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Mitochondria and Alzheimer's Disease: An Electron Microscopy Study

Stavros J. Baloyannis

Abstract

Alzheimer's disease is a progressive, irreversible presenile or senile neurodegenerative disorder, implicating mainly the mental faculties, characterized by decline of memory and judgment, learning impairment, loss of professional skills and verbal capacities, alterations of social behavior, decline of motor skills and eventual disarrangement of the autonomic equilibrium. Among the pathogenetic factors, oxidative stress and mitochondrial dysfunction may play an essential role. Alterations of mitochondria may enhance amyloid toxicity, which in turn may aggravate mitochondrial dysfunction. We describe ultrastructural alterations of mitochondria in the soma of neurons, in axons, dendritic profiles and synaptic terminals, in astrocytes in early cases of Alzheimer's disease on various areas of the cerebral and the cerebellar cortex, the hippocampus, the hypothalamus, the mammillary bodies and the medial geniculate body. The morphological and morphometric study of the mitochondria revealed an impressive polymorphism at any area of the brain. The mitochondria demonstrated variation of size and shape, fragmentation of the cristae and marked changes of their structure. The most dramatic mitochondrial alterations were observed in dendritic profiles, spines and synaptic terminals. A substantial number of astrocytes demonstrated mitochondrial alterations, which coexisted with fragmentation of Golgi apparatus and dilatation of the cisternae of the smooth endoplasmic reticulum. On the basis of our observations, we feel that therapeutic strategies aiming at protecting the mitochondria might be beneficial in the treatment of early cases of AD.

Keywords: Alzheimer's disease, mitochondria, Golgi apparatus, astrocytes, synapses, electron microscopy

1. Introduction

Alzheimer's disease (AD) is one of the most enigmatic and multidimensional neurodegenerative diseases of the brain. The high incidence in aging, the ongoing number of the patients and the social, humanitarian and economic impact of the disease [1], as well as the irreversible course of the disease, the failure of therapeutic interventions [2] and the fatal outcome impose on the neuroscientists and the society a combined attempt for the amelioration of the quality of life of the patients at least by the reduction of risk factors in the initial stages of the disease [3].

The clinical manifestation of Alzheimer's disease, starting from the inability to encode new memories, includes progressive and irreversible cognitive decline, affecting memory and judgment, loss of professional skills and verbal capacities, impairment of learning new informations and gradual disarrangement of the social behavior [4, 5] resulting in isolation of the patient in the framework of an obvious functional incapacity, encountering in vegetative state eventually.

The neuropathological background of AD mostly consists of selective neuronal loss [6, 7], substantial morphological and morphometric alterations of the synapses [8–11], marked mitochondrial alterations, even in the initial stages of the disease [12, 13], tau pathology [14] resulting in the formation of neurofibrillary tangles (NFT) by the accumulation of hyperphosphorylated tau protein [15], many inflammatory phenomena, alterations of brain capillaries [16] and various extensive extracellular deposits of Aβ peptide's polymers, in the form of polymorphic neuritic plaques, [17, 18].

Pathological alterations of the organelles in the soma, the axons, the dendrites and the synapses of neurons are observed in electron microscopy, even in the initial stage of the disease [19] in areas with minimal typical Alzheimer's pathology, namely aggregations of Aβ peptide and neurofibrillary tangles. The majority of the alterations of the organelles in Alzheimer's disease particularly concern the Golgi complex [19], the microtubules, the synaptic vesicles and mostly the mitochondria [20–22].

The etiopathology of the sporadic cases of Alzheimer's disease remains a real problem in spite of the multidimensional extensive ongoing research in the last decades [23, 24] on the crucial fields of genetics [25, 26], molecular biology [27, 28], neuropathology [29, 30], neuroimmunology [31, 32], pathophysiology [33], neuroimaging [34] and neurochemistry [35–38].

The pathogenetic mechanisms embrace a diverse range of hypotheses which attempt to decipher the real cause of memory and reasoning decline in AD. Among the many hypothesis, the most mattering are (a) the amyloid hypothesis [39, 40], (b) the metabolic and synaptic dysfunction hypothesis [41], (c) the hypothesis of translational neurodegeneration [42], (d) the tau hypothesis [43], (e) the hypothesis of neuroinflammation [44], (f) the cholinergic hypothesis [45], (g) the oxidative stress [46], (h) the vascular hypothesis [47, 48], (i) the glucose hypometabolism hypothesis [49], (j) the autoimmune hypothesis [50], (k) the endocrine hypothesis [51, 52], (l) the mitochondrial dysfunction [53, 54] and (m) the Golgi complex hypothesis [55–57].

Many of those hypotheses are basely interrelated, such as the amyloid hypothesis and the oxidative stress ones [58, 59], the amyloid and the tau hypothesis [60], the oxidative stress and the mitochondrial dysfunction [61], the mitochondrial dysfunction, energy deficiency and oxidative stress [61, 62], the mitochondria dysfunction and the synaptic pathology [22, 63], the tau pathology and the vascular hypothesis [64], the cholinergic dysfunction and the amyloid hypothesis [65], amyloid, tau and neurodegeneration hypothesis [66], the mitochondria and the dendritic hypothesis [67–69] and the immune reactions, microglia, tau, Aβ peptide, lipid processing and neurodegeneration hypothesis [70–73].

Mitochondria hypothesis advocates in favor of the important role that mitochondrial dysfunction may play in the early stages of Alzheimer's disease [21] by inducing energy deficiency and oxidative stress [22], which would be associated with β-amyloid (Aβ) neurotoxicity. It is well known that mitochondria, which has been defined as organelles in tissue culture since 1914 [74] are normally involved in aging

process [75–77], since mitochondrial function declines as the age advances, resulting in decrease of ATP production and increase of free oxygen radicals formation, given that ATP synthase is located in the inner mitochondrial membrane, playing a key role in the energy homeostasis of the cell.

