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Review article

Alzheimer, mitochondria and gender

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ABSTRACT

Epidemiological studies revealed that two-thirds of Alzheimer's disease (AD) patients are women and the drop of sex steroid hormones after the menopause has been proposed to be one risk factor in AD. Similarly, the decrease of circulating testosterone levels with aging may also increase the risk of AD in men. Studies attest the neuroprotective effects of sex hormones in animal models of AD, but clinical trial data remain controversial. Here, we discuss the implication of mitochondria in gender differences observed in AD patients and animal models of AD. We summarize the role of mitochondria in aging and AD, pointing to the potential correlation between the loss of sex hormones and changes in the brain redox status. We discuss the protective effects of the sex hormones, estradiol, progesterone and testosterone with a specific focus on mitochondrial dysfunction in AD. The understanding of pathological processes linking the loss of sex hormones with mitochondrial dysfunction and mechanisms that initiate the disease onset may open new avenues for the development of gender-specific therapeutic approaches.

Contents

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1. Introduction

Brain aging is marked by a gradual decline in energy metabolism coupled with an increased oxidative stress (Yin et al., 2014). Since the brain is a highly specialized organ with significant energy requirements, the age-dependent modifications in cerebral bioenergetic and redox homeostasis may lead to neuronal disturbances and, eventually, neurodegeneration. Brain hypometabolism and oxidative stress are a prominent and early event of Alzheimer's disease (AD) that can be observed even before the appearance of the two histopathological hallmarks of the disease – extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFT) (Perry et al., 2000; Schmitt et al., 2012; Yao et al., 2009). Since the incidence rate for AD increases exponentially after 60 years, especially during the 7th and 8th decades of life, advancing age remains the main risk factor of the disease that currently affects about 2% of the population in industrialized countries and accounts for more than 60% of all dementia cases (Prince et al., 2013). With the extended average lifespan, this neuropathology, that is marked by a progressive cognitive and physical decline, will become increasingly burdensome and costly in the coming years as AD prevalence is expected to quadruple by 2050 (Brookmeyer et al., 2007).

Epidemiological studies showed that women represent two-thirds of AD patients and exhibit a greater vulnerability to the disease compared to men (Mielke et al., 2014). These observations were corroborated by animal studies showing that in most of the transgenic AD mouse models, Aβ deposits were more striking in females compared to age-matched males (see details in Section 4). Based on these observations, hormonal deficit in post-menopausal women, characterized by a sudden drop in circulating estrogen levels, has been proposed to be another risk factor in AD (Vest and Pike, 2013). Numerous evidence highlighted the neuroprotective effect of estrogens in cellular and animal models, in particular, their bearing upon mitochondrial metabolism (Grimm et al., 2012). However, beneficial effects of hormonal replacement therapy (HRT) are still under debate. Similarly, evidence based on human and animal studies suggested that androgen deprivation also represents a risk factor for AD pathogenesis in men (Pike et al., 2009; Rosario et al., 2010, 2011).

Together, these observations indicate that reproductive senescence, especially in women, may represent an additional risk to develop AD. However, the mechanisms underlying sex hormone-dependent neuroprotection are not well understood, nor the implication of mitochondria in this process.

In this review, we summarize the role of mitochondria in brain aging and AD, as well as the link between mitochondrial dysfunction and the loss of sex hormones in both females and males. We give an overview of evidence showing gender differences in the pathogenesis of the disease in both AD patients and animal transgenic models, and further we discuss the protective effects of sex steroid hormones on Aβ peptide and hyperphosphorylated tau-induced neurodegeneration with specific regard to their deleterious effects on mitochondria.

