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Role of mitochondria in the oxidative stress of Alzheimer disease I

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Role of mitochondria in the oxidative stress of Alzheimer disease

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ABSTRACT

The leading cause of dementia in adults is Alzheimer's disease (AD), which accounts for more than 60% of age-related dementia cases worldwide. This progressive neurodegenerative disorder is defined by cognitive loss and accumulation of amyloid-β plaques and neurofibrillary tangles in the brain, accompanied by synapse abnormalities and neuron loss. The deposits are composed of misfolded protein aggregates, AD is therefore commonly characterized as a protein-misfolding disease. Remarkably, increased oxidative stress and mitochondrial dysfunction are prominent in neurons of affected regions of the brain and recognized as critical components of AD. Consequently, neurons are oxidatively damaged by free radicals triggering the course of this chronic neurodegenerative disease.

SIGNIFICANCE OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the sixth leading cause of death in the US and the main cause of dementia in the elderly, with no effective therapeutic approach to treat or slow down the progression of the chronic neurodegeneration **(1)**. AD is a progressive neurodegenerative disorder that affects wide areas of the brain cortex and hippocampus (**Figure 1**). Besides abnormal accumulation of hyperphosphorylated tau, formation of amyloid-β aggregates and neuroinflammation, progressive synaptic abnormalities and neuronal death linked to oxidative stress and failure of mitochondria are persistent pathological hallmarks related to development and progression of AD **(2)**. Over the last years, oxidative stress, free radical damage, altered patterns and deposition of transition metals, and mitochondrial dysfunction are documented in neurodegenerative processes by our studies **(3-11)**.

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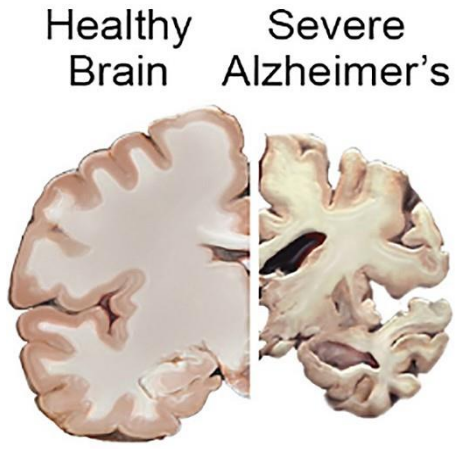

Figura 1
Changes of the brain in advanced Alzheimer's disease. Cross sections of the brain show atrophy, or shrinking, of brain tissue caused by Alzheimer's disease. (www.nia.nih.gov/health/alzheimers--disease-fact-sheet).

OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

Oxidative stress is a redox state resulting from altered cellular homeostasis of the antioxidant mechanisms or an overall imbalance between the generation and detoxification of reactive oxygen species (ROS). The brain is particularly susceptible to oxidative stress due to its high energy demand and high consumption of oxygen that consequently produces enormous amounts of ROS in the presence of high levels of oxidation prone poly-unsaturated fatty acids **(4, 8)**. Increased oxidative stress is implicated in accelerating the aging processes, by oxidizing cellular components such as DNA, RNA, structural proteins, enzymes and membrane lipids. In fact, excessive lipid peroxidation and protein oxidation are increased in AD in comparison with healthy age-matched subjects, especially in neurons of the brain regions affected by AD: hippocampus, cortex and amygdala (**Figure 2**). Remarkably, the oxidative damage in the brain impacts the genetic information of neurons, causing breaks in DNA strands, cross-linking and mutations, as demonstrated with increased levels of 8-hydroxydeoxyguanosine (8-OHdG) and 8-hydroxyguanosine (8-OHG) which are typical biomarkers of DNA and RNA oxidation **(12, 13)**. The widespread oxidative stress in AD is related with significant global decrease in antioxidants of affected neurons including glutathione, NAD, vitamins A, C and E, among others **(14)**. Oxidative stress is caused by a dramatic reduction in the activity of key antioxidant enzymes in the AD affected brain, such as superoxide dismutase (SOD) **(15)**, glutathione peroxidase (GPx), free sulfhydryls and glucose phosphate dehydrogenase **(16, 17)** and heme oxygenase **(18)**, indicating a possible altered homeostatic balance in AD subjects.