In addition, morphological alterations of mitochondria, resulting in deficiency of mitochondrial electron transport proteins, with considerable consequences upon the energy supply of nerve cells have been described in Alzheimer's disease and other degenerative conditions of the brain [12, 21, 78, 79], which are also associated with oxidative stress [80].

It is also particularly noticeable that morphological abnormalities of mitochondria are seen in neurons lacking neurofibrillary tangles [12] suggesting that mitochondrial degeneration might be among the earliest signs of Alzheimer's morphological alterations.

The fact that maternal influence seems to be a risk factor for Alzheimer's disease morbidity, according to epidemiologic studies [81, 82], and to combined neuropsychological and neuroimaging investigations [83] plead in favor of the substantial role that mitochondria may also play in the pathogenetic cascade of Alzheimer's disease.

In this perspective article, we attempted to describe the ultrastructural alterations of mitochondria in various neocortical and subcortical areas of the brain of patients who suffered from Alzheimer's disease at the early stages.

2. Material and methods

2.1 Material

This electron microscope study is based on examination of 25 brains obtained at autopsy 2–7 hours after death at a room temperature of 40°C. All of the brains were derived from patients aged 55–80 years, who have had a history of dementia, which was definitely diagnosed 1 or 3 years prior to the end of their life.

The patients fulfilled on repeated clinical examinations and assessments all the psychological, psychiatric and neurological criteria of AD [84–86]. The patients have had 18 years of education, and had a fluency in their native language, two of them being also bilingual with equal fluency in both of the languages. The usual diagnostic assessment was based on the medical history, the physical examination, including cardiological investigation, neurological examination, psychiatric evaluation and detailed neuropsychological testing.

The cognition of the patients was evaluated by battery of neuropsychological testing [87], including mini mental state examination (MMSE) [88, 89], dementia rating scale (DRS) [90, 91], ADAS-COX test [92, 93] and the brief memory executive test (BMET) [94].

All the patients underwent an EEG examination and a carotid examination by duplex Doppler. Neuroimaging was performed including computerized tomography (CT), magnetic resonance imaging (MRI) of the brain and a single-photon emission computed tomography (SPECT) [95]. All the methods of clinical and laboratory investigations were evocative for Alzheimer's disease. The patients passed away due to heart arrest.

In addition, we dissected and examined in electron microscopy 25 brains, which were unremarkable from the neuropathological point of view, derived from apparently healthy individuals of the same age range with the AD patients, using them as normal controls.

2.2 Methods

2.2.1 Electron microscopy

Multiple samples of a small size (2 × 2 × 2 mm) were excised from the hippocampus, the prefrontal area of the cortex, the superior parietal lobe, the occipital pole, the visual cortex, the Hessl gyri of the temporal neocortex, the vermis of the cerebellum and the cerebellar hemispheres, the hypothalamus, the mammillary bodies and the medial geniculate bodies. The samples were selected bilaterally and immersed directly in Sotelo's fixing solution [96], composed of 1% paraformaldehyde, 2.5% glutaraldehyde in cacodylate buffer 0.1 M, adjusted at pH 7.35.

Then all the specimens were post fixed in 1% osmium tetroxide for 30 min at a room temperature of 18°C and dehydrated in graded alcohol solutions and in propylene oxide twice. After dehydration, the specimens were embedded in araldite mixture and cut in ultrathin sections by a Reichert ultratome.

The sections were placed on the grids where they were contrasted with uranyl acetate and lead citrate, and studied in a Zeiss electron microscope of the type 9aS.

The study electron microscopy examination was particularly focused on the morphology of the organelles, mainly on the mitochondria of neurons and astrocytes. In addition, the Golgi complex, the endoplasmic reticulum, the endosomes, the dendritic profiles, the spines, the axons, the axonic collaterals and the synaptic components were studies in all of the sections.

The morphometric estimation was carried out on micrographs of a standard magnification of 56,000×. The analysis of each macrograph was performed with an image analyzer. The surface area of mitochondria as well as the volume and the circularity ratio (CR) were calculated on a total of 8000 mitochondria.

The statistical analysis of the data was evaluated by Student t tests.

3. Results

The ultrastructural study of the mitochondria revealed an impressive polymorphism at any area of the brain. The mitochondria demonstrated a wide variation of size and shape in the soma, the axons, the dendrites and the synaptic terminals in the majority of the neurons (**Figure 1**). The majority of the mitochondria demonstrated fragmentation of the cristae and obvious disarrangement of their interior
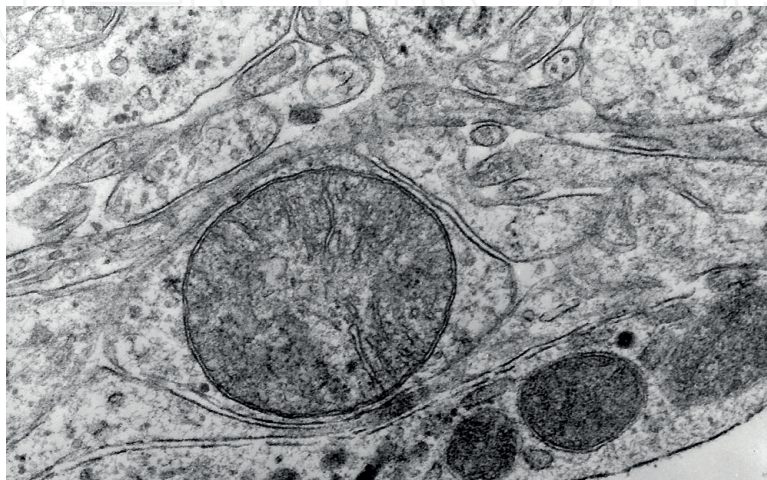

Figure 1.
Large round mitochondrion in a dendritic profile in the molecular layer of the cerebellum in a case of AD. Electron micrograph Mag. 248,000×.

structure (**Figures 1** and **2**). The mitochondria in the presynaptic terminals were either small and round with few cristae (**Figure 3**) or very large showing disruption of the cristae (**Figure 4**).

