

Minireview

Molecular Links between Mitochondrial Dysfunctions and Schizophrenia

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Schizophrenia is a complex neuropsychiatric disorder with both neurochemical and neurodevelopmental components in the pathogenesis. Growing pieces of evidence indicate that schizophrenia has pathological components that can be attributable to the abnormalities of mitochondrial function, which is supported by the recent finding suggesting mitochondrial roles for *Disrupted-in-Schizophrenia 1* (DISC1). In this minireview, we briefly summarize the current understanding of the molecular links between mitochondrial dysfunctions and the pathogenesis of schizophrenia, covering recent findings from human genetics, functional genomics, proteomics, and molecular and cell biological approaches.

INTRODUCTION

The prevalence rate of schizophrenia is 0.5 to 1% worldwide, and the genetic liability of schizophrenia is high (~ 0.81) (Hall et al., 2007; Stephan et al., 2009). The characteristic features of schizophrenia have been categorized into three major symptom domains (American Psychiatric Association, 2000). Positive symptoms, including hallucinations, delusions, and paranoia, can be relieved in part through the use of current antipsychotic medications that have been developed by altering the dispositions of conventional medications. Negative symptoms representing asocial behavior and diminished motivation and cognitive symptoms including deficits in working memory and conscious control of behavior have typically been beyond the domain of pharmacological control with only few exceptions. Furthermore, the complex pathogenetic factors underlying schizophrenia, including multiple genetic risk factors and environmental stimuli, most likely interact to modulate both early and late alterations in typical brain development. Mitochondria are multifunctional organelles that generate cellular energy via the oxidative phosphorylation system, regulate calcium buffering, and contain regulators for cellular apoptosis. Mitochondrial function is even more prominent in neurons due to the energetically-expensive nature of neuronal activities, and is important in the dynamic regulation of local calcium concentrations, especially in the distal parts of neuronal processes (Chan, 2006; Mattson et al., 2008). Interestingly, alterations in the metabolism and hypoplasia of mitochondria in schizophrenia specific brain cir-

cuits are commonly observed in schizophrenic patients (Ben-Shachar and Laifenfeld, 2004; Mattson et al., 2008; Shao et al., 2008). Moreover, schizophrenia-like symptoms have been described in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) (Prayson and Wang, 1998; Suzuki et al., 1990). Inheritance of maternal mtDNA mutations or variants may explain the high prevalence of the disease in familial schizophrenia patients (Doi et al., 2009; Malaspina et al., 1998; Swerdlow et al., 1999). In this context, the recent finding of the DISC1-Mitofilin complex in mitochondria is noteworthy, as DISC1 is a promising candidate susceptibility gene for schizophrenia and is currently the subject of extensive studies (Brandon et al., 2009; Chubb et al., 2008; Millar et al., 2000). Therefore, multiple lines of research support the idea that mitochondrial dysfunction is a potential factor in the development of schizophrenia. In this minireview, we briefly summarize the current understanding of potential molecular links between the pathogenesis of schizophrenia and mitochondrial dysfunction.

Gene expression profiling and mtDNA polymorphisms

Transcriptomes and proteomes in patients with schizophrenia have been analyzed to examine the molecular players associated with the pathogenesis of schizophrenia (Altar et al., 2005; Horvath et al., 2011; Mimics et al., 2000). Comparative transcriptome profiling has revealed several groups of genes that are associated with schizophrenia, major depressive disorder, and bipolar disorder. For example, genes involved in energy metabolism and mitochondrial function are down-regulated in schizophrenic patients (Konradi et al., 2012). Large-scale microarray analyses of the postmortem brains of schizophrenic patients have revealed that a small fraction of mitochondrial genes is down-regulated, providing support for the mitochondrial dysfunction hypothesis of schizophrenia (Iwamoto et al., 2005).

Gene expression profiling in model animals has also been used to characterize the relationships between specific genes and their molecular pathways. Specifically, protein expression profiling using MALDI-TOF-MS in the amygdala of methamphetamine-sensitized rats, often used as an animal model for positive symptoms of schizophrenia, revealed that proteins related to oxidative stress, apoptosis and synaptic, cytoskeletal, and mitochondrial functioning were differentially expressed (Iwazaki

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et al., 2008). Rats exposed to prenatal hypovitaminosis D displayed dysregulation of biological pathways including oxidative phosphorylation, redox balance, cytoskeletal maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity and neurotransmission. The genes involved in these altered pathways are closely associated with main mitochondrial functions. Furthermore, the dysregulated genes screened in this animal model are in accord with those identified in schizophrenia patients (Eyles et al., 2007).

