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Mitochondrial multifaceted dysfunction in schizophrenia; complex I as a possible pathological target

Dorit Ben-Shachar *

Laboratory of Psychobiology, Department of Psychiatry, Rambam Health Care Campus, B. Rappaport Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion-IIT, Haifa, Israel

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ABSTRACT

Mitochondria are key players in various essential cellular processes beyond being the main energy supplier of the cell. Accordingly, they are involved in neuronal synaptic transmission, neuronal growth and sprouting and consequently neuronal plasticity and connectivity. In addition, mitochondria participate in the modulation of gene transcription and inflammation as well in physiological responses in health and disease. Schizophrenia is currently regarded as a neurodevelopmental disorder associated with impaired immune system, aberrant neuronal differentiation and abnormalities in various neurotransmitter systems mainly the dopaminergic, glutaminergic and GABAergic. Ample evidence has been accumulated over the last decade indicating a multifaceted dysfunction of mitochondria in schizophrenia. Indeed, mitochondrial deficit can be of relevance for the majority of the pathologies observed in this disease. In the present article, we overview specific deficits of the mitochondria in schizophrenia, with a focus on the first complex (complex I) of the mitochondrial electron transport chain (ETC). We argue that complex I, being a major factor in the regulation of mitochondrial ETC, is a possible key modulator of various functions of the mitochondria. We review biochemical, molecular, cellular and functional evidence for mitochondrial impairments and their possible convergence to impact in-vitro neuronal differentiation efficiency in schizophrenia. Mitochondrial function in schizophrenia may advance our knowledge of the disease pathophysiology and open the road for new treatment targets for the benefit of the patients.

1. Introduction

Schizophrenia is a complex and one of the most severe brain disorders, which affects main human capabilities; reality perception, emotion, cognition and social functioning (McGlashan, 1988). Schizophrenia onset is at adolescence with about 1% worldwide prevalence and is considered mostly independent of culture identity or ethnicity (Messias et al., 2007). Currently, there is no biochemical or imaging clear-cut accepted test and diagnosis of schizophrenia is entirely based on clinical assessment. Despite decades of research efforts, the etiology and pathophysiology of schizophrenia are still largely unknown. This is partly due to the longitudinal nature of schizophrenia pathophysiology, which most likely begins in-utero reaching into adulthood, the multifactorial etiology, probably involving a yet undetermined number of interacting genetic, epigenetic and environmental influences, and the inaccessibility of the living human brain for routine clinical and scientific investigations. Despite these limitation ample data accumulated over the years, point toward several possible etiological hypotheses. The first and most accepted etiology in schizophrenia is the imbalances in neurotransmitter systems, mainly in the dopaminergic (Kapur and Remington, 2001; Matthysse, 1974; Seeman, 1987), glutamatergic (Deakin et al., 1989; Kantrowitz and Javitt, 2010; Konradi and Heckers, 2003), and GABAergic (Caruncho et al., 2004; Frankel et al., 2000; Frankle et al., 2015; Lewis et al., 1999) and their disrupted interactions (Carlsson et al., 2001; Menschikov et al., 2016). Additional theories for schizophrenia pathogenesis include genetic and environmental factors (Bleuler, 1963; Fatjo-Vilas et al., 2008; McGuffin, 2004), impaired neural development and connectivity (Conrad and Scheibel, 1987; Marenco and Weinberger, 2000; McGlashan and Hoffman, 2000; White and Hilgetag, 2011), neuroinflammation (Tomasik et al., 2016; Trépanier et al., 2016) as well as abnormal bioenergetics (Ben-Shachar and Laifenfeld, 2004; Fujimoto et al., 1992; Takahashi et al., 1994; Yuksel et al., 2015).

