Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 320–330

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Mitochondrial dysfunction and Alzheimer's disease

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ARTICLE INFO

Article history:
Received 1 April 2010
Received in revised form 31 May 2010
Accepted 5 July 2010
Available online 16 July 2010

Keywords:
Alzheimer's disease
APOE4
Mitochondrial DNA (mtDNA)
Mitochondrial dysfunction
Mitochondrial haplogroups
Oxidative stress

ABSTRACT

To date, one of the most discussed hypotheses for Alzheimer's disease (AD) etiology implicates mitochondrial dysfunction and oxidative stress as one of the primary events in the course of AD. In this review we focus on the role of mitochondria and mitochondrial DNA (mtDNA) variation in AD and discuss the rationale for the involvement of mitochondrial abnormalities in AD pathology. We summarize the current data regarding the proteins involved in mitochondrial function and pathology observed in AD, and discuss the role of somatic mutations and mitochondrial haplogroups in AD development.

1. Introduction

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder and the leading cause of dementia (Querfurth and LaFerla, 2010). It is characterized predominantly by the presence of amyloid beta (Aβ) deposition, intracellular neurofibrillary tangles (NFT), progressive synapse and neuronal loss, inflammatory responses, oxidative stress and mitochondrial dysfunction. AD has an insidious onset and it has been estimated that neurodegeneration begins 20–30 years before the clinical manifestations become evident (Mistur et al., 2009).

To date, despite intensive efforts to delineate the mechanisms underlying AD, it remains still unclear what exactly drives the pathogenesis and what is its consequence on the molecular level. There have been many hypotheses proposed to explain the origins of AD. Currently, one of the most debated hypotheses implicates mitochondrial dysfunction and oxidative stress as early events in AD development and potential therapeutic targets. In this article we will focus on the role of mitochondria and mitochondrial DNA (mtDNA) variation in AD, providing an overview of the current data regarding their role and position in AD pathogenesis. We will discuss the rationale for the role of mitochondrial abnormalities in AD pathology.

2. Mitochondrial dysfunction as an early event in AD

Mitochondria are dynamic organelles required for a myriad of biosynthetic processes and provide most of the cellular ATP demand by oxidative phosphorylation (OXPHOS). Moreover, they maintain Ca^{2+} homeostasis and take part in apoptosis.

Mitochondria contain a multicopy semi-autonomous genome (mtDNA), encoding 13 subunits of the electron transport chain (ETC) complexes, 2 rRNAs and 22 tRNAs. The remaining ETC subunits and approximately 1500 other mitochondrial proteins are coded by nuclear DNA (Wallace and Fan, 2009). Therefore, the subunit assembly, mitochondrial metabolic rate and the level of free radical generation, which constitute a physiologically important by-product of OXPHOS, are determined by dual genetic control.

Increasing evidence suggests that mitochondrial dysfunction accompanies aging and age-related neurodegenerative disorders. A large number of studies implicate defects in mitochondrial function as an early event in the course of AD. Mitochondrial dysfunction has been described in brains (Devi et al., 2006; Gibson et al., 1998), fibroblasts and blood cells (Parker et al., 1990; Valla et al., 2006, Wang et al., 2008b) of AD patients, as well as in AD transgenic mouse models

Abbreviations: ABAD, amyloid-beta (Aβ) binding alcohol dehydrogenase; AD, Alzheimer's disease; APOE2, Apolipoprotein E epsilon-2 allele; APOE3, Apolipoprotein E epsilon-3 allele; APOE4, Apolipoprotein E epsilon-4 allele; APP, amyloid precursor protein; ATP, Adenosine-5'-triphosphate; Aβ, amyloid beta; CMRglc, cerebral metabolic rate for glucose; COX, cytochrome c oxidase; CR, control region; CypD, cyclophilin D; DLP1, dynamin-like protein 1; FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; ETC, electron transport chain; KDHC, alpha ketoglutarate dehydrogenase complex; LHON, Leber's hereditary optic neuropathy; MCI, mild cognitive impairment; mtDNA, mitochondrial DNA; Mfn1, mitofusin 1; Mfn2, mitofusin 2; OPA1, optic atrophy 1 protein; mPTP, mitochondrial permeability pore; NFT, neurofibrillary tangles; OXPHOS, oxidative phosphorylation; PDHC, puryvate dehydrogenase complex; PET, positron emission tomography; PiB, Pittsburgh compound B; PreP, presequence protease; ROS, reactive oxygen species; rRNA, ribosomal ribonucleic acid; TCA, tricarboxylic acid; TOM40, mitochondrial translocase of outer mitochondrial membrane 40 homolog; tRNA, transfer ribonucleic acid.

