Neuroscience and Biobehavioral Reviews 48 (2015) 10–21

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Mitochondrial dysfunction in schizophrenia: Pathways, mechanisms and implications

Ashwini Rajasekaran[a], Ganesan Venkatasubramanian[b], Michael Berk[c,d], Monojit Debnath[a,*]

[a] Department of Human Genetics, National Institute of Mental Health & Neurosciences, Bangalore 560029, India
[b] Translational Psychiatry Laboratory, Neurobiology Research Centre and Department of Psychiatry, National Institute of Mental Health & Neurosciences, Bangalore, 560029, India
[c] IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia
[d] Department of Psychiatry, the Florey Institute of Neuroscience and Mental Health, and Orygen Youth Health Research Centre, University of Melbourne, Parkville, Australia

ARTICLE INFO

Article history:
Received 23 June 2014
Received in revised form 4 October 2014
Accepted 7 November 2014
Available online 15 November 2014

Keywords:
Schizophrenia
Mitochondria
Inflammation
Oxidative stress
Neuroprogression

ABSTRACT

Mitochondria play a critical role in regulating cellular functions including bioenergetics, calcium homeostasis, redox signalling, and apoptotic cell death. Mitochondria are also essential to many aspects of neurodevelopment and neuronal functions. However, mitochondrial impairment may affect bioenergetics in the developing brain and alter critical neuronal processes leading to neurodevelopmental abnormalities.

Schizophrenia is a chronic and severe neuropsychiatric disorder of neurodevelopmental origin. Immuno-inflammatory pathway is one of the widely appreciated mechanisms that has consistently been implicated in the neurodevelopmental origin of schizophrenia. However, the source of inflammation and the underlying neurobiological mechanisms leading to schizophrenia are yet to be fully ascertained. Recent understanding reveals that perturbation of mitochondrial network dynamics might lead to various nervous system disorders with inflammatory pathologies. Mitochondrial deficit, altered redox balance and chronic low-grade inflammation are evident in schizophrenia. It is hypothesized that oxidative/nitrosative stress responses due to mitochondrial dysfunctions might activate immuno-inflammatory pathways and subsequently lead to neuroprogressive changes in schizophrenia. Herein, we summarise the current understanding of molecular links between mitochondrial dysfunctions and pathogenesis of schizophrenia based on evidence from genomics, proteomics and imaging studies, which together support a role for mitochondrial impairment in the pathogenetic pathways of schizophrenia.

Contents

* Corresponding author. Tel.: +91 80 26995121; fax: +91 80 26564830.
E-mail address: monozeet@gmail.com (M. Debnath).

http://dx.doi.org/10.1016/j.neubiorev.2014.11.005
0149-7634/

1. Introduction

Schizophrenia is a chronic, debilitating neurodevelopmental disorder with a global prevalence of approximately 1% (Saha et al., 2005). Although abundant factors and mechanisms have been put forward to understand the pathogenesis of schizophrenia, its etiopathology remains unknown (Van Os and Kapur, 2009; Insel, 2010). Recent conceptualisation of neurodevelopmental model emphasises schizophrenia as a disorder marked by early, arguably prenatal priming, and early adult triggering. It is characterised by reduced synaptic connectivity (McGlashan and Hoffman, 2000; Faludi and Mirnics, 2011), and multiple dysregulated neural systems, especially dopaminergic and glutamatergic (Bauer et al., 2012). The developmental trajectory has been proposed to include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways, implying altered excitatory–inhibitory balance in the prefrontal cortex (Insel, 2010). Reduced myelination is also being envisaged to alter connectivity. In addition, multiple lines of evidence have suggested the association of schizophrenia with progressive changes in the brain structure, such as lateral ventricular enlargement, caudate enlargement, grey and white matter abnormalities, volumetric reductions of frontal and temporal lobes as well as hippocampus (Vita et al., 2012; Puri, 2010; Olabi et al., 2011; DeLisi, 2008), lending prima facie evidence toward neurodevelopmental origin of schizophrenia. It is noteworthy that such changes are shown to be mediated by neuroprogressive immuno-inflammatory, oxidative and nitrosative stress (IO&NS) and cell death pathways that are influenced by a diversity of environmental factors (Anderson et al., 2013a; Berk et al., 2013a; Davis et al., 2014; Venkatasubramanian and Debnath, 2013). Mitochondria are one of the important cellular organelles that play crucial roles in IO&NS and cell death pathways. It is also evident that mitochondria can modulate neuronal activity, morphogenesis and plasticity of spines and synapses (Li et al., 2004). Factors related to mitochondrial fission and fusion are essential for embryonic development and synapse formation in mice (Chen et al., 2003; Ishihara et al., 2009). Defects in these processes result in improperly developed neurons. Impaired mitochondrial function resulting in abnormal cellular energy state affects neurodevelopment, possibly by affecting neuronal connectivity, neurotransmission, and myelination. These observations provide support toward mitochondrial involvement in neurodevelopmental origin of schizophrenia. Recently, abnormal neuronal differentiation, as a consequence of mitochondrial dysfunction has been shown in hair follicle-derived induced pluripotent stem cells in schizophrenia patients (Robicsek et al., 2013).