The mitochondrion, a cellular organelle involved in the regulation of a variety of complex cellular and physiological processes, is of relevance for most of the currently prevailing hypotheses in schizophrenia. Mitochondria, the cell energy source, have a crucial role in additional key cellular processes, such as keeping intracellular Ca^{2+} homeostasis, producing reactive oxygen species (ROS), activating the intrinsic apoptotic pathway as well as heme and steroid production, thereby driving

* Laboratory of Psychobiology, Department of Psychiatry, Rambam Health Care Campus and B. Rappaport Faculty of Medicine, Technion ITT, POB 9649, Haifa 31096, Israel.
E-mail address: shachar@tx.technion.ac.il.

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biochemical and molecular processes involved in various cell functions in health and disease. The role of mitochondria in brain development and differentiation (Kasahara and Scorrano, 2014; Solá et al., 2013), neuronal activity, sprouting and plasticity (Ben-Shachar and Laifenfeld, 2004; Courchet et al., 2013; Kang et al., 2008; Li et al., 2004) has been widely reported. In addition, it has been shown that mitochondria are targets for neurotransmitters and interact with dopamine, serotonin and glutamate (Ben-Shachar et al., 2004; Brenner-Lavie et al., 2008; Chen et al., 2008; White and Reynolds, 1996). This diversity of mitochondrial functions raised the interest in mitochondrial research in the last decade across pathologies (Picard et al., 2016) including mental disorders. Numerous evidence from studies using a wide array of experimental techniques ranging from imaging studies to ultrastructural methods to genetic and molecular means, suggests a role for mitochondria in mental disorders in general and in schizophrenia in particular. The present article focuses on cellular, molecular and biochemical evidences for mitochondria dysfunction in schizophrenia, based on studies of brain postmortem specimens, somatic cells and induced pluripotent stem cells (iPSCs) differentiated into dopaminergic and glutamatergic neurons. Specific attention is paid to the first complex, (complex I), of the ETC and its pathological interaction with dopamine, as a possible main cause for mitochondrial dysfunction in schizophrenia. Additionally, we discuss the relevance of these processes to impaired brain bioenergetics, neuronal plasticity and connectivity and thereby their consequent cognitive and behavioral anomaly, characteristic of schizophrenia. Imaging bioenergetics and metabolic pathway impairments driven by mitochondrial dysfunction as well as mitochondrial relevant genetic findings are beyond the scope of this article.

2. Mitochondrial complex I

The oxidative phosphorylation system (OXPHOS) is the cellular mechanism for energy production in the form of ATP. It is comprised of four respiratory enzyme complexes (complexes I–IV) and two electron transfer shuttling proteins, coenzyme Q (CoQ) and cytochrome *c*, which are arranged in a specific orientation in the inner mitochondrial membrane (Fig. 1A). Reduced electron carriers such as NADH (complex I substrate) and FADH2 (complex II substrate) generated from glycolysis and the citric acid cycle, release electrons that are ultimately transferred through the respiratory chain to molecular oxygen. This process is coupled to proton translocation across the inner membrane of the mitochondria forming an electrochemical gradient with a proton motivation force of ~200 mV, which enables ATP synthesis by the fifth complex, ATP synthase. Each complex of the ETC consists of multiple subunits encoded either by the nuclear DNA (nDNA) (70 subunits) or by the mitochondrial DNA (mtDNA) (13 subunits).