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doi:10.1016/j.pnpbp.2010.07.004

(Caspersen et al., 2005; Eckert et al., 2008; Hauptmann et al., 2009; Li et al., 2004; Lustbader et al., 2004; Manczak et al., 2006; Reddy et al., 2004; Yao et al., 2009), cell-lines expressing mutant amyloid precursor protein (APP) or treated with Aβ (Keil et al., 2004). Mitochondrial dysfunction is present at all stages of the disease and worsens with AD progression. Moreover, it is not restricted to the brain, which suggests that AD may be a systemic disorder (Parker et al., 1990).

3. Mitochondrial cascade hypothesis

Since 1992 the amyloid cascade hypothesis has dominated the Alzheimer's disease research (Hardy and Higgins, 1992; Swerdlow and Khan, 2009). According to this theory, AD is initiated and driven by prolonged elevation of Aβ levels (Hardy and Higgins, 1992). Aβ is a product of proteolytic cleavage of amyloid precursor protein (APP) and its aggregates are believed to trigger a cascade of cellular events, including mitochondrial dysfunction, tau hyperphosphorylation and synaptic degradation. Amyloid cascade hypothesis has been challenged by Swerdlow and Khan (2004, 2009), Swerdlow et al. (2010) who proposed an alternative scenario, the mitochondrial cascade hypothesis. The mitochondrial cascade hypothesis posits that mitochondrial dysfunction is the primary event in sporadic AD that drives its pathology (Swerdlow and Khan, 2009). Moreover, in contrast to the amyloid cascade hypothesis, it assumes that brain aging and AD are convergent events. In addition, the mitochondrial cascade hypothesis postulates that mitochondrial baseline function and durability are genetically determined. However, it remains to be elucidated whether mitochondrial dysfunction is a consequence of AD pathology or occurs early in AD pathogenesis. Our review article will demonstrate the state of the art in the research of mitochondrial impairment role in AD.

Although the brain represents only 2% of the body weight, it uses approximately 20% of the total body basal oxygen consumption (Cash et al., 2001). This high energy requirement is largely driven by neuronal demand for energy to maintain ion gradients across the plasma membrane, which is critical for the generation of action potentials (Simpkins and Dykens, 2008). The limited glycolytic capacity of neurons makes them highly dependent on OXPHOS as a source of energy. In neurons mitochondria are significantly more likely to be localized at synapses and are pivotal for their normal function, supplying them with ATP for neurotransmission and maintaining calcium homeostasis (Chang and Reynolds, 2006). Consistently, mitochondrial dysfunction, changed mitochondrial number and perturbed mitochondrial dynamics, impairing the transport of mitochondria from the neuronal body to synapses, can affect synaptic physiology and lead to compromised neuronal plasticity (Anandatheerthavarada and Devi, 2007; Atamna and Frey, 2007; Li et al., 2004).

One of the best documented metabolic defects in AD is the severe reduction of the cerebral metabolic rate for glucose (CMRglc) measured by positron emission tomography (PET) using a glucose analog, 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), as a tracer. CMRglc serves as a direct measure of synaptic functioning and density (Mosconi et al., 2008). Compromised cerebral metabolism precedes both neuropsychological impairment and the cortical atrophy in AD, and its extent and topography correlate with the degree of cognitive impairment (Mosconi et al., 2009; Rabinovici et al., 2010). In comparison with normal age-matched cognitively intact controls, AD patients display reduced uptake of FDG in the parietotemporal, posterior cingulate, and to a lesser extent in frontal cortices and medial temporal lobes (Mosconi et al., 2007, 2008, 2009). Given that the characteristic pattern of brain hypometabolism is present already at the preclinical stage of AD, it has been consistently detected on FDG–PET: 1.) in persons with mild cognitive impairment (MCI), 2.) in presymptomatic individuals carrying mutations responsible for early-onset familial AD, 3.) in cognitively normal elderly individuals followed for several years after PET until they declined to MCI and eventually to AD, 4.) in middle-aged individuals who expressed subjective memory complaints and were carriers of the *APOE4* (Apolipoprotein E epsilon-4) allele (Mosconi et al., 2007, 2008, 2009).