Indeed, several mitochondria relevant genes, including complex I through IV and mitochondrial ATPase, display altered expression levels in patients with schizophrenia. Moreover, some of the genes relevant to mitochondrial functions showed up-regulated expression levels. Mitochondrial leucyl-tRNA synthetase (LARS2) and heat shock protein 70 kDa 1A and B (HSP 70 kDa 1A and B) were up-regulated in the postmortem prefrontal cortices in schizophrenia patients (Arion et al., 2007; Munakata et al., 2005). However, the expression analyses of mitochondrial proteins are not always consistent in schizophrenia, demanding further clarification. For example, schizophrenia-specific reductions of mRNA and protein levels of complex I subunits, NDUFV1, NDUFV2 and NADUFS1, were found in the prefrontal cortex and striatum (Ben-Shachar and Karry, 2008). On the other hand, mRNA and protein levels of two subunits NDUFV1 and NDUFV2 of complex I were decreased in the prefrontal cortex, but increased in the ventral parietooccipital cortices of patients, while the levels of subunit NADUFS1 were not changed (Karry et al., 2004).

Sequencing analyses of whole mtDNA variants and heteroplasmy levels in brain specimens in a cohort of schizophrenia patients provided evidence that mutations in mitochondrial DNA sequences also appear to contribute to the deficiencies of mitochondria-relevant gene expression. The synonymous base pair substitutions in the coding regions of the mtDNA genome in dorsolateral prefrontal cortex of individuals with schizophrenia were elevated by 22% ($p = 0.0017$) compared to controls (Rollins et al., 2009). Three non-synonymous homoplasmic variants in the MT-ATP6 gene of ATP synthase were also identified by analyzing the mtDNA of 93 Japanese schizophrenic patients. Novel heteroplasmic variants 1227G > A on the mitochondrial 12S ribosomal RNA, 5578T > C on the mitochondrial tRNA for tryptophan, and 13418G > A on the mitochondrial NADH dehydrogenase subunit 5 were found (Ueno et al., 2009). Additionally, 1296T > A (Leu446His) triggers a non-conservative substitution in the NADH dehydrogenase 4 subunit of complex I, suggesting that the substitution of Leu to His could alter complex I activity in patients (Martorell et al., 2006). Collectively, the altered expressions of mitochondria-relevant genes support the hypothesis of a close relationship between mitochondrial dysfunction and schizophrenia.

Hypoplasia of mitochondria

Hypoplasia of mitochondria in brain regions related to schizophrenia-specific circuits has been observed in postmortem studies of schizophrenic patients (Uranova, 1988). Notably, decreased numbers of mitochondria were found in presynaptic buttons in the dopaminergic neurons of the substantia nigra of patients with schizophrenia (Kolomeets and Uranova, 1997). Approximately 20% reductions in the number of mitochondria throughout neuropils have been observed in the caudate and the putamen of schizophrenia patients, representing significant reductions compared to control levels ($p < 0.05$). Moreover, decreases in the number of mitochondria in axon terminals of drug-naïve patients with schizophrenia have also been observed. Interestingly, this phenomenon has not been observed

in patients taking antipsychotic medications, suggesting that neuroleptic treatments may reverse mitochondria hypoplasia (Kung and Roberts, 1999). Research also indicates that the numbers of mitochondria per synapse in the caudate nucleus and putamen differ significantly among treatment-responsive, resistant, and control subjects. Treatment-responsive patients appeared to have reduced proportions (37-43%) of mitochondria per synapse in the caudate nucleus and putamen compared to control subjects. In the putamen, treatment-responsive patients had 34% decreases in the number of mitochondria compared to treatment-resistant subjects. These results suggest that the number of mitochondria per synapse may be associated with responsive to neuroleptic treatments (Somerville et al., 2011).

Furthermore, reductions in mitochondria are likely to be associated with both prognosis and symptom type in patients with schizophrenia. Significant decreases in the mitochondrial density of oligodendroglial cells in the caudate nucleus and prefrontal areas were observed in patients, especially those with prominent negative symptoms (Uranova et al., 2001). Abnormalities in the ultrastructures of lymphocytes, including abnormally large lymphocytes and morphologically atypical lymphocytes, have been observed in schizophrenia patients. Moreover, the frequencies of these abnormal mitochondrial ultrastructures are positively correlated with the severity of psychotic symptoms (Uranova et al., 2007). Significant reductions in the mitochondrial volume and density of astrocytes in the CA3 hippocampal regions of schizophrenia patients with disease durations greater than 21 years have been reported (Kolomeets and Uranova, 2010). These findings suggest collectively that deficits in the mitochondria found in astrocytes are associated with the development and maintenance of schizophrenia.