It should be underlined that in areas of the brain with minimal Alzheimer's pathology, such as the cerebellum, the visual, the acoustic cortex, the mammillary bodies and the hypothalamus, mitochondria demonstrated obvious morphological alterations. Very large mitochondria were observed in the soma and the dendritic profiles of Purkinje cells (**Figure 5**), in the granule cells (**Figure 6**) as well as in the climbing fibers, the mossy fibers and the synaptic terminals of parallel fibers (**Figure 7**). Large number of small mitochondria with disruption of cristae was observed in the visual cortex (**Figure 8**) and the acoustic cortex (**Figure 9**).

Mitochondrial alterations were also observed in many synaptic profiles in the suprachiasmatic and the paraventricular hypothalamic nuclei of AD brains (**Figure 10**).

The morphometric estimation of the mitochondria in the soma, the dendrites and the dendritic spines of a considerable number of neurons of the suprachiasmatic nucleus in AD brains revealed that they have an average diameter of 440 ± 250 nm and a mean axial ratio of 1.7 ± 0.2 [97].

The polymorphism of the mitochondria was the most frequent finding at any studied area of the cortex of the brain hemispheres, the cerebellum and the subcortical structures. Small round mitochondria intermixed with very large ones with disarrangement of the cristae and accumulation of fibrillary elements (**Figure 11**) or dense osmiophilic material (**Figure 12**). The mitochondria in the dendritic profiles and the synaptic terminals at the prefrontal cortex were large occupying the majority of the volume of the synaptic component (**Figure 1**). Large mitochondria were also observed in axonic collaterals among the myelinated fibers at the prefrontal and the parietal cortices (**Figure 13**). Small mitochondria were frequently observed in association with Golgi complex alterations in the soma of neurons and astrocytes (**Figure 14**).

A substantial number of astrocytes demonstrated small or very large mitochondria with disruption of the cristae in association with dilated cisternae of the smooth endoplasmic reticulum (**Figure 15**). Small mitochondria were also observed
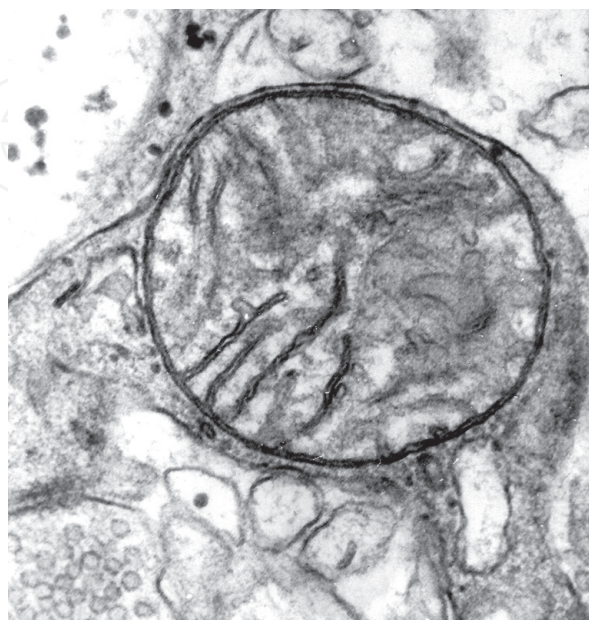

Figure 2.
Large mitochondrion in a postsynaptic terminal in the molecular layer of the cerebellum in a case of AD. The disruption of the mitochondrial cristae is obvious. Electron micrograph Mag. 248,000×.
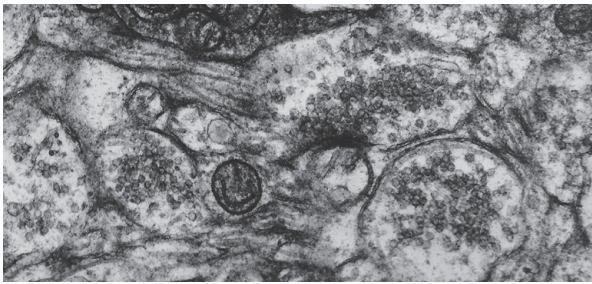
Figure 3.
Small round mitochondria in Purkinje cell dendritic spines (postsynaptic components) in the molecular layer of the cerebellum in a case of AD. Electron micrograph Mag. 248,000×.
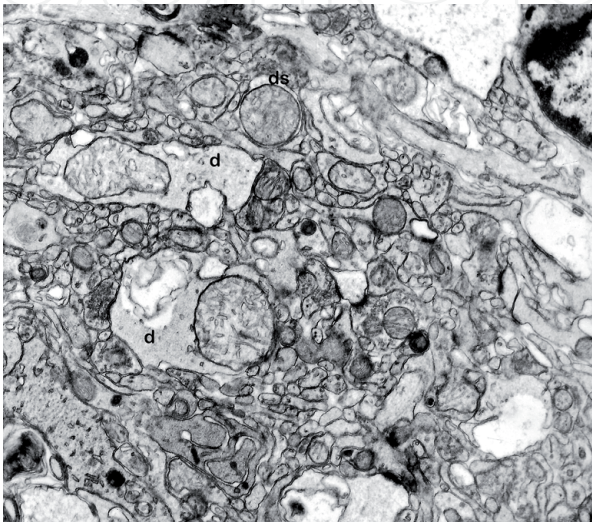

