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Curcumin prevents mitochondrial dysfunction in the brain of the senescence-accelerated mouse-prone 8

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ABSTRACT

The aging brain suffers mitochondrial dysfunction and a reduced availability of energy in the form of ATP, which in turn may cause or promote the decline in cognitive, sensory, and motor function observed with advancing age. There is a need for animal models that display some of the pathological features of human brain aging in order to study their prevention by e.g. dietary factors. We thus investigated the suitability of the fast-aging senescence-accelerated mouse-prone 8 (SAMP8) strain and its normally aging control senescence-accelerated mouse-resistant 1 (SAMR1) as a model for the age-dependent changes in mitochondrial function in the brain. To this end, 2-months old male SAMR1 ($n = 10$) and SAMP8 mice ($n = 7$) were fed a Western type diet (control groups) for 5 months and one group of SAMP8 mice ($n = 6$) was fed an identical diet fortified with 500 mg curcumin per kg. Dissociated brain cells and brain tissue homogenates were analyzed for malondialdehyde, heme oxygenase-1 mRNA, mitochondrial membrane potential (MMP), ATP concentrations, protein levels of mitochondrial marker proteins for mitochondrial membranes (TIMM, TOMM), the mitochondrial permeability transition pore (ANT1, VDAC1, TSPO), respiration complexes, and fission and fusion (Fis, Opa1, Mfn1, Drp1). Dissociated brain cells isolated from SAMP8 mice showed significantly reduced MMP and ATP levels, probably due to significantly diminished complex V protein expression, and increased expression of TSPO. Fission and fusion marker proteins indicate enhanced mitochondrial fission in brains of SAMP8 mice. Treatment of SAMP8 mice with curcumin improved MMP and ATP and restored mitochondrial fusion, probably by up-regulating nuclear factor PGC1α protein expression. In conclusion, SAMP8 compared to SAMR1 mice are a suitable model to study age-dependent changes in mitochondrial function and curcumin emerges as a promising nutraceutical for the prevention of neurodegenerative diseases that are accompanied or caused by mitochondrial dysfunction.

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1. Introduction

The capacity of cells to respond to endogenous and exogenous stressors, such as an overproduction of reactive species (also known as oxidative stress), decreases with age and is in part due to a lack of energy to maintain defense and repair mechanisms. Mitochondria are particularly sensitive to age-related changes that cause deficits in the activities of the complexes of the respiratory chain. This phenomenon, termed mitochondrial dysfunction, is characterized by a decrease in mitochondrial membrane potential (MMP) and energy production in the form of adenosine triphosphate (ATP). Mitochondrial dysfunction is inter alia caused by oxidative stress and represents an early event in aging and in the pathogenesis of age-related neuronal cell death and degenerative diseases (Ames et al., 1993; Eckert et al., 2012).

Mitochondria are highly dynamic organelles. Mitochondrial fission and fusion are responsible for mitochondrial dynamics (Fig. 1), which is controlled by specific proteins (Jendrach et al., 2005). Mitochondrial fission mainly occurs by interaction of the cytosolic GTPase dynamin-related protein 1 (Drp1) with an outer-mitochondrial membrane-anchored protein, mitochondrial fission protein 1

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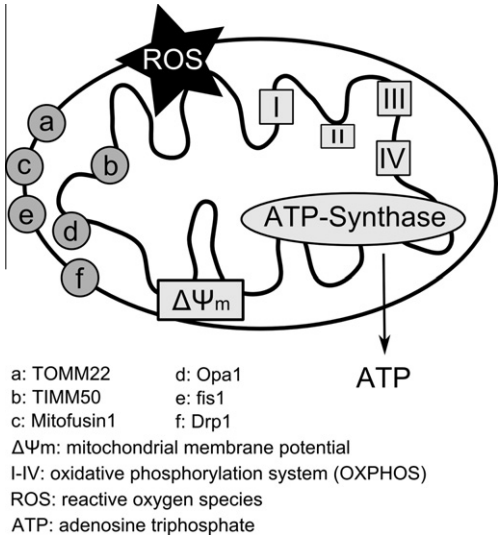

Fig. 1. Mitochondria are complex, network-forming organelles, consisting of inner and outer membranes composed of phospholipid bilayers and proteins. Mitochondria constantly undergo fission and fusion processes that are controlled by various proteins. Mitofusin1, a protein found in the outer mitochondrial membrane, as well as optic atrophy 1 (Opa1, located in the intermembrane space) are key players in the regulation of mitochondrial fusion. Dynamin related protein 1 (Drp1) and fission 1 (Fis1) proteins, which are located in the outer mitochondrial membrane, are involved in controlling fission events. Translocase of the outer/inner mitochondrial membrane (TOMM/TIMM) are protein complexes found in the outer or inner mitochondrial membrane, respectively. These complexes are involved in the transport of mitochondrial proteins that are encoded in the cell nucleus into the intermembrane space and mitochondrial matrix. The inner mitochondrial membrane harbors the proteins of the electron transport system (complex I-IV). While electrons from electron donors (e.g. NADH or succinate) are transported through the complexes along the inner mitochondrial membrane, protons are transferred from the matrix to the intermembrane space via complex I, III and IV. Thus an electrochemical proton gradient is built across the inner mitochondrial membrane that creates a mitochondrial membrane potential ($\Delta\psi m$). $\Delta\psi m$ represents the driving force for complex V (F_0/F_1-ATPase) that produces adenine triphosphate (ATP) from adenine diphosphate (ADP) and inorganic phosphate. At the end of the electron transport system, complex IV transfers electrons to oxygen to produce water. Failure in this electron transport, e.g. caused by dysfunction of one or more of the complexes of the respiratory chain, leads to incomplete reduction of oxygen and production of reactive oxygen species (ROS), such as hydrogen peroxide. ROS can damage macromolecules, including DNA, proteins, and lipids, which can lead to dysfunctional cell components, formation of even more ROS and eventually to cell death.