NADH dehydrogenase activity

Altered brain energy metabolism is one of the most consistent observations reported by both *in vivo* brain imaging and post-mortem studies of schizophrenic patients. Metabolic alterations in schizophrenic brains are observed through reductions in the expressions of a number of genes and proteins related to the regulation of ornithine and polyamine metabolism, the mitochondrial malate shuttle system, the transcarboxylic acid cycle, aspartate and alanine metabolism, ubiquitin metabolism, and creatine phosphate metabolism (Klushnik et al., 1991; Middleton et al., 2002). Above all, abnormalities of brain glucose oxidation are commonly found in neurological diseases, including schizophrenia (Blass, 2002). Elevated cerebrospinal fluid concentrations of lactate, a product of extra-mitochondrial glucose metabolism, have been observed in schizophrenia patients. This finding suggests that schizophrenia may experience increases in anaerobic glucose metabolism due to impaired mitochondrial metabolism (Regenold et al., 2009). Accordingly, the functionalities of each component of the respiratory chain complex (I-VI) in the brains of schizophrenia patients have received attention. NADH dehydrogenase, also referred to as Complex I, is the largest protein complex of the respiratory chain and acts as a portal through which electrons are transported into the oxidative phosphorylation system. Critically, reduced activity of NADH dehydrogenase has been observed in the basal ganglia (Maurer et al., 2001). Moreover, reductions in the expressions of mRNAs and proteins of NADH dehydrogenase subunits NDUFV1 and NDUFV2 were found in the prefrontal cortex (Ben-Shachar and Karry, 2008) (Karry et al., 2004), leading support to the hypofrontality hypothesis of mitochondrial dysfunction in schizophrenia. In addition, a recent finding implicates that the aberrant mitochondrial network dy-

namics, including fusion and fission, might also have a relevance to the NADH dehydrogenase abnormalities in schizophrenia patients (Rosenfeld et al., 2011).

To determine whether abnormalities in mitochondrial NADH dehydrogenase contribute to the pathogenesis of schizophrenia, rats with hippocampal damage or neonatal rats exposed to hypoxia, common animal models for schizophrenia, were assessed and significant prepubertal increases and postpubertal decreases in all three subunits of NADH dehydrogenase were found in rats with neonatal hippocampal lesions (Ben-Shachar et al., 2009). Abnormal expression of NADH dehydrogenase appears to be specific to certain brain regions and animal models. Comparative proteomic analyses of mitochondria from the cerebral cortex and hippocampus of Sprague-Dawley rats have been performed to assess responses to antipsychotic medication. The levels of proteins related to the respiratory electron transport chain of oxidative phosphorylation, including NDUFA10, NDUFV2, NDUFS3, ATP5B, ATP6V1B2, and ATP6V1A1, showed significant changes in quantity (Ji et al., 2009). Dopamine *per se* has been shown to impair mitochondrial function without affecting cell viability through interactions with NADH dehydrogenase, potentially explaining dopamine related pathological processes in non-degenerative disorders, such as schizophrenia (Brenner-Lavie et al., 2008). In particular, when human neuroblastoma SH-SY5Y cells are exposed to dopamine, mitochondrial respiration driven by NADH dehydrogenase is inhibited. This process is not linked to the generation of reactive oxygen species, implicating that dopamine can alter mitochondrial respiration by inhibiting NADH dehydrogenase activity (Brenner-Lavie et al., 2009). Furthermore, a positive correlation between cerebral glucose metabolism and peripheral NADH dehydrogenase activity in basal ganglia and thalamus was identified in high positive schizophrenics with positive and negative syndrome scale scores greater than 20 by FDG-PET scanning (Ben-Shachar et al., 2007), further supporting the links between peripheral NADH dehydrogenase activity, cerebral glucose metabolism, and the pathophysiology of schizophrenia.

Overall, based on genetic analyses and comparative symptomatic studies performed mostly using neuro-imaging techniques, the altered activity of NADH dehydrogenase appears to signify the mitochondrial dysfunction linked to impaired brain metabolism in schizophrenia.

