

Mitochondria and Alzheimer's disease

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Abbreviations: AD, Alzheimer's Disease; mtDNA, mitochondrial DNA; CytOX, Cytochrome c Oxidase; ROS, Reactive Oxygen Species; APP, Amyloid Precursor Protein; A β PP, Amyloid- β Precursor Protein; ER, Endoplasmic Reticulum

Editorial

Alzheimer's disease (AD) is an insidiously progressive presenile and senile dementia of an unavoidable tragic outcome, affecting millions of humans, which became a serious medical challenge for aging population in our era, inducing at the same time many ethical, social and economic problems. The phenomenology of the disease is mostly characterized by profound memory loss, visuo-spatial disorientation, loss of professional skills, learning inability, language disturbances, mood and behavioral changes¹ and autonomic disorders, phenomena which appear increasingly as the disease advances, resulting in a vegetative state eventually.

The etiopathological background of the disease involves a substantial number of cellular and biochemical mechanisms, which co-operate progressively in plotting the clinical and morphological pattern of the disease. However, the real crucial causative factors remain still invisible, in spite of the persistent continuous augmentation of the research efforts.

The multiple genetic loci, associated with familial AD,² may plead in favor of its heterogeneity and support the idea that the clinical characters and the course of the disease are the eventual consequences of various metabolic, neurochemical and morphological alterations, based on a broad genetic background,³ on which aging and many environmental factors may contribute as triggering or additional potentiating agents. Moreover the increased risk of Alzheimer's disease in sporadic cases, when a maternal relative is afflicted with the disease, advocates in favor of a maternally derived factor, which is related probably to mitochondrial DNA (mtDNA).

It is well established that the implication of amyloid- β peptide, A β PP and tau protein play a very important role in the pathogenesis of AD,⁴ without enlightening sufficiently the innermost pathological procedures. According to "amyloid cascade" hypothesis, amyloidogenesis, which is the production of the amyloid- β peptide (A β peptide), a cleavage product of the β -amyloid protein precursor (A β PP)⁵⁻⁷ is the most possible causative component in both familial and sporadic types of AD, given that the elevated intra- or extracellular levels of A β oligomers protofibrils are believed to be of considerable pathogenic significance, due to their excessive neuronal and synaptic toxicity.^{8,9} It is hypothesized that a chronic disequilibrium and instability between the production and clearance of amyloid- β peptide and its molecular misfolding may lead step by step to synaptic alterations and glial activation.¹⁰

From the neuropathological point of view, AD is mostly characterized by (a) selective neuronal loss, (b) marked synaptic

loss, which play the most important role in the tragedy of the gradual decline of the mental capacities, (c) morphological mitochondrial abnormalities, (d) cytoskeletal alterations, (e) axonal dystrophy, (f) neuropil threads, (g) capillary changes, (h) blood brain barrier disruption and (i) inflammatory responses. Among them, the most characteristic morphological findings of definite diagnostic value, as real hallmarks of AD are (a) the tau pathology in the form of neurofibrillary tangles and (b) the extracellular extensive deposits of polymers of amyloid β peptide, in the form of neuritic plaques.

Morphological alterations of the neuronal organelles, concerning mainly microtubules, mitochondria, and Golgi apparatus affecting protein trafficking, have been described by histochemical techniques as well as in electron microscopy.¹¹

It must be emphasized that mitochondrial alterations are particularly prominent in neurons, which show loss of dendritic spines, abbreviation of the dendritic arbors and synaptic alterations.¹² In addition, many morphological alterations of AD, which are associated mostly with oxidative damage¹³ could be well linked to mitochondrial changes, since blockage of mitochondrial energy production shifts amyloid β -protein precursor metabolism to increased amyloidogenic activity.^{14,15}