Before appearance of symptoms and confirmation of AD diagnosis, the brain exhibits a period of significant oxidative imbalance correlated with mild cognitive impairment (MCI). Overall, subjects with MCI show increased oxidative damage and decreased levels of antioxidants, increased lipid peroxidation, protein glycation, and oxidation of DNA/RNA that exceed that of advanced AD **(4, 8)**. This phase of oxidative stress appears at the very early stage of AD, even before appearance significant neuropathological hallmarks of AD. These complex mechanisms in neurons derived of high oxidative stress seem to be an early and critical event in the initiation and progression of AD pathology.

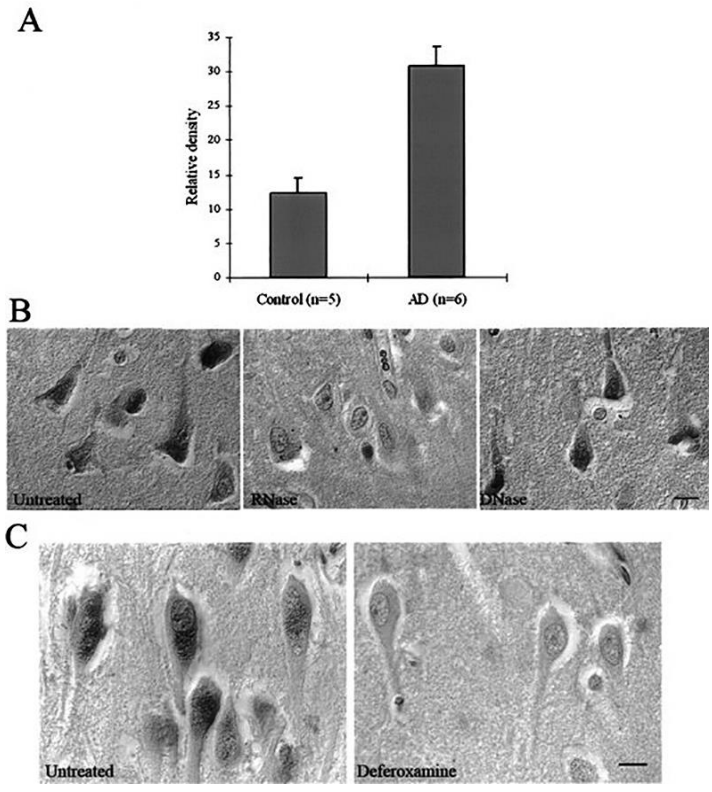

Figure 2
Oxidative stress in Alzheimer's disease. Redox activity is increased in CA1 pyramidal neurons in AD. (A) tissue sections of hippocampus from AD and age-/PMI-matched control brains (control, n = 5; AD, n = 6) were examined by redox staining. (B) Redox staining of AD with RNase treatment. (C) Tissue section with deferoxamine reducing redox staining. Scale bar 10 μm. From: Kazuhiro Honda et al. J. Biol. Chem. 2005; 280: 20978-20986

MITOCHONDRIAL DYSFUNCTION

Mitochondria are the neuronal organelles that most extensively contribute to oxidative stress, mainly through overproduction of ROS through inefficiencies in respiration (**Figure 3**). Another prominent and early feature of AD is mitochondrial dysfunction, which is characterized by an inefficient production of ATP from glucose and overproduction of ROS due to alterations in antioxidant systems and transport mechanisms **(19)**. The early decline in glucose metabolism in the brain during AD correlates with changes in cognition in MCI and AD, mainly by under-expression of key genes that code for the mitochondrial electron transport chain **(4, 19)**. Consequently, the calcium transport mechanisms suffer dyshomeostasis, and sporadic mutations in the mtDNA arise in the brain of AD subjects due to presence of ROS and failure of DNA repair machinery in affected neurons. Ultimately, mitochondrial dysfunction can trigger neuronal death by activation of cell death pathways **(4, 19)**.