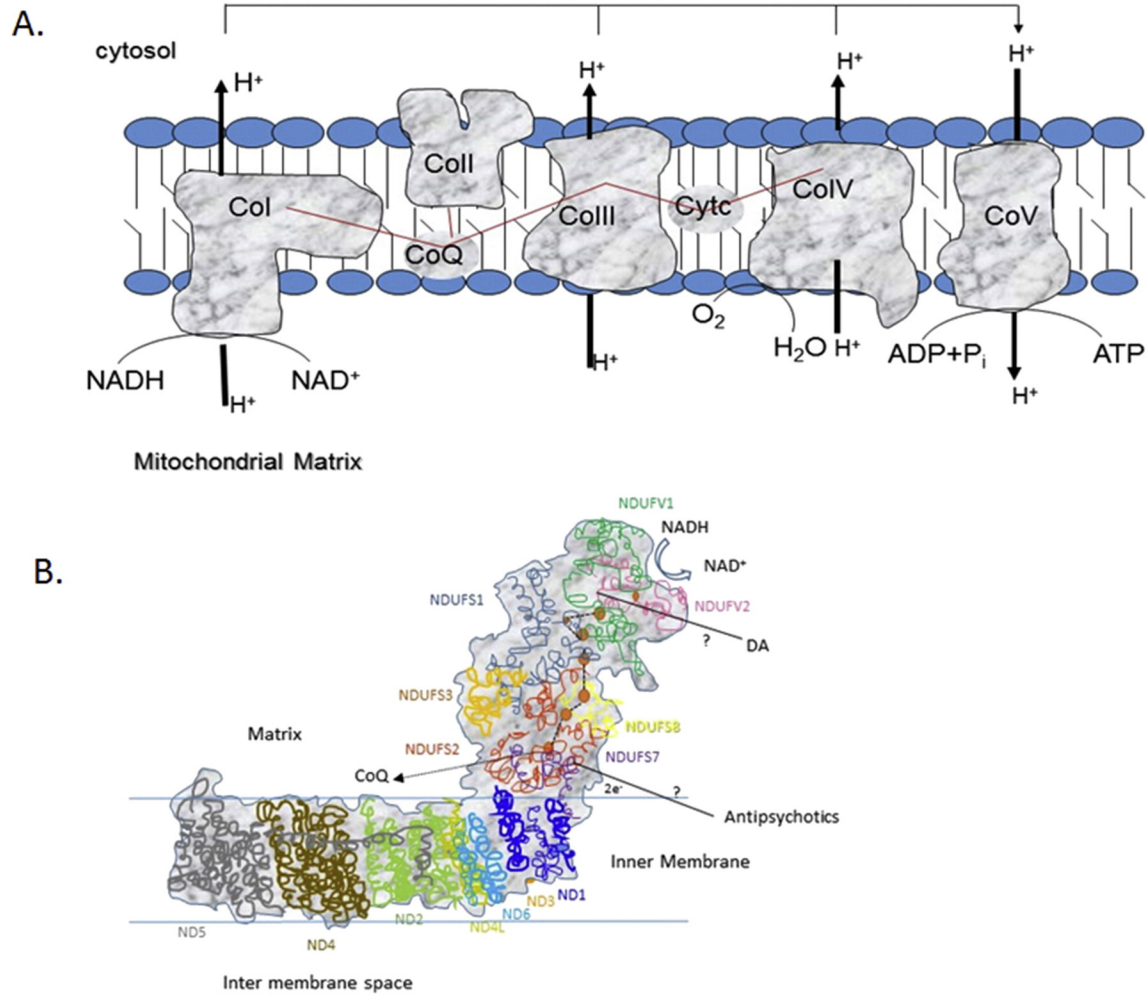

Fig. 1. A schematic presentation of mitochondrial oxidative phosphorylation system (OXPHOS) (A) and complex I (ColI) (B). Through the (OXPHOS) the electrons flow from the electron donors NADH (ColI) and $FADH_2$ (ColII) to oxygen reducing it to water. This reaction is coupled with the proton pumping from the matrix through the inner mitochondrial membrane, which generates an electrochemical gradient used for ATP synthesis by CoV. Complex I has an L-shape structure with 14 core subunits, out of its 44–45 subunits, well conserved among species in mammals. Seven subunits are encoded by the mitochondrial DNA and are embedded in the inner membrane of the mitochondria. In SZ reduced ColI activity associated with mRNA and protein levels of NDUFV1, NDUFV2 and NDUFS1 has been reported. Less consistent changes were reported for its other subunits and for the other complexes of the OXPHOS.

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