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Mitochondria: Mitochondrial membranes in brain ageing and neurodegeneration☆

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ABSTRACT

Mitochondria are membrane bound organelles that provide cellular energy in form of ATP. In addition to ATP synthesis mitochondria are key regulators of calcium homeostasis, free radical production, steroid synthesis and apoptosis, each of these factors could also be associated with essential mechanisms involved in neurodegenerative diseases. Recent studies revealed that changes in mitochondria membrane fluidity might have a direct impact on membrane-based processes such as fission-associated morphogenic changes, opening of the mitochondrial permeability transition pore or oxidative phosphorylation at the complexes of the electron transport chain. We investigated synaptosomal plasma and mitochondrial membranes isolated from brains of mouse models for ageing, Alzheimer's disease, Huntington's disease and Amyotrophic lateral sclerosis. Membrane properties are disease specifically altered, identifying mitochondrial membranes as targets for possible therapeutic strategies in neurodegenerative diseases.

This article is part of a Directed Issue entitled: Bioenergetic dysfunction, adaptation and therapy.

1. Introduction

Mitochondria are membrane bound organelles supplying energy to cells in form of adenosine triphosphate (ATP). ATP is produced by the generation of an electrochemical proton gradient by the oxidative phosphorylation at the complexes of the electron transport chain (ETC), located in the inner mitochondrial membrane. Besides ATP synthesis mitochondria are key regulators of calcium homeostasis, fatty acid oxidation, steroid synthesis and apoptosis (Turner and Schapira, 2010).

Increasing evidence suggests that mitochondrial dysfunction plays an important role in brain ageing and the pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS) (Eckert et al., 2012). Dysfunction of single enzyme complexes, production of reactive oxygen species (ROS), mitochondrial permeability transition pore opening (mPTP), enhanced apoptosis, and structural alterations of mitochondria are believed to be crucial for the onset and progression of neurodegenerative diseases (Napoli et al., 2006; Bilsland et al., 2008; Casley et al., 2002). Strong evidence indicates that these membrane based processes are associated with alterations in membrane fluidity (Aleardi et al., 2005; Colell, 2003; Ricchelli et al., 1999; Muller et al., 2010). Membrane fluidity is expressed as polarization (anisotropy) of the fluorescent probe 1,6-diphenyl-1,3,5-hexatriene (DPH) that mainly reflects to acyl-chain flexibility of the phospholipid bilayer (Eckert et al., 2001). The fluidity of biological membranes is determined by the membrane lipid composition and individual phospholipids differ in their physical characteristics, including their interaction with cholesterol and the level of unsaturation (Fajardo et al., 2011). However, a recent meta-analysis confirmed the validity of DPH anisotropy as a determinant for bilayer phospholipid properties (for details refer to Fajardo et al., 2011).

2. Membranes in mitochondrial function

Mitochondria are complex, network forming organelles, involved in different metabolic pathways (Nijtmans et al., 2004). Mitochondria have inner (IMM) and outer (OMM) phospholipid bilayer membranes that consist of embedded proteins and lipids (Fig. 1). Both bilayers differ in protein to phospholipid ratio and in lipid composition. Differences in the structural and compositional properties of these membranes affect fundamentally physiological processes like integral protein distribution and function and

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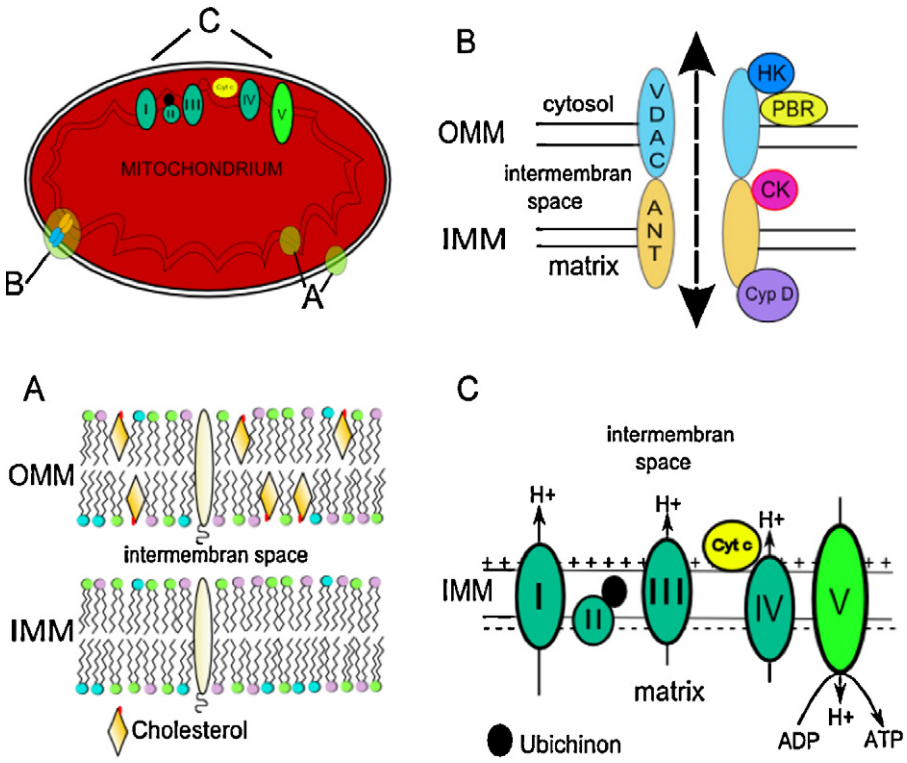

