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Alzheimer disease as a vascular disorder: Where do mitochondria fit?

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ABSTRACT

Although the precise culprit in the etiopathogenesis of Alzheimer disease (AD) is still obscure, defective mitochondria functioning has been proposed to be an upstream event in AD. Mitochondria fulfill a number of essential cellular functions, and it is recognized that the strict regulation of the structure, function and turnover of these organelles is an immutable control node for the maintenance of neuronal and vascular homeostasis. Extensive research in postmortem brain tissue from AD subjects, and AD animal and cellular models revealed that mitochondria undergo multiple malfunctions during the course of this disease. The present review summarizes the current views on how mitochondria are implicated in both AD-related neuronal and cerebrovascular degeneration. The understanding of the mitochondrial mechanisms underlying AD pathology is critical to design more effective strategies to halt or delay disease progression.

1. Introduction

Alzheimer disease (AD) is the most common age-related disorder, which affects more than 35 million people worldwide (Querfurth and LaFerla, 2010). The clinical symptoms of AD are characterized by a progressive cognitive deterioration together with impairments in behavior, language, and visuospatial skills, culminating in the premature death of the individual (Querfurth and LaFerla, 2010). These traits are accompanied by neuropathological features observed in postmortem AD brains, including a selective neuronal and synaptic loss in cortical and subcortical regions, deposition of extracellular senile plaques, mainly composed of amyloid-β (Aβ) peptide, presence of intracellular neurofibrillary tangles (NFT) containing hyperphosphorylated tau protein, and cerebral amyloid angiopathy (CAA) (Querfurth and LaFerla, 2010). Increasing literature supports a vascular–neuronal axis in AD since shared risk factors for AD, vascular dementia and cardiovascular disease implicate vascular mechanisms in the development and/or progression of AD (Humpel, 2011). In this sense, AD can be considered a vascular disorder.

Over the last decades several hypotheses have emerged in an attempt to explain the mechanisms underlying the complexity of AD pathology. Until recently, the most prevailing hypothesis was the "amyloid cascade hypothesis," which proposes that pathological assemblies of Aβ are the cause of both sporadic and familial forms of AD (sAD and fAD, respectively), whereas other neuropathological alterations are downstream consequences of an abnormal Aβ accumulation (Hardy and Selkoe, 2002). However, Aβ has not been proven to be required for the onset and progression of sAD (Hoyer, 2004). Therefore, Swerdlow and Khan proposed the "mitochondrial cascade hypothesis," which explains many of the biochemical, genetic and pathological features of sAD (Swerdlow and Khan, 2004). According to this hypothesis: (1) inheritance determines mitochondrial baseline function and robustness; (2) mitochondrial robustness determines how mitochondria change with age; and (3) when mitochondrial alterations reach a threshold, AD histopathology and symptoms ensue (Swerdlow and Khan, 2004). Meanwhile, a "chicken-and-egg" dilemma still persists: is mitochondrial dysfunction the cause of Aβ overproduction or is Aβ overproduction the trigger of mitochondrial dysfunction?

The first part of this review is aimed to critically discuss and summarize the current knowledge regarding the involvement of mitochondria in AD-related neuronal degeneration, putting focus on mitochondrial biogenesis, dynamics, and turnover. Considering that the vascular component of AD, which translates very early into cerebral hypoperfusion, may contribute to neuronal and cognitive deficits (Benarroch, 2007), the second part of this review highlights the role of cerebrovascular abnormalities in the onset of AD pathology and emphasizes the possible pathogenic implications of mitochondria in

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cerebrovascular degeneration. Elucidation of the putative mitochondrial mechanisms underlying neuronal and cerebrovascular defects in AD pathology could be important to establish new and feasible therapeutic interventions.

2. Role of mitochondria in Alzheimer disease-related neuronal dysfunction

Mitochondria are ubiquitous and dynamic organelles that house many crucial cellular processes in eukaryotic organisms. These dynamic organelles are the master coordinators of energy metabolism and are responsible for the generation of over 90% of cellular ATP through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation system. Notably, mitochondria are one of the major sources of reactive oxygen species (ROS) and, consequently, highly susceptible to oxidative damage. In addition, mitochondria represent a convergence point for death signals triggered by both extracellular and intracellular cues. As such, the mitochondria sit at a strategic position in the hierarchy of cellular organelles to either promote the healthy life of the cell or to terminate it (Moreira et al., 2010).

Neurons are critically sensitive to mitochondrial abnormalities since they have a limited glycolytic capacity making them particularly dependent on mitochondria for energy production. Neurons are metabolically active cells with high energy demand needed for synaptic transmission, axonal/dendritic transport, ion channels, and ion pumps activity, among others, which are energy-consuming processes (Kann and Kovacs, 2007). Functional mitochondria are supplied to the synaptic terminals by the microtubule-associated protein kinesin (anterograde transport), whereas dysfunctional mitochondria are returned to the soma by dynein (retrograde transport) (Sheng and Cai, 2012). The mechanisms that govern mitochondrial dynamics seem to interact with the mitochondrial transport apparatus to control mitochondrial morphology, mass and quality in neurons. During the mitochondrial life cycle, new mitochondria result from the division of pre-existing organelles (mitochondrial biogenesis) and old/damaged mitochondria are removed through selective degradation by autophagy (mitophagy), these two processes occurring in the soma. In between, mitochondria experience successive cycles of fusion and fission that allow the generation of a heterogeneous mitochondrial population. Fusion events are also crucial for the exchange of contents between mitochondria and enable damaged mitochondria to acquire components from healthy mitochondria, while fission is essential for mitochondrial trafficking along axons and sequestration of irreversibly damaged organelles to subsequent degradation by autophagy (Sheng and Cai, 2012). Disruption of mitochondrial dynamics (fission, fusion, motility and turnover) has been postulated to be critically involved in neurodegeneration by inducing distinctive defects in neurons (Chen and Chan, 2009). Therefore, the purpose of this section is to highlight the role of mitochondrial abnormalities in AD-associated neuronal degeneration putting focus on mitochondrial dynamics (Fig. 1).