Mitochondrial alterations, such as disruptions of mitochondrial function and mitochondrial dynamics, inducing considerable impairment of mitochondrial electron transport proteins, may be related to metabolic and energy deficiency, to alteration of neuronal signaling system¹⁶ in AD¹⁷⁻¹⁹ and other neurodegenerative disorders,^{20,21} in aging²² and in vascular lesions.²³ The fact that mitochondrial abnormalities are observed also in neurons, which lack neurofibrillary tangles pleads in favor of the hypothesis that mitochondrial degeneration may be an early sign of Alzheimer's pathology, associated mostly with dendritic alterations.²⁴

Mitochondrial abnormalities might be considered both as a cause and as an effect of the oxidative stress and calcium deregulation in AD,²⁵⁻²⁷ in diabetes associated with AD²⁸ and other age-related neurodegenerative disorders.^{29,30} The ultrastructural study of neurons in AD reveals an impressive polymorphism of mitochondria in the soma, the axons as well as in dendritic profiles and the synapses. Thus, the mitochondria demonstrate a wide variation of size and shape. A substantial number of them show disruption of the cristae, others incorporate osmiophilic material or show unusual polymorphism concerning the arrangement of the cristae, which sometimes have a concentric configuration or they are arranged in a parallel way to the long diameter of the organelle.^{11,18,19} From the morphometric point of view the ellipsoid mitochondria in AD appear to have an average diameter of 250 to 510 nm and a mean axial ratio of 1.7 ± 0.2 .¹⁹

It is well known that mitochondria are the only non-nuclear constituents of the cell with their own DNA (mtDNA) and the proper machinery for synthesizing RNA and proteins. They are instrumental for the energy equilibrium of the cell, given that they provide most of the energy for the cellular processes via oxidative phosphorylation of glucose, and by their involvement in other metabolic pathways. Their morphology is highly variable,³¹ sometimes controlled by cytoskeletal elements, especially by the neurofilament and the microtubules.³²

During the various neuronal processes approximately one third of the mitochondria are in motion along microtubules and actin filaments,^{33,34} transported to regions where ATP consumption and necessity for energy are particularly high. The number of the mitochondria also varies, according to energy state of the cell.

Mitochondria and mtDNA³⁵ are very sensitive to oxidative damage and inversely mitochondrial alterations may induce or increase the existing oxidative stress, suggesting that there is an intimate and early association between oxidative stress and mitochondrial abnormalities. The combined effect of high calcium ions with oxidative stress in association with amyloid- β peptide overproduction may damage mitochondrial function³⁶ and may be implicated, as substantial causative factor, in apoptosis of many systems.³⁷⁻³⁹

Some observations^{40,41} advocate that increased oxidative damage, decrease in energy metabolism and altered cytochrome c oxidase (CytOX) activity are among the earliest events in AD emphasizing, therefore, the role that the dysfunction of the mitochondria and the oxidation of ion channels⁴² may play in the pathogenesis of majority of the devastating neurological diseases.^{43,44} Reduced cytochrome oxidase activity has also been reported in platelets from patients suffered from AD⁴⁴ as well as in post mortem brain tissue, derived from patients suffered from AD.⁴⁵

It is important to be underlined that mitochondrial cytochrome c oxidase may be inhibited by a dimeric conformer of A β ,⁴² a phenomenon which is copper dependent.^{46,47} Oxidative stress, is reasonably associated with amyloid- β peptide accumulation in the neocortex,^{48,49} a fact which plays a crucial role in the pathogenetic mechanisms of AD, inducing extensive damage to the cytoplasm of vulnerable cells⁵⁰ by increasing mitochondrial reactive oxygen species (ROS) production,⁵¹ which would cause further impairment of mitochondrial function,⁵² since the lack of histones in mitochondrial DNA renders them a vulnerable target to oxidative stress, being more sensitive to oxidation than the nuclear DNA.^{53,54}

Mitochondrial changes are also clearly associated with the over expression of the amyloid precursor protein (APP),⁵⁵ the increase of amyloid- β , which may inhibit degradation of pre-sequence peptides by PreP, resulting in accumulation of mitochondrial pre-proteins

and processing intermediates, inducing various mitochondrial dysfunctions.⁵⁶ Phosphorylated tau protein (PHF-1 epitope) may also potentiate the A β -induced mitochondrial injury⁵⁷ or the expression of the APP751 form in cultured cells.⁵⁸