Oxidative stress

Links between increased levels of the oxidative stress and pathophysiology of schizophrenia have also been proposed. In proteomic analyses of postmortem prefrontal cortices of schizophrenia patients, reduced protein levels of aconitase (ACO), enolase (ENO), pyruvate dehydrogenase (PDH), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and NADH dehydrogenase, all of which are known to be vulnerable to reactive oxygen species (ROS) damage, were consistently observed, suggesting increases in ROS in these brain samples (Blass, 2002; Prabakaran et al., 2004). Increased cerebral mitochondrial oxidative phosphorylation may be associated with increases in oxygen flux and subsequent electron leakage from the electron transport chain, leading to the formation of superoxide radicals and other ROS (Bae et al., 2011). These ROS may result in increased lipid peroxidation in neuroglial membranes, thereby accounting for increased ethane excretion. In accordance with these observations, Wistar rats that received chronic treatment with d-amphetamine, resulting in increased psychosis-related behaviors, also showed increased production of ROS in mitochondrial particles of the prefrontal cortex and

hippocampus (Frey et al., 2006). This condition has also been observed in schizophrenia patients with histories of violent behaviors (Treasaden and Puri, 2008).

The mitochondrial systems governing homeostatic responses to oxidative stress also appear to be compromised in schizophrenia. For example, polymorphisms of genes related to antioxidant enzymes are consistently associated with schizophrenia. In particular, a functional polymorphism (Ala9Val) affecting the human manganese superoxide dismutase (Mn-SOD) of the mitochondria was proposed to contribute to the pathogenesis of schizophrenia, because significantly different genotypic distributions were observed in Ala/Ala, Ala/Val and Val/Val subjects (Akyol et al., 2005). Altered antioxidant enzyme activities in patients may contribute to membrane dysfunction and are more likely to be associated with negative symptoms (Yao et al., 2001). Thus, it is noteworthy that the supplementation of well-known antioxidants, such as alpha lipoic acid, in animal models of schizophrenia improves mitochondrial function and reverses schizophrenia-related behavioral deficits (Seybolt, 2010). These results imply that mitochondrial dysfunction caused by oxidative stress may be an important factor in the pathophysiology of schizophrenia and may provide potentially novel therapies for schizophrenia.

Disrupted-in-Schizophrenia 1 (DISC1) in mitochondria

DISC1, one of the major schizophrenia-susceptibility genes, is thought to explain many molecular aspects of schizophrenia and related mood disorders. Familial mutations in the DISC1 gene, including t(1;11)(q42.1;q14.3) translocation, are associated with symptoms related to schizophrenia, bipolar disorders, and recurrent major depression. DISC1 mediates neurodevelopment, including neurite outgrowth, neuronal migration, neurogenesis, intracellular cAMP signaling, and many other neuronal processes in collaboration with various cellular factors such as nuclear distribution gene E-like 1 (NDEL1) (Burdick et al., 2008), GSK3beta (Mao et al., 2009), and phosphodiesterase 4B (PDE4B) (Millar et al., 2005b).

Brandon et al. initially reported the association of DISC1 with mitochondria in cultured cortical neurons, and a putative mitochondrial localization signal has been identified in the N-terminal region (Brandon et al., 2005). Truncated DISC1 in the C-terminus that mimics human mutations associated with schizophrenia appears to result in mitochondrial reorganization to form ring-like structures, indicating the potential involvement of DISC1 in mitochondrial fusion and/or fission (Millar et al., 2005a).

Recently, it has been reported that DISC1 plays a pivotal role for mitochondrial function in collaboration with a new mitochondrial interacting partner, Mitofilin (Fig. 1) (Park et al., 2010). Mitofilin is a single-span mitochondrial inner membrane protein with a long N-terminal region protruding toward the intermembrane space and is indispensable for regulating mitochondrial functions such as mitochondrial cristae morphology (Mun et al., 2010) and the maintenance of mitochondrial DNA (Rossi et al., 2009). Mitofilin was initially identified in yeast two hybrid screening using an adult brain library screen with full-length DISC1 as a bait, and was confirmed in subsequent studies (Millar et al., 2003; Park et al., 2010). Park et al. provided convincing evidence of the existence of a functional DISC1-Mitofilin complex. A fraction of DISC1 appears to be localized into the mitochondrial intermembrane space where DISC1-Mitofilin complex formation occurs. In the same study, functional deficiencies of DISC1 were also associated with a number of mitochondrial dysfunctions such as decreased NADH dehydrogenase activities in the electron transport chain, reduced ATP contents, al-