(Fis1). Fusion processes are chiefly regulated by the two GTPase isoforms mitofusin 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (Opa1). Mitochondrial fission and fusion events, including the exchange of matrix (Liu et al., 2009; Twig et al., 2006), inner and outer membrane proteins (Muster et al., 2010), and mtDNA proteins (Gilkerson, 2009), take place within a few minutes (Bereiter-Hahn and Voth, 1994; Jendrach et al., 2005). Under physiological conditions, fission and fusion are carefully balanced (Jendrach et al., 2008). Mitochondrial dynamics allow the complementation of mtDNA mutations in vitro and in vivo (Legros et al., 2004), which supports the hypothesis that mitochondrial fission and fusion dynamics play a role in the mitochondrial quality control system (Bossy-Wetzel et al., 2003; Mai et al., 2010).

The mitochondrial permeability transition pore (mPTP) is a multiprotein complex that spans the inner and outer mitochondrial membranes and consists of, among other proteins, the adenine nucleotide translocator (ANT), voltage dependent anion channel (VDAC), and translocator protein (TSPO; also known as peripheral benzodiazepine receptor, PBR) (Azarashvili et al., 2010; Halestrap and Brenner, 2003). The mPTP controls the permeability of the mitochondrial membrane for small molecules (<1500 kDa) and is thus involved in regulating mitochondrial function. The opening of the mPTP ultimately leads to dysfunction of mitochondria and cell death by apoptosis (Azarashvili et al., 2010; Halestrap and Brenner, 2003).

The fast-aging senescence-accelerated mouse-prone 8 (SAMP8) and the normally aging senescence-accelerated mouse-resistant 1 (SAMR1) strains were developed by selective breeding from a common genetic background of AKR/J mice (Takeda, 1999). At a comparably early age, SAMP8 mice develop many age-related pathologies that are also observed in humans (Takeda, 1999). Brain concentrations of biomarkers of oxidative stress increase with age and are higher in SAMP8 than in SAMR1 mice (Alvarez-Garcia et al., 2006; Petursdottir et al., 2007). Thus, SAMP8 mice, when compared to their control SAMR1, may be a good model to study changes in oxidative processes involved in brain aging, the pathology of neurodegenerative diseases, and their modulation by dietary factors (Bayram et al., 2012a,b; Schiborr et al., 2010b).

Many of the above-described age-dependent alterations of brain cells can be slowed-down or prevented by dietary nutraceuticals such as the curry constituent curcumin (Eckert et al., 2012; Schaffer et al., 2012). Curcumin (diferuloylmethane) is a lipophilic phenolic substance predominantly present in the rhizome of the plant turmeric (*Curcuma longa*) that is absorbed similarly to other lipid-soluble dietary factors and traverses the blood–brain barrier (Begum et al., 2008), where it can be detected at low concentrations (Schiborr et al., 2010a). A large number of biological functions of curcumin, including antioxidative, anti-inflammatory, cholesterol-lowering, anti-proliferative, and neuroprotective activity, have been reported (Bengmark, 2006; Eckert et al., 2012; Kamal-Eldin et al., 2000).

The aim of the present experiment was to investigate the suitability of the fast-aging SAMP8 strain and its normally aging control SAMR1 as a model for the age-dependent changes in mitochondrial function in the brain and to study the potential of dietary curcumin to prevent mitochondrial dysfunction in this mouse model of accelerated aging.

2. Materials and methods

2.1. Experimental animals and diets

The animal experiment was performed in accordance with the guidelines for the care and use of animals for experimental procedures and approved by the Ministry of Agriculture, Environment and Rural Areas of the state of Schleswig-Holstein (Germany). Thirteen male senescence-accelerated mice-prone 8 (SAMP8) and ten male senescence-accelerated mice-resistant 1 (SAMR1) aged 5–8 weeks (mean body weight ± SD; SAMP8, 25.5 ± 2.2 g; SAMR1, 28.6 ± 2.4 g) were obtained from Harlan Winkelmann GmbH (Borchen, Germany). The mice were housed individually in type II polypropylene cages equipped with softwood bedding, a water bottle, a mouse house, and a table tennis ball in a climate-controlled room (temperature, 22 ± 2 °C; humidity, 55 ± 5%) with a 12 h light/dark cycle. One paper towel per day was placed on top of each cage for nest-building. Mice were maintained on a pelletized Western type diet with 21% milk fat and 0.15% cholesterol (composition of the basal diet (g/kg): maize starch, 280; butter fat, 210; casein, 180; vitamin, mineral and trace element premix, 63.5; sucrose, 71; guar gum, 60; dextrose, 50; cellulose, 50; gelatin/collagen hydrolysate, 31; DL-methionine, 3.5; cholesterol, 1.5; Altromin Spezialfutter GmbH & Co. KG, Lage, Germany). The basal diet contained 35 mg all rac-α-tocopheryl acetate and 3000 IU vitamin A per kg and was free from ascorbic acid, synthetic and natural antioxidants other than the ones specified.

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