2. Mitochondrial dysfunction in aging: the beginning of the end in AD?

Mitochondria play a central role in eukaryotic cell survival and death because they are orchestrating both energy metabolism and apoptotic pathways. They are considered as the "powerhouses of cells", providing the universal cellular fuel *via* adenosine triphosphate (ATP) generation that is accomplished through oxidative phosphorylation (OXPHOS) from nutritional sources. They contribute to plenty of cellular functions, including apoptosis, cell growth and differentiation, regulation of intracellular calcium homeostasis, alteration of the cellular reduction–oxidation (redox) state and synaptic plasticity. In this context, mitochondria are particularly important in the nervous system that requires for about 20% of the body's total basal oxygen consumption for neuronal energy support (Shulman et al., 2004).

Unfortunately, an inevitable by-product of the mitochondrial respiration is the formation of superoxide anion radicals ($O_2^{\bullet -}$), mostly by the mitochondrial complexes I and III involved in the electron transport chain (ETC) (Jezek and Hlavata, 2005; Turrens, 2003). $O_2^{\bullet -}$ can be converted into other reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) and the highly reactive hydroxyl radical ($OH^{\bullet}$) through enzymatic and non-enzymatic reactions (Adam-Vizi and Chinopoulos, 2006; Balaban et al., 2005; Turrens, 2003). According to the "free-radical theory of aging" proposed in 1956 by Harman (Harman, 1956), when ROS are produced in excess, they can induce an oxidative stress, damaging proteins and DNA, and inducing lipid peroxidation, with the corresponding mitochondrial structures as the first targets of toxicity. Especially, long polyunsaturated fatty acid chains of mitochondrial membranes are very susceptible to oxidation and may lead to the membrane depolarization and consecutively to mitochondrial impairments (Harper et al., 2004). In turn, ROS-induced mitochondrial dysfunction may lead to an enhancement of superoxide anion radicals production by the ETC, triggering a "vicious cycle" of oxidative stress (Kalous and Drahota, 1996; Lee and Wei, 1997; Wallace, 2005). As a result, mitochondrial dysfunctions have been implicated in the pathogenesis of neurodegenerative disorders, including AD, that are characterized by a cerebral hypometabolism and an impaired homeostasis in the redox status.

Changes in mitochondrial bioenergetics and redox homeostasis are both hallmarks of normal brain aging. We recently summarized the common features observed in both brain aging and AD, placing mitochondrial in the center of pathological events that separate normal and pathological aging (Grimm et al., 2016b). In a general manner, a decrease in mitochondrial activity, including OXPHOS, protein level and activity of complexes involved in the ETC, can be observed with increasing age (reviewed in (Grimm et al., 2016b; Leuner et al., 2012a). In parallel, antioxidant defenses are decreased, such as glutathione (GSH) and superoxide dismutase (SOD) activity and/or content, which may result in an increased free-radical production and triggers a vicious cycle of oxidative stress leading to neurodegeneration.

A lot of studies support the central role of mitochondria in the early neurodegenerative process occurring in AD (reviewed in (Eckert et al., 2011)). Defects in brain metabolism and increased oxidative stress were found in brains from AD patients and AD transgenic mice even before the appearance of Aβ plaques and NFT (Perry et al., 2000; Schmitt et al., 2012; Yao et al., 2009). The peptide Aβ is generated *via* the proteolytic cleavage of the amyloid precursor protein (APP) by the enzyme β-secretase and γ-secretase, unlike the non amyloidogenic pathway using the α-secretase (LaFerla et al., 2007). NFTs are formed by an aberrant intracellular accumulation of microtubule-associated tau proteins (MAPT) within neurons, resulting of an abnormal tau hyperphosphorylation and its assembly into filaments (Brunden et al., 2009).

Both proteins, Aβ and abnormal tau, were shown to have a direct impact on mitochondrial function (reviewed in (Schmitt et al., 2012)). More specifically, data from cellular and transgenic animal models demonstrated that the presence of Aβ impairs the mitochondrial membrane potential, decreases the mitochondrial complex IV activity and the production of ATP, as well as increases the levels of ROS (Keil et al., 2004; Rhein et al., 2009a,b). Of note, mitochondria are highly dynamic organelles that continuously fuse and divide in order to maintain a homogeneous mitochondrial population by mixing their content of DNA, lipids