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Review

Mitochondrial dysfunction as a central actor in intellectual disability-related diseases: An overview of Down syndrome, autism, Fragile X and Rett syndrome

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ABSTRACT

Clinical manifestations typical of mitochondrial diseases are often present in various genetic syndromes associated with intellectual disability, a condition leading to deficit in cognitive functions and adaptive behaviors. Until now, the causative mechanism leading to intellectual disability is unknown and the progression of the condition is poorly understood.

We first report latest advances on genetic and environmental regulation of mitochondrial function and its role in brain development. Starting from the structure, function and regulation of the oxidative phosphorylation apparatus, we review how mitochondrial biogenesis and dynamics play a central role in neurogenesis and neuroplasticity. We then discuss how dysfunctional mitochondria and alterations in reactive oxygen species homeostasis are potentially involved in the pathogenesis of various neurodevelopmental syndromes with a special focus on Down, Rett, Fragile X syndromes and autism spectrum disorders. Finally, we review and suggest novel therapeutic approaches aimed at improving intellectual disability by activating mitochondrial function and reducing oxidative stress to amiliorate the quality of life in the subjects affected.

Contents

Abbreviations: ANT, adenine nucleotide transporter; ASD, autism spectrum disorders; cAMP, 3′-5′-cyclic adenosine monophosphate; CNS, central nervous system; CREB, cAMP responsive element-binding protein; Drp1, dynamin-related protein 1; DS, Down syndrome; DSCR1, Down syndrome critical region 1; DYRK1A, dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A; EGCG, epigallocatechin-3-gallate; FMR, fragile X mental retardation; FMRP, fragile X mental retardation protein; Fsp1, fission 1 protein; FXTAS, fragile X-associated tremor/ataxia syndrome; Hsa21, human chromosome 21; ID, intellectual disability; iPSCs, induced pluripotent stem cells; MeCP2, methyl-CpG-binding protein 2; MD, mitochondrial diseases; miRNA, microRNA; mitomiR, mitochondrial microRNA; MRC, mitochondrial respiratory chain; Mfn1, mitofusion 1; Mfn2, mitofusin 2; NADH, reduced nicotinamide adenine dinucleotide; Nrf1, nuclear respiratory factor 1; OS, oxidative stress; OXPHOS, oxidative phosphorylation; PGC1α, peroxisome-proliferator-activated receptor c coactivator 1 α; PKA, protein kinase A; RNS, reactive nitrogen species; ROS, reactive oxygen species; RTT, Rett syndrome; SOD1, superoxide dismutase 1; TFAM, mitochondrial transcription factor.

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1. Introduction

Mitochondria are structurally complex, biochemically active and dynamically motile organelles. The number of mitochondria per cell varies from several hundred to several thousand, depending on the cell type, and fulfil a wide range of functions, including, but not limited to the production of ATP, the main energy transfer molecule in cells, the biosynthesis of amino acids, the buffering of specific ions and the management of reactive oxygen species (McBride et al., 2006; Shetty et al., 2012).

In the central nervous system (CNS), energy supply is fundamental in a wide range of cellular functions. Indeed, the CNS, which represents only the 2% of the total body weight, consumes about 20% of oxygen inspired at rest (Silver and Erecinska, 1998). Since most neuronal ATP is generated by mitochondrial oxidative phosphorylation (OXPHOS), neurons critically depend on mitochondrial energy metabolism and oxygen supply to execute the complex processes of neurogenesis, neurotransmission and synaptic plasticity (Ames, 2000; Erecinska et al., 2004; Kann and Kovács, 2007). Neuronal functions supported by mitochondrial ATP production include, among others, the assembly of the actin cytoskeleton for the generation of growth cones and development of pre-synaptic compartments, membrane potential generation, synaptic vesicle recycling and endocytosis (Attwell and Laughlin, 2001; Verstreken et al., 2005; Lee and Peng, 2008).

The critical role of mitochondria in the development and function of neurons is further illustrated by the functional heterogeneity shown by these organelles in different neuronal cell types, brain regions and neuronal compartments. Dendritic, somatic, axonal, and presynaptic segments of neurons have different energy demands, which require local adaptation of energy supply, as well as local cellular signals interconnecting neuronal and mitochondrial metabolic activity (Kann and Kovács, 2007).

In this line, neuronal function and survival have been demonstrated to be very sensitive to mitochondrial dysfunction. Metabolic and neurological diseases, aging, as well as cancer represent valuable examples of the now recognized interplay between mitochondrial dysfunction and diseases of the CNS (Wallace, 2005). Those diseases further support the pivotal role of these organelles in the pathophysiology of intellectual disability (ID)-related syndromes.

As a whole, available literature does suggest that a better characterization of the mechanisms interplaying among mitochondrial function, energy metabolism and neuronal activity may be of crucial value for the understanding of neuronal physiology and pathophysiology in various neurological diseases. Moreover, advances in the understanding of the biology of mitochondria under physiopathological conditions are expected to lead to novel approaches for the treatment of neurodevelopment disorders.

After a brief introduction to the structure and function of mitochondria and the molecular mechanisms known to regulate mitochondrial homeostasis, the current knowledge on the regulatory roles for mitochondria in the function and plasticity of neurons and the implications of mitochondrial dysfunction in the pathogenesis of a range of ID-related syndromes are reviewed.

2. Structure and function of mitochondria

2.1. The oxidative phosphorylation apparatus

Mitochondria are double membrane-bound organelles highly efficient in their ability to utilize O_2 and metabolic substrates to produce cellular energy in the form of ATP (Krauss, 2001; Kann and Kovács, 2007).

The OXPHOS apparatus is the molecular machinery responsible for energy production, located in cristae, structures formed by the inner mitochondrial membrane. This apparatus consists of five mitochondrial respiratory chain (MRC) complexes organized in an assembly line-like manner within and across the inner mitochondrial membrane, with supramolecular organization (see Fig. 1). The MRC complexes generate the ATP that is essential for all biological processes, particularly in CNS for the excitability and survival of neurons and for protein phosphorylation reactions that mediate synaptic signalling and related long-term changes in neuronal structure and function (Mattson et al., 2008).

Thirteen of the proteins of the MRC are directly encoded by the mitochondrial genome. The remaining mitochondrial proteins are encoded by nuclear genes and mediate processes such as the regulation of ion homeostasis, stress responses, cell survival and signal transduction.

Complex I (NADH dehydrogenase) is the main site of entrance of reducing equivalents into the electron transport chain and a crucial point of respiration. It catalyzes oxidation of reduced nicotinamide adenine dinucleotide (NADH), thus regenerating the oxidized form of nicotinamide-adenine dinucleotide (NAD^+) for the tricarboxylic acid cycle and fatty acids oxidation, and passes the electrons to coenzyme Q10 (ubiquinone) (Hirst, 2009). Complex II (succinate dehydrogenase) has a covalently attached flavin adenine dinucleotide (FAD) cofactor and couples the oxidation of succinate to the reduction of coenzyme Q10 (Tomitsuka et al., 2009). Coenzyme Q10, is responsible for transferring electrons from complexes I and II to complex III (coenzyme Q10–cytochrome *c* reductase) which extracts additional electron energy and passes electrons to cytochrome *c*, a mobile protein that transfers electrons to complex IV (cytochrome *c* oxidase) (Solmaz and Hunte, 2008). Complex IV enables the terminal reduction of O_2 to H_2O and retains all partially reduced intermediates until full reduction is achieved (Turrens, 2003).

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