Figure 4.
Very large mitochondria in dendritic profiles (d) and dendritic spines (ds) in the molecular layer of the cerebellum in a case of AD. The disruption of the mitochondrial cristae and the disarrangement of the interior structure are obvious. Electron micrograph Mag. 56,000×.
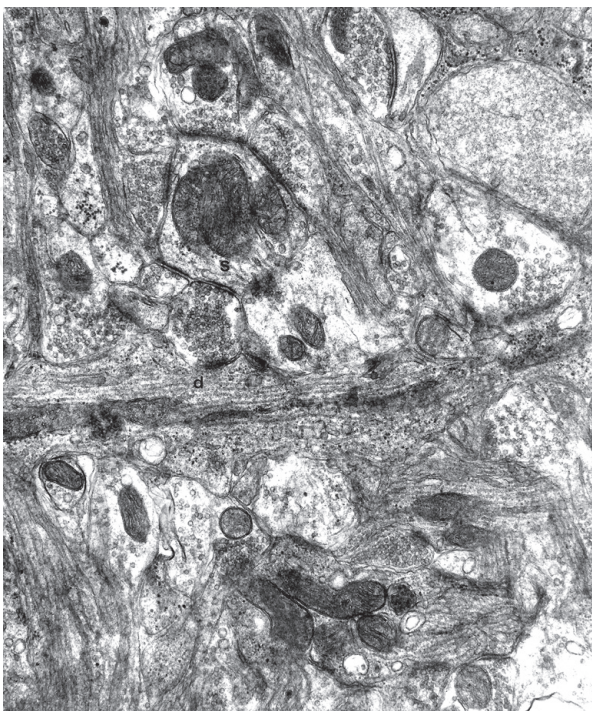

Figure 5.
Very elongated and large mitochondria in dendritic profiles (d) and dendritic spines (ds) in the molecular layer of the vermis of the cerebellum in a case of AD. The presynaptic terminals of the parallel fibers (pf) contain small round dense mitochondria. Electron micrograph Mag. 124,000×.
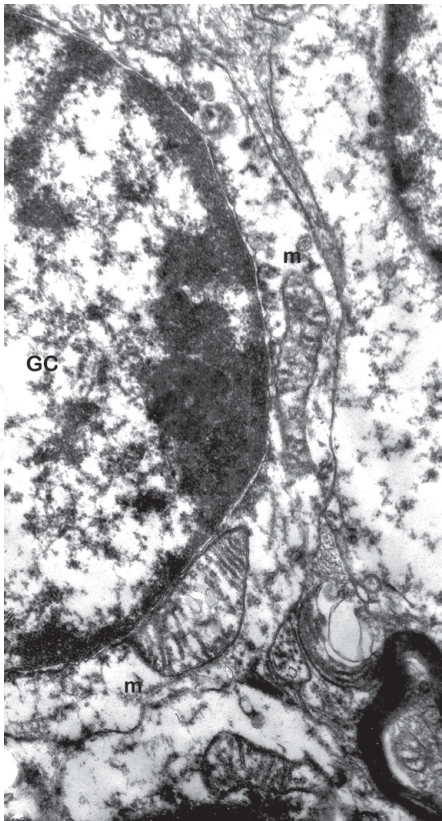
Figure 6.
Large abnormal mitochondria (m) in the perikaryon of a granule cell (GC) of the vermis of the cerebellum in a case of AD. Electron micrograph Mag. 124,000×.
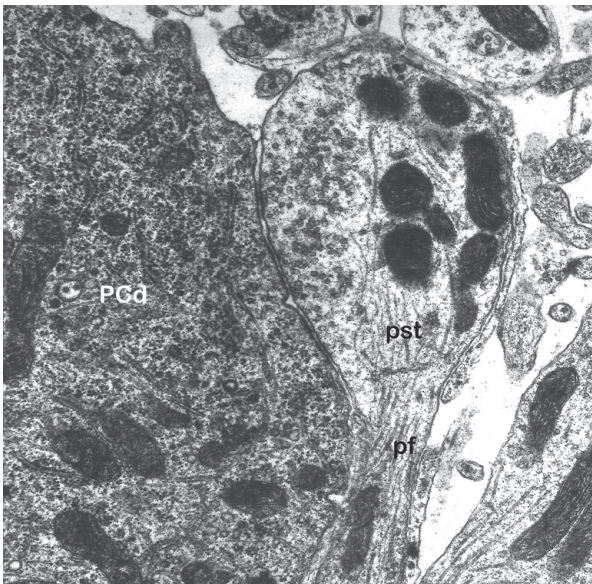

Figure 7.
Small dense mitochondria in a presynaptic terminal (pst) of a parallel fiber (pf) in contact with a large dendritic branch of Purkinje cell (PCd) in the molecular layer of the left cerebellar hemisphere in a case of AD. Electron micrograph Mag. 124,000×.

in oligodendrocytes in the subcortical white mater in association with dilated cisternae of the smooth endoplasmic reticulum and alterations of the Golgi complex (**Figure 16**).

The dendritic spines of the cortical neurons were dramatically reduced in number and size and most of the presynaptic terminals included small round and dense mitochondria and were also characterized by the dramatic poverty of the synaptic vesicles (**Figure 17**), a finding advocating in favor of a previous concept that the

Figure 8.
Mitochondria with obvious disruption of the cristae in presynaptic terminal (prs) in the visual cortex in a case of AD. Electron micrograph Mag. 124,000×.
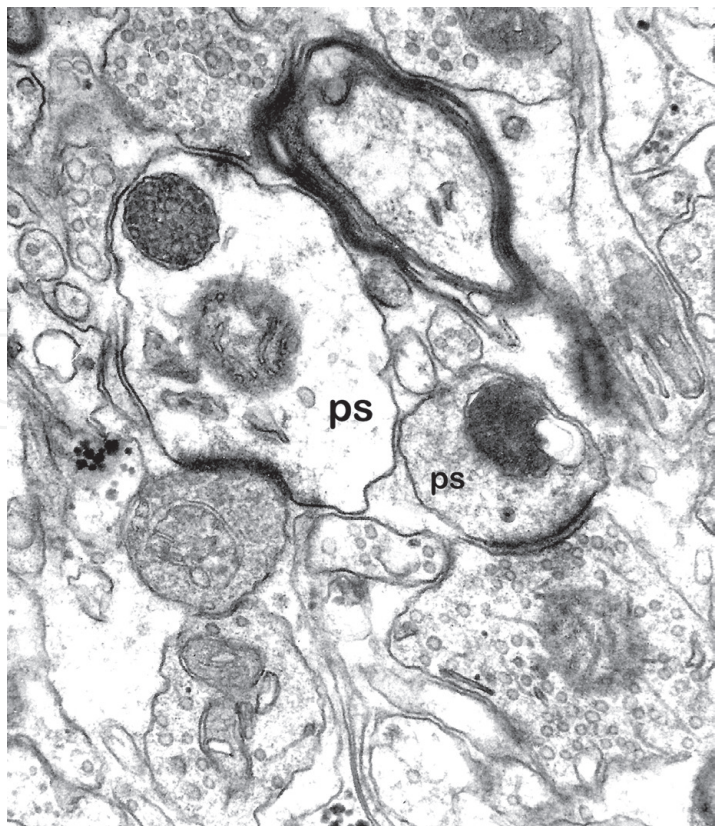