Structural integrity and dynamics of mitochondria are compromised in AD, as observed through immunohistochemistry and electron microscopy. Particularly, tissue sections of AD subjects revealed significant alterations in internal substructures, enlargement and reduction of number of mitochondria in affected neurons **(4, 19)**. These observations correlate with altered expression of fundamental mitochondrial fission and fusion proteins DLP1, OPA1, Mfn1/2 and Fis1 in the brain from AD subjects, confirming that alterations and structural damage in mitochondria are accompanied with progression of AD pathology. Alterations in mitochondrial systems and dynamics are directly linked with increased

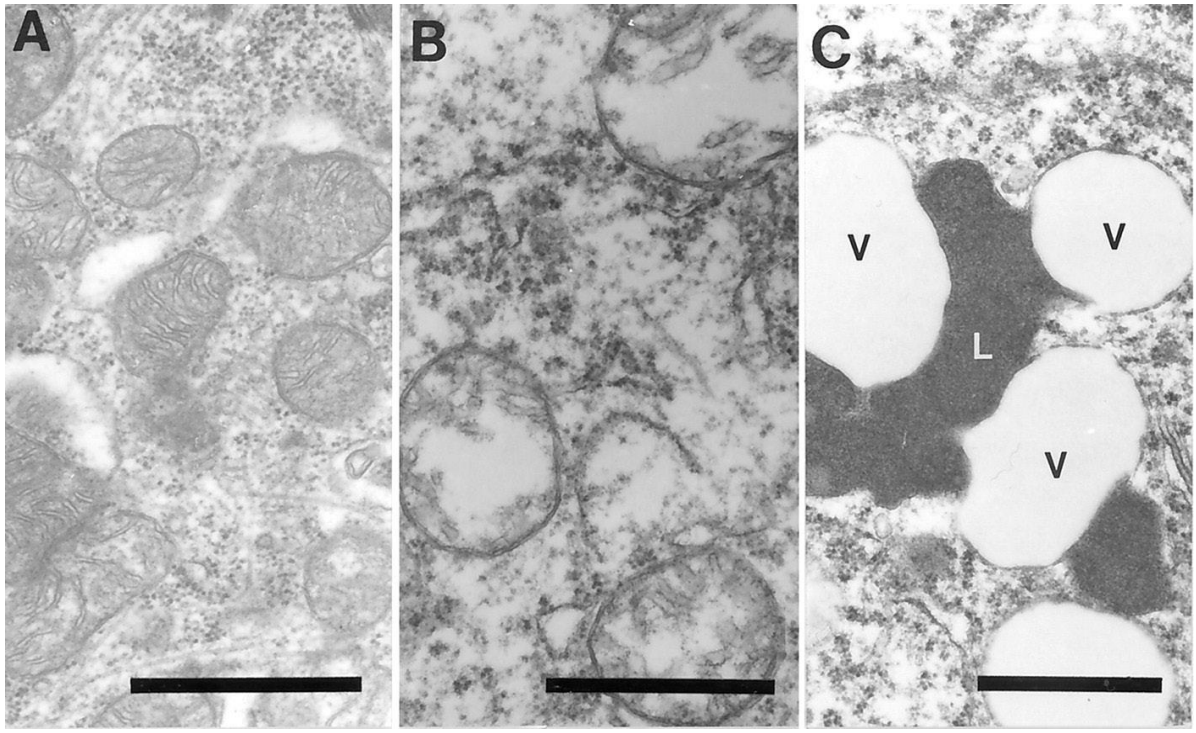

Figure 3
Mitochondrial dysfunction in Alzheimer's disease. Electron microscopy imaging of tissue sections revealed the morphology of mitochondria and lipofuscin in specimens removed at biopsy showed intact mitochondria (A), mitochondria with broken cristae (B), and vacuoles associates with lipofuscin indicated by a V and lipofuscin indicated by an L (C). Scale bar 1 μm.
From: Keisuke Hirai et al. J. Neurosci. 2001; 21:3017-3023

ROS, overall modification of brain bioenergetics, altered calcium transport and compromised integrity of mtDNA **(20, 21)**.

CONCLUSION

There are not effective treatments for AD and the few available are limited to slowing the progression and symptomatic relief. Over the last years, the role of oxidative stress in the pathogenesis of AD has been confirmed with observation of significant increase in lipid peroxidation, DNA/RNA damage and protein oxidation over the course of the disease. Similarly, mitochondrial dysfunction plays a critical role in overproduction of ROS and oxidative stress in affected areas of the brain. Understanding of the complex responses of neurons to oxidative stress and consequent mitochondrial dysfunction will open possibilities to identify new molecular targets closely related with development of AD, that could be used as diagnostic and prognostic indicators for Alzheimer's disease.

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