Another consistently detected defect in mitochondrial metabolism in brains of AD patients, is the deficiency in alpha ketoglutarate dehydrogenase complex (KDHC) and puryvate dehydrogenase complex (PDHC), as well as in cytochrome oxidase (COX) (Bubber et al., 2005; Gibson et al., 1998, 2000; Ko et al., 2001; Mastrogiacomo et al., 1993). KDHC and PDHC are key enzymes of tricarboxylic acid (TCA) cycle, whereas COX forms complex IV of ETC. Reductions in these enzyme activities favour reactive oxygen species (ROS) generation (Su et al., 2008) and are not limited to the areas of AD pathology and neuron death. Furthermore, in a study of TCA enzymes in AD, decreased activities of KDHC and PDHC were accompanied by the decrease in isocitrate dehydrogenase (Bubber et al., 2005). In contrast, activities of succinate and malate dehydrogenases were increased. The alterations in TCA cycle enzyme activities correlated with the clinical state, suggesting that their imbalance may lead to declined brain function (Bubber et al., 2005).

Cytochrome oxidase activity significantly decreases with age, which is accompanied by the decline in mitochondrial respiratory function (Ojaimi et al., 1999; Sohal et al., 2008). The decrease in COX activity in AD is more pronounced. Notably, although COX subunit levels remain unchanged, complex IV is catalytically abnormal in AD (Valla et al., 2006). Reduced COX activity was observed in brains, fibroblasts and platelets of AD patients (Bosetti et al., 2002; Cardoso et al., 2004; Mutisya et al., 1994; Parker, 1991; Parker et al., 1990, 1994; Valla et al., 2006), in platelets of individuals with MCI (Valla et al., 2006), as well as in cybrids containing mtDNA from AD patients (Cardoso et al., 2004; Trimmer et al., 2004; Swerdlow et al., 1997). Moreover, the triple transgenic AD mice model, with combined Aβ and tau pathologies, demonstrates deregulation of several proteins, of which one third comprises mitochondrial proteins mainly related to complexes I and IV of OXPHOS. Owing to the involvement in the study also pR5 mice and APP^{sw}PS2^{N1411} double transgenic mice, the authors delineated that the deregulation of complex IV was Aβ dependent (Rhein et al., 2009). On the other hand, Cottrell et al. (2001, 2002) demonstrated that COX-deficient neurons were more frequent in AD brains in comparison with the control group, however, these COX-deficient neurons were not associated with amyloid plaques, NFT or markers of apoptosis.

Cybrid lines with mtDNA from AD patients model morphologic and biochemical phenotype observed in the patients' brains (Khan et al., 2000, Trimmer et al., 2000, 2004). They exhibit decreased ETC activity, increased oxidative stress, reduced mitochondrial membrane potential, abnormal mitochondrial morphology, increased basal Ca2+ level, increased cytosolic cytochrome c, increased caspase-3 activity, increased intracellular Aβ, and the development of Congo red-positive deposits in vitro (Cardoso et al., 2004; Cassarino et al., 1998; Keil et al., 2004; Khan et al., 2000; Trimmer et al., 2000, 2004; Sheehan et al., 1997; Swerdlow et al., 1997). Moreover, they show reduced COX activity and overexpress Aβ42 and Aβ40 (Khan et al., 2000). In vitro application of sodium azide, the COX inhibitor, alters APP processing towards amyloidogenic cleavage (Gabuzda et al., 1994). Consistently, OXPHOS uncoupling, ATP synthase inhibition and COX inhibition drive APP processing towards the amyloidogenic pathway (Webster et al., 1998) and tau phosphorylation (Swerdlow and Khan, 2009). In addition, cybrids demonstrated that mtDNA is at least partly responsible for reduced COX activity in AD (Swerdlow and Khan, 2009). For instance, cybrids with mtDNA from individuals with a mother affected by AD demonstrated lower COX activity than cybrids containing mtDNA from individuals with affected fathers (Davis et al., 1997).

The notion that COX deficiency drives increased oxidative damage and predisposes for the formation of Aβ was challenged by Fukui et al.