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Physical exercise as a possible strategy for brain protection: Evidence from mitochondrial-mediated mechanisms

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ABSTRACT

Aging and neurodegenerative conditions such as Alzheimer and Parkinson diseases are characterized by tissue and mitochondrial changes that compromise brain function. Alterations can include increased reactive oxygen species production and impaired antioxidant capacity with a consequent increase in oxidative damage, mitochondrial dysfunction that compromises brain ATP production, and ultimately increased apoptotic signaling and neuronal death. Among several non-pharmacological strategies to prevent brain degeneration, physical exercise is a surprisingly effective strategy, which antagonizes brain tissue and mitochondrial dysfunction. The present review aims to discuss the role of physical exercise in the modulation of the mechanisms involved in neuroprotection including the activation of signaling pathways underlying brain protection.

Contents

Abbreviations: AIF, apoptosis inducing factor; ATP, adenosine triphosphate; AD, Alzheimer disease; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium; CAT, catalase; Cu/Zn-SOD, copper/zinc superoxide dismutase; Drp1, dynamin-related protein 1; ETC, electron transport chain; FCCP, carbonyl cyanide p-[trifluoromethoxy]-phenyl-hydrazone; Fis1, fission 1; GPx, glutathione peroxidase; GSH, glutathione; GSSH, glutathione disulfide; HSPs, heat shock proteins; Mn-SOD, manganese superoxide dismutase; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; Mfn, mitofusin; Opa1, optic atrophy type 1; PD, Parkinson disease; PGC-1α, peroxisome proliferator-activated receptor-γ co-activator 1-α; RCR, respiratory control ratio; ROS, reactive oxygen species; SOD, superoxide dismutase; SIRT1, silent information regulator 1; UCPs, uncoupling proteins; $\Delta\psi m$, transmembrane electric potential; 8-OHdG, 8-hydroxydeoxyguanosine.

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1. Introduction

Aging is accompanied by structural and neurophysiological alterations in the brain, leading to variable degrees of cognitive decline associated with neurodegenerative diseases. In fact, with increasing life expectancy, age-related neurodegenerative disorders are dramatically becoming more prevalent and represent one of the major health problems in our society. However, the etiology of most neurodegenerative diseases, such as Alzheimer (AD) and Parkinson (PD) diseases, is highly complex and multifactorial. These diseases are not only consequence of genetic predisposition but also a result from environmental and endogenous factors (Correia et al., 2010; Migliore and Coppede, 2009a,b). Hypertension, hypercholesteromia, obesity, diabetes and chronic inflammation can significantly influence the onset and the progression of neurodegenerative diseases (for refs see Kern and Behl, 2009).

Viable mitochondria are vital to the homeostasis of mammalian systems. The decline of mitochondrial function can be a primary contributor to the aging process (Aliev et al., 2009a; Bishop et al., 2010; Boveris and Navarro, 2008a) and to the development of several neuropathological conditions (Aliev et al., 2009b). In most mammalian studies, the decline of mitochondrial function is associated with health impairment and shorter lifespan and may contribute to brain aging and increased neuronal susceptibility to age-related pathologies (Bishop et al., 2010; Haigis and Yankner, 2010; Lin and Beal, 2006; Moreira et al., 2010b). Among other factors, the overproduction of mitochondrial reactive oxygen species (ROS) could be a crucial contributor to brain senescence and neurodegeneration (Boveris and Navarro, 2008b; Gilmer et al., 2010; Meng et al., 2007; Navarro and Boveris, 2007b, 2010). The gradual and chronic accumulation of oxidation products can also compromise brain cell structure and its constituents, particularly mitochondrial structure and function, and trigger apoptotic pathways that ultimately result in neuronal death (Andersen, 2004; Boveris and Navarro, 2008a).