Figure 9.
Small dense mitochondria in postsynaptic terminal (ps) in the acoustic cortex in a case of AD. Electron micrograph Mag. 124,000×.
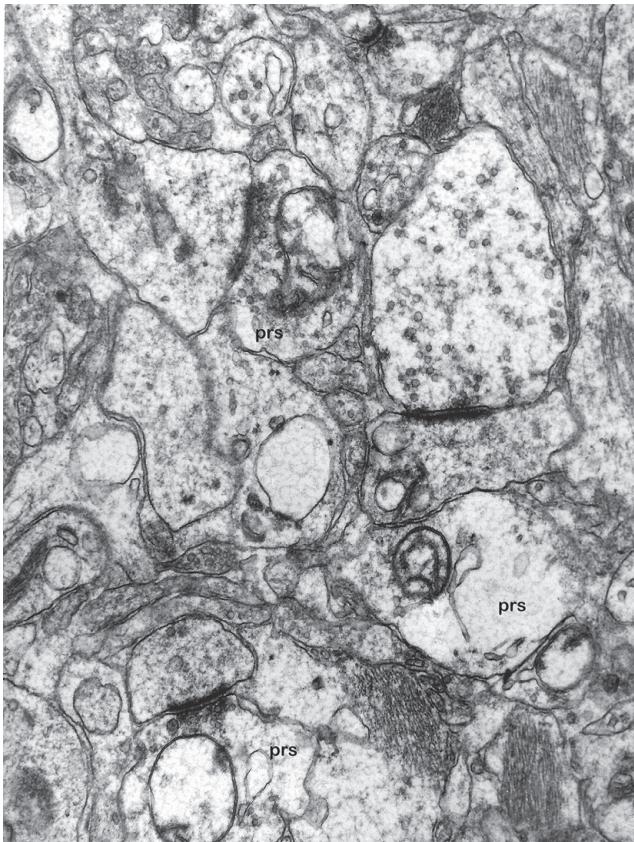
Figure 10.
Small abnormal mitochondria with disruption of the cristae and disintegration of the interior structure in the suprachiasmatic nucleus of the hypothalamus in a case of AD. Electron micrograph Mag. 124,000×.
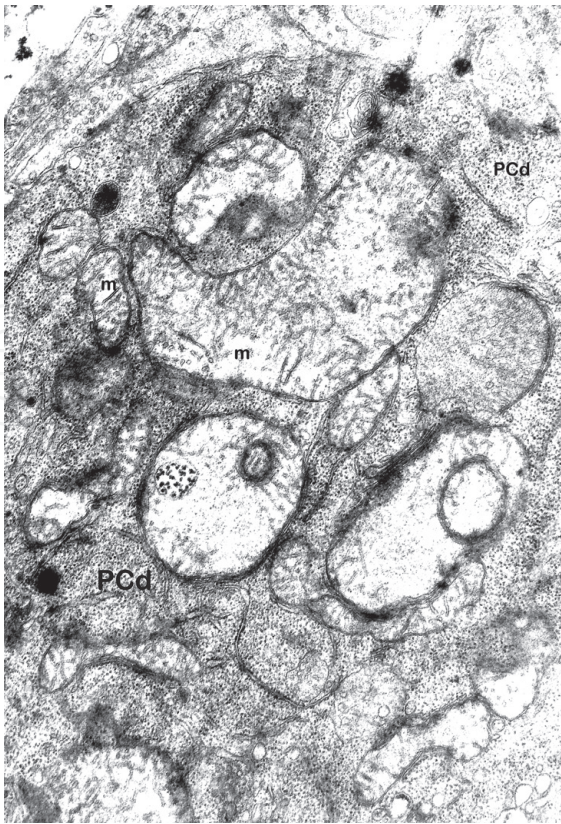

Figure 11.
Very large mitochondria (m) intermixed with small ones (m) in a dendritic profile of Purkinje cell (PCd) in the vermis of the cerebellum in a case of AD. Electron micrograph Mag. 124,000×.
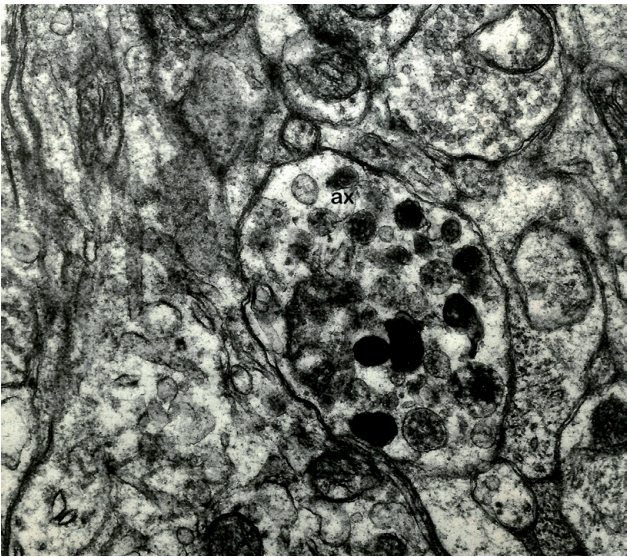
9