Ultra-structural changes leading to mitochondrial dysfunctions have been proposed to be a key pathway in the pathogenesis of schizophrenia (Prince et al., 1999; Ben-Shachar, 2002; Park and Park, 2012; Somerville et al., 2011). It is evident that altered complex I activity can impair cellular respiration and perturb mitochondrial network dynamics in schizophrenia (Ben-Shachar et al., 1999; Dror et al., 2002; Rosenfeld et al., 2011). Compromised brain energy metabolism and oxidative stress due to mitochondrial dysfunction has been documented in schizophrenia (Prabakaran et al., 2004). In addition, various risk determinants of schizophrenia such as genetic, dysregulated neurotransmitter systems, environmental toxins, prenatal malnutrition, infections and substance abuse could lead to mitochondrial pathology (Meyer et al., 2013; Park et al., 2010; Brisch et al., 2014; Jousse et al., 2014). Mitochondrial dysfunctions have also been shown to contribute to neurodegeneration and cognitive impairments, features which are commonly found in schizophrenia (Schon and Manfredi, 2003; Picard and McEwen, 2014). Despite this understanding, it is not known whether mitochondria mediated pathogenesis of schizophrenia is a primary cause of toxicity or secondary response to damage.

Emerging research suggests a putative connection between mitochondrial dysfunction and inflammation (as reviewed in López-Armada et al., 2013; Naik and Dixit, 2011). The synergistic effect of mitochondrial impairment and neuroinflammation might trigger a vicious cycle leading to neuronal death. This illustrates the significant contribution of neuroinflammation to the underlying process of neuroprogression, which is conceptualised as a progressive, stage-related process of neurodegeneration, reduced neuronal plasticity and neurogenesis. Recent understanding indicates that neuroprogression, a dominant research paradigm of schizophrenia, can be contributed by mitochondrial as well as IO & NS pathways (Anderson et al., 2013b). This article aims to review recent advances in the field underlying mitochondria-related pathways in schizophrenia based on evidence derived from genomics, proteomics, and imaging studies.

2. Neurobiological attributes of mitochondria

2.1. Role of mitochondria in neurodevelopment and neuronal functions

Nervous system development is a highly complex process involving neural stem cell proliferation which further differentiates into neurons in the process of neurogenesis. These highly proliferative neuronal stem cells and post mitotic neurons require differential energy demands, which are supplied by mitochondria. During the process of neuronal differentiation, the number of mitochondria per cell increases, and neuronal differentiation is dependent both on ATP production and mitochondrial mass (Vayssiere et al., 1992; Mattson et al., 2008). Mitochondria play a role in axogenesis by clumping at the base of the 'to be axon' neurite. During axogenesis, mitochondria gain entry into the budding axon. Even when neurons are provided with alternate source of ATP, impaired mitochondrial function leads to complete cessation of axogenesis (Mattson and Partin, 1999). Mitochondria are highly mobile and actively traffic between subcellular compartments such as synaptic terminals, dendrites, cell body and the axon involved in neuroplasticity. Mitochondrial trafficking in the developing brain supports the formation of dendrites and axons, as mitochondria get placed at the sites of high ATP use, such as presynaptic and postsynaptic sites (MacAskill et al., 2009; Wilson et al., 2013). Brain mitochondrial energy metabolism changes during the stages of development (embryonic to early postnatal), signifying the role of mitochondria in sustaining differential energetic requirements. However, impairment of mitochondrial function inhibits the