2.1. Mitochondrial bioenergetics abnormalities in Alzheimer disease

Accumulating evidence shows that defective mitochondrial metabolism sets up a cascade of pathological events that underlies neuronal degeneration in AD pathology (Moreira et al., 2010). In AD, the most consistent defect is the decline in the activity of mitochondrial cytochrome *c* oxidase (COX). In 1990, Parker and collaborators reported for the first time the existence of an impaired COX activity in the platelets of AD patients, this observation being confirmed by subsequent studies performed in lymphocytes and postmortem brain tissue from AD subjects (Bosetti et al., 2002; Kish et al., 1992; Valla et al., 2006). Swerdlow et al. (1997) also reported that AD cybrids (a cytoplasmic hybrid cell line generated by the transfer of mitochondria from platelets obtained from AD patients into mitochondrial DNA-depleted recipient neuron-based cells) presented an extensive defect in mitochondrial function characterized by reduced COX activity and increased free radical production. Impaired activities of the mitochondrial respiratory chain complexes I and III has also been documented in platelets, lymphocytes, and brain tissue from AD subjects (Bosetti et al., 2002; Kish et al., 1992; Valla et al., 2006). The decline in mitochondrial metabolism in AD brains was corroborated by the observation that the activities of TCA enzymes were impaired. Further, changes in the activity of TCA enzymatic complexes (specifically pyruvate dehydrogenase complex) correlated with AD clinical state, suggesting a coordinated mitochondrial alteration during the development of AD (Bubber et al., 2005). The decline in mitochondrial metabolism is also associated with exacerbated oxidative stress and damage. Moreira et al. (2007a) have depicted a relationship between mitochondrial dysfunction and oxidative damage by demonstrating that the antioxidant compounds lipoic acid and *N*-acetyl cysteine abrogated mitochondrial-related oxidative stress in AD fibroblasts.

2.1.1. Aβ and mitochondrial bioenergetics

In an attempt to decipher the mechanisms underlying mitochondrial abnormalities associated to AD, *in vitro* studies demonstrated that the exposure of cultured neurons to Aβ resulted in increased production of mitochondrial superoxide anion ($O_2^{-\bullet}$), ATP depletion, and increased mitochondrial calcium (Ca^{2+}) uptake potentiating the opening of mitochondrial permeability transition pore (mPTP) and apoptosis (Hashimoto et al., 2003). The mPTP is a voltage-dependent, high-conductance, nonselective channel that spans the inner and outer mitochondrial membranes that, under certain circumstances, allows the release of apoptotic agents (Moreira et al., 2001). It was also found that Aβ induced membrane lipid peroxidation and the formation of 4-hydroxynonenal (Bruce-Keller et al., 1998), which impaired the function of synaptic mitochondria (Keller et al., 1997). In general, *in vitro* studies suggest that Aβ is the causative agent in AD and mitochondrial dysfunction is a secondary event. However, studies performed in animal models of AD and human subjects challenge this idea. In brain samples from human AD subjects it was observed that mitochondrial abnormalities and oxidative damage occurred before Aβ plaque formation (Nunomura et al., 2001). In triple transgenic mice of AD, oxidative stress (Resende et al., 2008) and mitochondrial bioenergetic deficits (Yao et al., 2009) preceded AD pathology. Furthermore, alterations in the mitochondrial proteome of the cerebral cortices of triple transgenic AD mice occurred before the deposition of senile plaques and NFT (Chou et al., 2011). A recent study from our laboratory shows that brain mitochondrial abnormalities induced by sucrose intake were associated with a concomitant increase in Aβ levels (Carvalho et al., 2012), supporting the idea that metabolic abnormalities, including mitochondrial dysfunction, potentiate Aβ formation. These findings clearly demonstrate that mitochondrial abnormalities and oxidative stress are causative events in AD. However, evidence shows that during the development of AD, Aβ exacerbates mitochondrial dysfunction. This neurotoxic peptide is able to cross mitochondrial membranes and interact with mitochondrial components, thus exacerbating mitochondrial dysfunction in AD (Moreira et al., 2010). Hansson Petersen et al. (2008) observed that Aβ peptide import into mitochondrial cristae occurred via the translocase of the outer membrane (TOM) import machinery. An accumulation of full-length and carboxy-terminally truncated AβPP across mitochondrial import channels was observed in brain tissue from AD subjects, inhibiting the entrance of nuclear-encoded COX subunits IV and Vb proteins and leading to a decrease in COX activity and an increase in hydrogen peroxide (H_2O_2) levels (Devi et al., 2006). Anandatheerthavarada et al. (2003) also found an accumulation of full-length amyloid β precursor protein (AβPP) in the mitochondrial compartment in a transmembrane-arrested form that impaired mitochondrial function. It was also observed that Aβ can bind and interact with different mitochondrial molecules such as Aβ-binding alcohol dehydrogenase (ABAD) potentiating mitochondrial failure by increasing the mitochondrial membrane permeability and