Figure 12.
Very small dense mitochondria in an axonic profile (ax) in the acoustic cortex in a case of AD. Electron micrograph Mag. 124,000×.
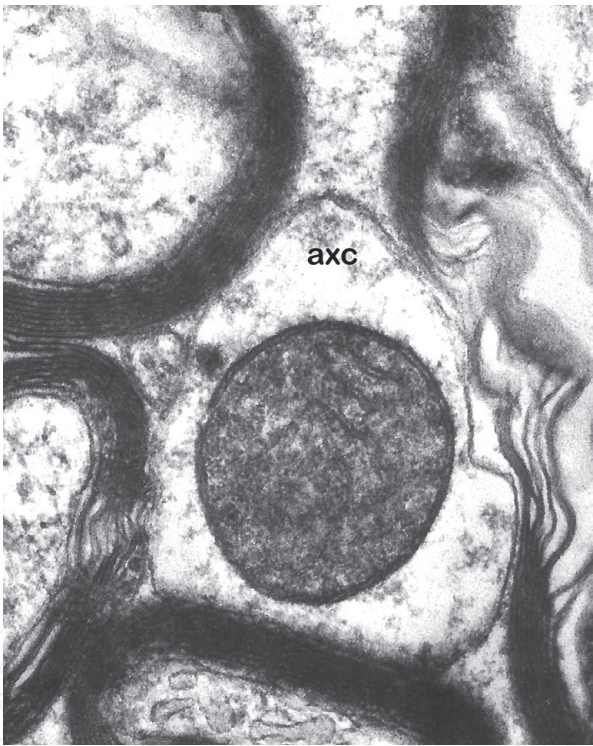

Figure 13.
Large mitochondrion in an axonic collateral among myelinated fibers in the prefrontal area of the cortex in a case of AD. Electron micrograph Mag. 124,000×.

morphological alterations of the synapses and dendritic spines coincide, as a rule, with marked mitochondrial alterations [22].

In morphometric estimation, the mitochondria in normal control aged brains appeared to have an average diameter of 250–650 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. In Alzheimer's disease, ellipsoid mitochondria of Purkinje cells appeared to have an average diameter of 250–510 nm and a mean axial ratio of 1.7 ± 0.2. Round mitochondria were characterized by a mean radius of 280 nm.

Figure 14.
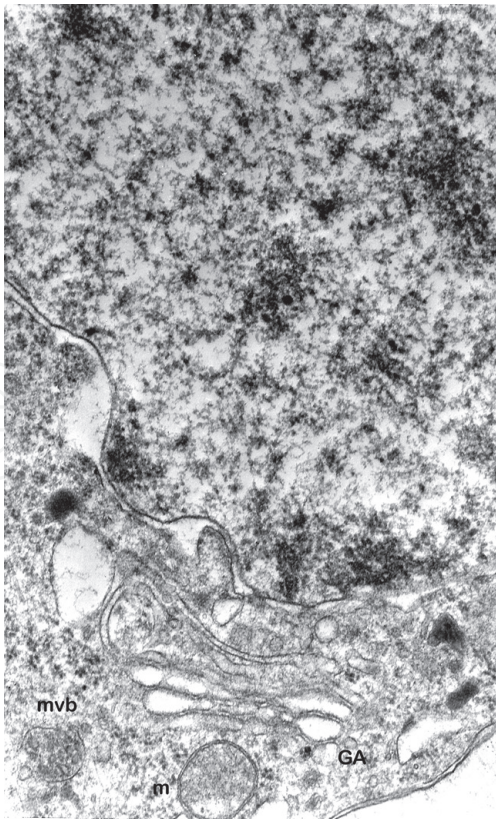*Small mitochondrion (m) near dilated cisternae of Golgi apparatus (GA) and multivesicular body (mvb) in the soma of an astrocyte in the prefrontal area of the cortex of a case of AD. Electron micrograph Mag. 54,000×.*
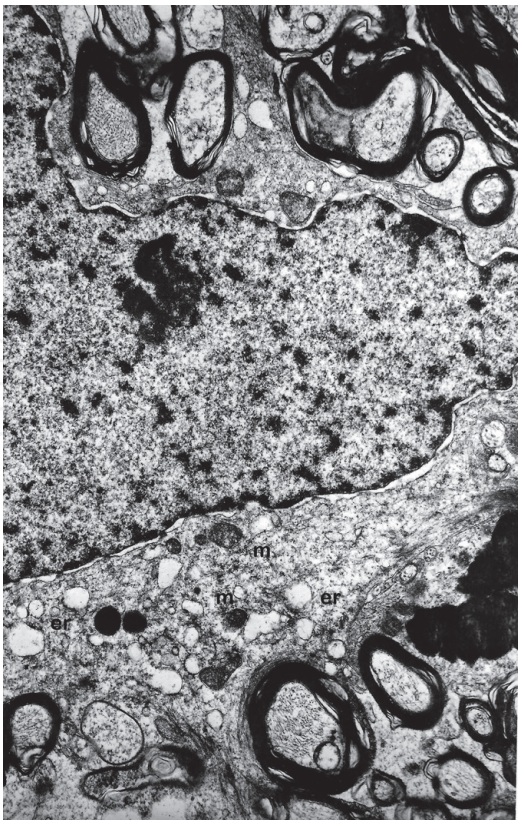