It is well documented that generation of amyloid- β peptide may occur in the endoplasmic reticulum (ER), the Golgi apparatus, the lysosomes as well as on the cell surface,^{59,60} been accumulated in the endosomes, the lysosomes, the multivesicular bodies⁶¹ and the mitochondria.⁶²

In AD intraneuronal amyloid precursor protein and amyloid- β peptide are mostly localized to mitochondria.⁶² Mitochondrial uptake of amyloid- β peptide is mediated by the translocase, which is located on the outer mitochondrial membrane (TOM import machinery).⁶³ The binding site for amyloid beta has been identified in the matrix space of the mitochondria, as alcohol dehydrogenase (ABAD), which participates in the metabolism of aldehydes and its deficiency may be involved in the generation of oxidative radicals and in mitochondrial toxicity.⁶⁴ Amyloid- β peptide may also induce mitochondrial dysfunctions by interaction with cyclophilin D, which is a subunit of the mitochondrial permeability transition pore.⁶⁵ A β PP cleaved by mitochondrial γ -secretase⁶⁶ is usually in a transmembrane-arrested orientation in the mitochondria, in contact with the mitochondrial translocation complexes.⁶⁷ In addition, alterations in the lipid composition of cellular membranes may influence the proteolytic processing of A β PP and increase the release of Alzheimer's amyloid β -peptide from membranes.⁶⁸

Mitochondrial interactions and interconnections with neurofilament and microtubules have been described at the level of electron microscopy as well as in fluorescence microscopy, dynamic light scattering, atomic force microscopy and sedimentation assays,⁶⁹ which clarify the substantial role that mitochondria may play in plotting the profile of morphological alterations in AD.⁷⁰⁻⁷²

Morphometric studies of the mitochondria in non-nerve cells in AD revealed a significant reduction in mitochondria density in endothelial cells of brain capillaries^{73,74} as well as in fibroblasts and other cells obtained from patients suffered from AD. Mitochondria from fibroblasts grown in tissue culture from skin samples of AD patients taken at autopsy, take up significantly less calcium than do fibroblast mitochondria from age matched normal controls, suggesting that fibroblast mitochondria in AD have impaired calcium transport processes and show increased sensitivity to oxygen free radicals.⁷⁵ It is important to emphasize that the mitochondrial genome plays an essential role in risk for AD and maternal family history is associated with AD biomarkers.⁷⁶⁻⁷⁸ Many protein systems are also essential in mitochondrial morphological integrity and in binding to the cytoskeleton.^{79,80} Mitochondrial porin is an outer-membrane protein that forms regulated channels (Voltage Dependent Anionic Channels) between the mitochondrial inter membrane space and the cytosol. Porin may play an important role in binding to neurofilament and microtubules,⁸⁰ since porin rich domains contain most of the binding sites for MAP2. In addition recent evidence suggest that amyloid- β peptide increases the contact points between endoplasmic reticulum and mitochondria, a phenomenon that occurs in cellular stress,⁸¹ which usually increases ER-mitochondrial coupling.⁸²

On the basis of the substantial role that mitochondrial pathology⁸³ and mitochondrial genetic defects⁸⁴⁻⁸⁷ seems to play in the pathogenetic cascade of AD^{15,88} new strategies inducing protection to mitochondria by inhibition of mitochondrial β -oxidation,⁸⁹⁻⁹² inhibition of ERK-DLP1 signaling and mitochondrial division,⁹³ regulating calcium

trafficking in the endoplasmic reticulum or via mitochondria⁹⁴ and controlling mitochondrial calcium uptake.^{95,96} by the administration of efficient antioxidant factors and natural antioxidants.⁹⁷ or using nanotechnology.⁹⁸ and supporting the neuroplasticity.⁹⁹ may be introduced in the treatment of early cases of Alzheimer's disease.

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None.

Conflicts of interest

None.

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