Considering the importance of mitochondrial machinery in neuronal function, mitochondria are a potential target for pharmacological and non-pharmacological approaches to counteract neurodegenerative disorders. Physical exercise has been proposed as one of the best non-pharmacological strategies that can be used to antagonize brain dysfunction associated with age-related neurodegenerative diseases (Radak et al., 2010). Endurance training involves a series of adaptations usually leading to the upregulation of tissue protective mechanisms (Ascensao et al., 2007; Goto et al., 2007; Somani and Husain, 1996). These adaptations include increased mitochondrial biogenesis and function, and improvement in antioxidant networks, leading to a more effective control of free radical production. These same responses have also been reported in brain tissue, suggesting that physical exercise is an important therapeutic and/or protective mediator of neuroprotection through mitochondrial-mediated mechanisms (Navarro et al., 2004). Indeed, mitochondria are essential organelles involved in appropriate bioenergetic adaptation of neurons, increased neuronal activity and synaptic plasticity in response to exercise (Dietrich et al., 2008). Additionally, moderate exercise triggers regulatory responses that delay some age-dependent brain mitochondrial decline such as increased oxidative stress and decreased mitochondrial enzymatic activities (Navarro et al., 2004).

The present review discusses neurodegenerative mechanisms mediated by mitochondrial dysfunction and describes the potentiality of physical exercise as a mediator of neuroprotection. The role of mitochondria as critical organelles responsible for adaptive responses with potential beneficial effects in prevention and/or attenuation of neurodegenerative diseases is also described.

2. Mitochondrial dysfunction in aging and neurodegeneration

2.1. Mitochondria and the brain

Functional mitochondria are crucial for ATP production, intracellular calcium (Ca^{2+}) regulation as well as for redox and apoptotic signaling. In particular, neurons require large amounts of energy and need to conduct this energy waves across long distances. Mitochondria supply most of the energy used in neurons through oxidative phosphorylation. ATP-dependent processes such as ion transport, receptors function, vesicle release and recycling of neurotransmitters are critically dependent on mitochondrial bioenergetics (Chan, 2006; Hoppins et al., 2007; Knott and Bossy-Wetzel, 2008). Importantly and as will be described below, the ability of mitochondria to fuse, divide and migrate throughout the extended neuronal processes explain their plasticity in terms of ATP supply where it is most needed (Lovas and Wang, 2012). Mitochondria also play a vital role in synaptic maintenance through their ability to buffer cytosolic Ca^{2+} (Knott and Bossy-Wetzel, 2008).

2.2. Aging and neurodegeneration: role of mitochondrial dysfunction and oxidative stress

The mechanistic distinctions between normal aging and neurodegenerative diseases are difficult to define. Throughout normal brain aging, gradual alterations are expected to occur in memory and cognition processes, as well as in physical or motor skills, although in a much less severe rate than in neurodegenerative diseases. Numerous theories have attempted to explain the aging process from molecular to systemic level, reflecting the complexity of the whole process. One of the most highlighted, "the free-radical theory of aging", was first postulated by Harman (1956), and has been subject of an intense debate in the scientific community. Briefly, this theory sustains that critical cellular components are under constant injury by free radicals, resulting in structural damage and altered function in many of these components. A few years later, Harman (1972) modified his own theory into the new "mitochondrial theory of ageing", based on the dependency of mammalian cells and systems on healthy mitochondria and their inherent production of free radicals. In this revised theory, a progressive cellular aging occurs due to accumulating oxidative damage to mitochondria and failure of cellular bioenergetic processes.

Mitochondrial dysfunction is associated with the pathogenesis of several neurodegenerative diseases, including AD for (refs see Moreira et al., 2010a) and PD (for refs see Arduino et al., 2010). Mitochondrial dysfunction plays a critical role in the pathologic mechanisms of neurologic disorders or diseases associated with the aging process (Beal, 2005; Morais and De Strooper, 2010; Moreira et al., 2010b; Nicholls, 2009; Soane et al., 2007). Dysfunctional mitochondrial machinery induces the disruption of energy metabolism that culminates with a decrease in ATP production, Ca^{2+} buffering impairment and exacerbated generation of ROS (Beal, 2005). Whereas brain mitochondrial dysfunction is an important component of neurodegeneration, age-related decline in mitochondrial function is controversial (Table 1), with data suggesting either no alterations (Davies et al., 2001; Gilmer et al., 2010; Meng et al., 2007) or significant disruption of mitochondrial respiration (Moreira et al., 2003; Petrosillo et al., 2008), and in the activity of individual electron transport chain (ETC) complexes (Boveris and Navarro, 2008b; Kwong and Sohal, 2000; Long et al., 2009; Navarro and Boveris, 2010; Petrosillo et al., 2008; Sandhu and Kaur, 2003). In this regard, Gilmer et al. (2010) reported age-related decline in mitochondrial ATP producing ability, together with increased oxidative damage in specific brain