Figure 15.
Small mitochondria (m) among dilated cisternae of smooth endoplasmic reticulum (er) in the soma of an astrocyte in the parietal cortex of a case of AD. Electron micrograph Mag. 54,000×.
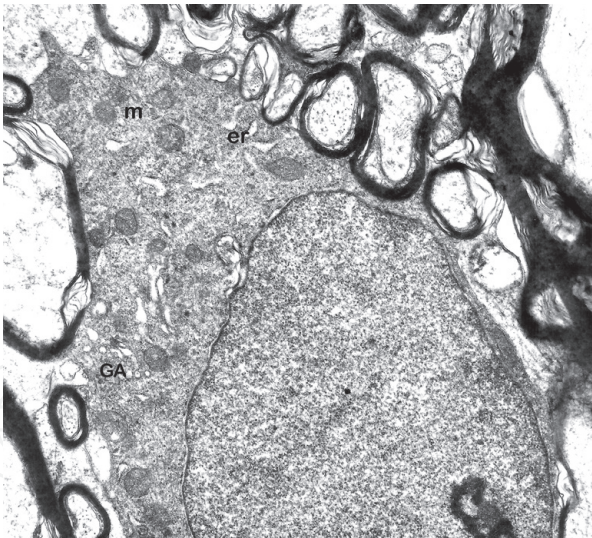
Figure 16.
Small mitochondria (m) among dilated cisternae of smooth endoplasmic reticulum (er) and fragmented cisternae of Golgi apparatus in the soma of an oligodendrocyte in the subcortical white matter of the parietal lobe of a case of AD. Electron micrograph Mag. 54,000×.
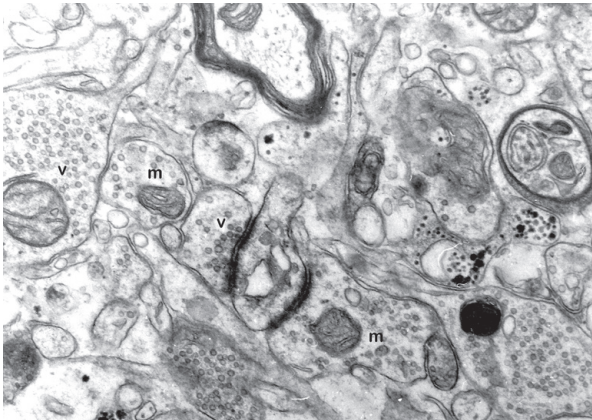

Figure 17.
Small mitochondria (m) in presynaptic profiles which show a dramatic poverty of synaptic vesicles (v) in the molecular layer of the cerebellum of AD. Electron micrograph Mag. 124,000×.

4. Discussion

Mitochondria play an essential role in energy supply of the cells, given that they provide most of the energy by oxidative phosphorylation of glucose, been basely key organelles for energy production involved in many metabolic pathways of the cell [98]. Mitochondrial dysfunction, associated with aging may be also a crucial factor in neurodegenerative disorders including Alzheimer's disease.

Decrease in energy metabolism and altered cytochrome C oxidase (CytOX) activity are among the earliest detectable defects in AD [99], affecting presumably neuronal plasticity and synaptogenesis. It is important to underline that reduced respiratory activity has also been reported in platelets of patients who suffered from AD [100], in the early stages of the disease. In addition, postmortem cytochrome-C oxidase activity is lower than normal in the cerebral cortex and in the platelets of AD patients [101] and mutations in cytochrome-C oxidase genes have been reported in late-onset AD [102].

Mitochondria and mtDNA are very sensitive to oxidative damage, such as protein oxidation and lipid peroxidation and inversely mitochondrial alterations may induce or enhance the existing oxidative stress, a fact pleading for an intimate

and early association between oxidative stress and mitochondrial abnormalities [103, 104].

In addition, the combined effect of high calcium ions with oxidative stress may induce serious impairment of the mitochondrial function, leading to release of cytochrome C and triggering the initiation of the intrinsic pathway for apoptosis in many systems [105–107].

Oxidative stress can also enhance the production and the aggregation of Aβ [108] as well as the hyperphosphorylation of tau protein, which contribute extensively in the pathogenetic mechanism of AD [109]. The overproduction of Aβ peptide in AD induces fission and fragmentation of mitochondria, a fact that further increases oxidative stress and causes a considerable decline of energy production, which is associated with the increased expression of dynamin-related protein 1 (Drp1) [110]. The Aβ peptide enhances the activity of Drp1 protein in neurons, which subsequently induces morphological alteration of the mitochondria and increases the mitochondrial dysfunction in AD.

Mitochondrial alterations are closely connected with the over expression of the amyloid precursor protein (APP) and the amyloid-β peptide [58]. The Aβ peptides are generated either extracellularly or within the cisternae of the endoplasmic reticulum (ER) and the mitochondria. APP is folded and modified in the ER and transported through the Golgi complex to the plasma membrane. Transmembrane arrest of APP causes considerable impairment of mitochondrial function in neurons [111].

A substantial amount of amyloid-β peptide is generated in mitochondria-associated ER membranes (ER-MAMs or MAMs), which is a dynamic sub-compartment of the ER, which is connected with mitochondria [112]. In Alzheimer's disease, intraneuronal amyloid precursor protein and amyloid-β are mostly localized to mitochondria [112], where amyloid-β peptide may induce mitochondrial dysfunctions by interaction with cyclophilin D, which is a subunit of the mitochondrial permeability transition pore [113]. Amyloid-β peptide may also interact with Aβ binding alcohol dehydrogenase (ABAD) on the mitochondrial membranes and induce further mitochondrial dysfunction [114]. Moreover, alterations in the lipid composition of cellular membranes may influence proteolytic processing of AβPP and increase the release of Alzheimer's amyloid beta-peptide from membranes [115].

In addition, Aβ peptide inhibits protein influx in the mitochondria, resulting in mutation of mitochondrial DNA (mtDNA), aggravating therefore mitochondrial dysfunction and disintegration eventually [116]. Experimental studies, on the other hand, revealed that the soluble form of Aβ peptide causes a reduced mitochondrial membrane potential (MMP) and energy production [117].

Mitochondrial dysfunction on the other hand may play an important role for enhancing the neurotoxicity of the Aβ peptide in AD, aggravating furthermore the oxidative stress. Oxidative stress is reasonably associated with amyloid β peptide accumulation in the neocortex [118], a fact which plays a crucial role in the pathogenesis of Alzheimer's disease, inducing alterations to the cytoplasm of sensitive cells [119] by increasing reactive oxygen species (ROS) production [120]. This condition may cause further mitochondrial dysfunction, since the lack of histones in mitochondrial DNA makes them particularly vulnerable to oxidative stress [121, 122].