Fig. 1. Mitochondria – composition and function. (A) Mitochondria are composed of outer (OMM) and inner mitochondrial membranes (IMM). Both membranes are highly dynamic phospholipid bilayers and substantially differ in their composition. Cholesterol is almost exclusively found in OMM, whereas cardiolipin represents a unique phospholipid of IMM. OMM contain porins that are responsible for its high permeability. IMM, in contrast, harbour many proteins responsible for oxidative phosphorylation and ATP production. (B) The mitochondrial permeability transition pore (mPTP) opening is a key event in apoptosis. The mPTP spans inner and outer mitochondrial membranes. Main mPTP components are VDAC in the OMM and ANT in the IMM, forming the central core together with Cyc D, a matrix protein. Hexokinase II (HK), mitochondrial creatine kinase (CK), and the benzodiazepine receptor (PBR) are considered as possible regulatory components. (C) The oxidative phosphorylation system is located in the IMM. Respiratory complexes I, III and IV build up a mitochondrial membrane potential by pumping protons (H^+) from the matrix into the intermembrane space. This proton gradient is the driving force for complex V (ATP-synthase) to produce ATP from ADP.

alterations in membrane fluidity affect the function of membrane proteins (Fajardo et al., 2011).

OMM encloses the entire organelle; its phospholipid composition is similar to the endoplasmatic reticulum (ER), harbouring mainly phosphatidylcholin (PC). OMM contains numerous integral proteins such as porins like the voltage dependent anion channel (VDAC) that are highly permeable to molecules up to 1.5 kDa. The IMM is quite tight and contains the translocase of the inner membrane (TIM), the adenosine nucleotide transporter (ANT) and other carriers for the transport of proteins and other compounds (Martin et al., 2011).

The inner mitochondrial membrane harbours the proteins of the electron transfer system (ETS), responsible for oxidative phosphorylation. The mitochondrial oxidative phosphorylation system (OXPHOS) is the final biochemical pathway producing energy in form of ATP by consuming oxygen. From complex I and II electrons are transferred to complex III by Coenzyme Q (Ubichinon), the glycerophosphate dehydrogenase and the electron transferring flavoprotein. From complex III the electrons are transferred to oxygen via cytochrome *c* and complex IV. Simultaneously, an electrochemical proton gradient is build across the inner mitochondrial membrane (by complexes I, III, and IV). Complex V uses the resulting proton motive force to produce ATP (Fig. 1) (Brand et al., 2004). The ETS constantly generates low physiological levels of ROS, which exaggerate in consequence of mitochondrial dysfunction (Muller et al., 2010). The level of ROS production is controlled by oxygen donor concentration, the redox state of the ETC complexes, by antioxidative enzymes (e.g. superoxide dismutase, catalase), and by radical scavenger molecules (e.g. glutathione, vitamin E) (Muller et al., 2010).

IMM integrity is critical for ETC complex activity and ATP production is stabilized by cardiolipin, a phospholipid almost exclusively found within the IMM (Petit et al., 1994; Robinson, 1993). Mitochondria generally contain only small amounts of cholesterol, which are concentrated in the OMM (Comte et al., 1976).

3. Mitochondrial membranes and cell physiology

Mitochondrial membranes are dynamic two-dimensional fluids consisting mainly of proteins and lipids (Wisniewska et al., 2003). The dynamics of this bilayer (here termed as "fluidity") modulate numerous essential cell functions, including the regulation of the activity of membrane-associated enzymes, receptors and ion channels. The protein and lipid composition represents the key regulator of membrane fluidity, such as unsaturated fatty acids, type of phospholipid, and the cholesterol content (Fajardo et al., 2011). Even slight modifications of the composition alter the fluidity of membranes. Accordingly, a correlation between membrane fluidity and the mobility and function of single complexes of the mitochondrial respiratory chain has been established. For instance, F_0F_1-ATP-synthase activity is inversely related to the fluidity of the IMM (Madden et al., 1983; Montecucco et al., 1982; Ricchelli et al., 1999; Aleardi et al., 2005). Recent studies also revealed that changes in mitochondrial membrane fluidity might have direct impact on membrane-based processes such as fission-associated morphogenic changes, recruitment of pro-apoptotic factors and mPTP opening (Garofalo et al., 2007; Colell, 2003). It has been shown that fusion- (Mfn-1, OPA) and fission- (Drp-1, Fis1) proteins modulate the fluidity of mitochondrial membranes. Accordingly,

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