considerably to improving the biogenesis of mitochondria [139]. Besides, melatonin inhibits amyloidogenesis and promotes the non-amyloidogenic pathway [140], restoring also the equilibrium of the Ca2+ [141]. Recent neuropathological findings revealed that melanin-concentrating hormone (MCH) neurons in the lateral hypothalamic area of patients who suffer from AD undergo degeneration, a fact that may interpret the frequent sleep and metabolic disorders of the patients [142].

Also, it was observed, that the Zinc ion (Zn2+) supplementation in experimental models, contributed to ameliorating the mitochondrial function by the restoration of BDNF levels and improving cognition, although it might have negative effects on some cells lines [143].

A substantial body of evidence suggests that among the causative factors in the multifactorial labyrinth of AD, the hemodynamic disturbances resulting in chronic hypoperfusion of the brain [144–147] play also a crucial role in attenuating the mitochondrial dysfunction [148] and aggravating subsequently the mental condition of the patients [149]. The improvement of the blood supply of the brain should be among the principal therapeutic strategists in AD.

Mitochondrial alterations may be estimated as potential biomarkers, which would provide a prognostic response to treatment [150]. Mitochondria may be considered as a significant strategic point for therapeutical interventions in early cases of Alzheimer's disease.

## 6. Conclusions

Mitochondrial alterations may play an important role in the pathogenesis of Alzheimer's disease. In early cases of Alzheimer's disease marked morphological and morphometric alterations have been described by electron microscopy in various areas of the brain and the cerebellum.

The morphological alterations of the mitochondria seem to be independent of Alzheimer's pathology, given that they are observed in areas without or with minimal neuritic plaques or tau pathology.

Mitochondria may be considered as a significant strategic point for therapeutical interventions in early cases of Alzheimer's disease.

## Conflict of interest

The author declares no conflict of interest.

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