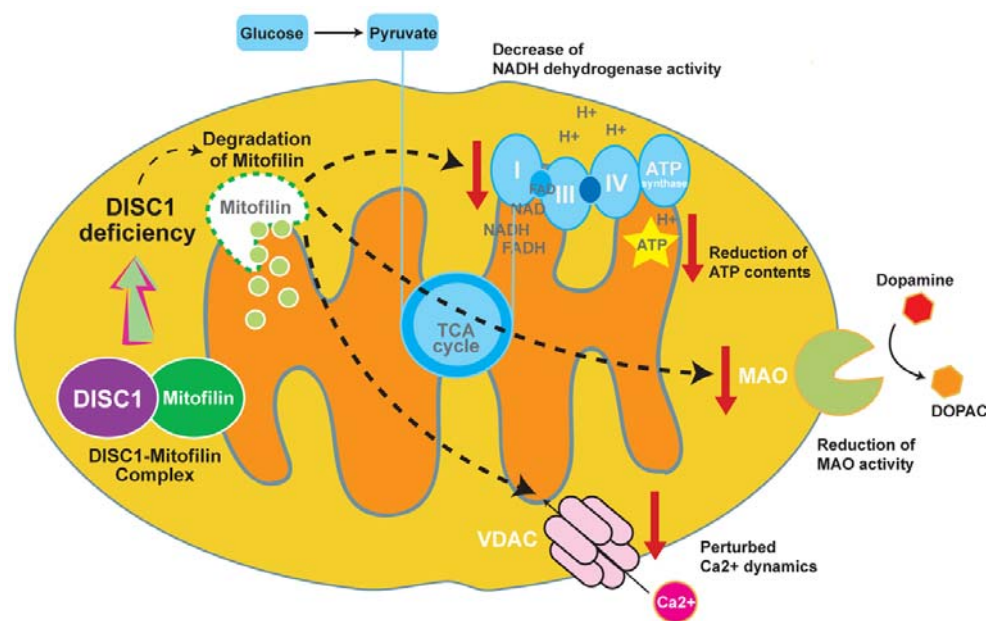


Fig. 1. DISC1-Mitofilin complex regulates mitochondrial functions. DISC1 is localized into intermembrane space of mitochondria and forms a functional complex with Mitofilin. Functional deficiency of DISC1 leads to loss of stability of Mitofilin, resulting in a number of mitochondrial dysfunctions, such as, decrease of NADH dehydrogenase activity, reduction of ATP contents, aberrant function of MAO, and perturbed calcium dynamics.

tered mitochondrial calcium dynamics, and reduced activity of monoamine oxidase (MAO), which can be attributable to the loss of Mitofilin stability as well as the increase in morphological abnormalities of the mitochondria.

Of these findings, the down-regulation of MAO activity due to DISC1 deficiency is of immediate interest because deficits of dopamine tone have proposed to be one of the most well established links to positive symptoms of schizophrenia. For example, aberrant functioning of MAO was first proposed during the early stages of pathological conditions in schizophrenia (Youdim and Holzbauer, 1976). Therefore, it is tantalizing to postulate that the compromised activity of MAO in DISC1-deficient cells might represent a cellular basis of the mesolimbic hyper-dopaminergic tone seen in schizophrenia. Further studies are required to uncover the detailed roles of DISC1 and Mitofilin in mitochondria and their links to the pathophysiology of schizophrenia and related mood disorders.

PERSPECTIVES

Understanding the molecular basis of schizophrenia is a daunting task, mostly due to contributions of genetic risk factors and environmental stimuli in the developmental stage that appear to generate multifaceted neurochemical and neurodevelopmental deficits in patients. The relevance of mitochondrial dysfunction to schizophrenia has been assessed by data from extensive genetic, molecular and cell biological, and conventional pathological studies. Although the findings from these studies led us to the consensus that mitochondrial dysfunction is a potential etiological factor in the development of schizophrenia, the mechanistic basis of this etiology remains elusive. In this context, it is noteworthy that DISC1, a major schizophrenia susceptibility factor, has emerged as a regulator of mitochondrial functions. Thus, how mitochondrial DISC1 is connected to proposed pathophysiology of schizophrenia such as mesolimbic hyper-dopaminergia and neurodevelopmental deficits in conjunction with Mitofilin and associated mitochondrial dysfunctions is of immediate interest.

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