It is important that morphological alterations of the mitochondria in AD are observed in areas of the brain with minimal Alzheimer's pathology, such as in the cerebellum, the hypothalamus and the mammillary bodies [123] suggesting that they are independent of the accumulation of neurofibrillary tangles and neuritic plaques.

It is well known that shape and the size of the mitochondria are highly variable [124], since they undergo continual fission and fusion, which are necessary for cell survival and harmonious adaptation to changing conditions [125] and are related, at the same time, with the processes of biogenesis [126] and the mitophagy [127].

In addition, mitochondrial morphology is sometimes controlled by the cytoskeleton, namely the neurofilaments and the microtubules [128]. The change of the shape of the mitochondria occurs mostly during their course through axons, dendrites and synaptic terminals via anterograde transport [129].

Many proteins are also important for the mitochondrial morphological integrity and for binding to the cytoskeletal components [130]. Porin is a protein in the outer membrane of the mitochondria that forms voltage-dependent anionic channels, between the mitochondrial inter membrane space and the cytosol [131]. Porin may play crucial role in binding to cytoskeleton [132], because porin-rich domains mostly contain binding sites for MAP2. In addition, recent evidence suggest that amyloid β increases the contact points between endoplasmic reticulum and mitochondria, a phenomenon that occurs in cellular stress, which usually increases ER-mitochondrial coupling [133].

Normally, approximately one-third of the mitochondria are in motion along with microtubules and actin filaments [128, 134], transported to regions where energy requirement is particularly high. The number of the mitochondria is adjusted, according to the requirement of energy by the cell. It is reasonable that the dysfunctional mitochondria may undergo mitophagy [135], a fact which is associated with neurodegeneration [136] and many devastating conditions of the brain.

Morphometric studies of the mitochondria in non-nerve cells in AD revealed a significant reduction in mitochondrial density in endothelial cells [137] as well as in fibroblasts and other cells obtained from patients with AD [138]. Mitochondria from fibroblasts grown in tissue culture from skin samples taken during autopsy of patients of AD, took significantly less calcium than did mitochondria of fibroblasts from age matched normal controls, suggesting that Alzheimer's fibroblast mitochondria have impaired calcium transport processes and showed increased sensitivity to oxygenic free radicals [139].

The most dramatic morphological alterations of the mitochondria are seen in dendritic profiles and the synaptic terminals. The defective mitochondria in AD neurons may not supply adequate levels of adenosine triphosphate (ATP), which is very important factor at the synaptic level for normal neural communication. The low levels of cellular ATP at nerve terminals may lead to the loss of synapses and considerable decline of synaptic function, causing serious cognitive impairment and profound dementia ultimately.

Mitochondrial alterations in AD are observed also in astrocytes, although mitochondrial dynamics of astrocytes are not yet extensively studied. Astrocytes participate in the degradation of neuronal mitochondria via the process of transmitophagy [140] that occurs following internalization of axonal mitochondria by astrocytic processes, which normally contain very small mitochondria [141]. Astrocytic alterations have been described in cases of familial Alzheimer's disease [142] as well as in advanced cased of sporadic type of Alzheimer's disease [143], demonstrating evidence of the toxicity of the Aβ peptide [144]. The mitochondrial alterations of the astrocytes in early case of Alzheimer's disease enhance the noxious role of the Aβ peptide on the function and the integrity of the astrocytes [145] with serious implications on neuroprotection [146] due to the increased excitotoxicity, which would be a reasonable consequence of the disruption of glutamate/GABA-glutamine cycle [147].

In all of the cases, it was noticed that the morphological alterations of mitochondria in neurons and astrocytes are frequently associated with the fragmentation of Golgi apparatus and the decrease of the vesicles in cis- and trans-Golgi network [19, 56]. The morphological alterations of the mitochondria and the fragmentation of Golgi complex coincide with the dendritic and synaptic pathology in early cases of Alzheimer's disease [22, 148].

Understanding the important role the mitochondrial factor plays in the etio-pathogenetic cascade of Alzheimer's disease [13], new therapeutic strategies aim at protecting the mitochondria [149] and preventing oxidative stress, calcium imbalance and eventual apoptosis might be beneficial in the treatment of early cases of AD.

5. Conclusions

The study in electron microscopy of various areas of the cerebral cortex, including the prefrontal area, the superior parietal lobe, the occipital pole, the visual cortex and the Hessl gyri of the temporal neocortex, and various areas of the cerebellar cortex, the hypothalamus, the mammillary bodies and the medial geniculate body in early cases of Alzheimer's disease, revealed serious morphological alterations of the mitochondria in the perikaryon, the dendritic branches the axons and the synapses.

The most dramatic alteration of the mitochondrial morphology was observed in the dendritic profiles, the dendritic spines and the synapses, associated with poverty of synaptic vesicles and accumulation of multi vesicular bodies.

The morphological alterations of the mitochondria were not dependent on the typical Alzheimer's pathology, since they were seen in areas with minimal β amyloid aggregations and no neurofibrillary tangles, such as the cerebellum, the hypothalamus and the visual cortex, suggesting that the mitochondrial alterations are not the direct consequence of amyloid toxicity.

Mitochondrial alterations were also seen in astrocytes and oligodendrocytes frequently in association with dilatation of the cisternae of the smooth endoplasmic reticulum and Golgi complex.

The mitochondria alterations induce a substantial decline of energy supply to neuronal processes, affecting the protein trafficking, the membrane dynamics as well as the synaptic activity, resulting in gradual synaptic and dendritic degeneration and in neuronal apoptosis eventually.

Mitochondria are strategic points in the pathogenetic field of Alzheimer's disease. New therapeutic strategies aiming at protecting the mitochondria, increasing the energy supply and preventing oxidative stress and calcium imbalance, might be beneficial in the treatment of early cases of AD.

Conflict of interest

No conflict of interest.

Nomenclature and abbreviations

AD   Alzheimer's disease

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