# Mitochondrial Dysfunction in Psychiatric Disorders

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## Abbreviations

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| ADP | Adenosine diphosphate |
| ASD | Autism spectrum disorder |
| ATP | Adenosine triphosphate |
| CNS | Central nervous system |
| ETC | Electron transport chain |
| $FADH_2$ | Flavin adenine dinucleotide |
| GSH | Glutathione |
| MD | Mitochondrial disorder |
| MELAS | Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes |
| mtDNA | Mitochondrial DNA |
| NAC | *N*-acetylcysteine |
| NADH | Nicotinamide adenine dinucleotide |
| nDNA | Nuclear DNA |
| OCD | Obsessive-compulsive disorder |
| POLG1 | Polymerase gamma-1 |
| ROS | Reactive oxygen species |
| TCA | Tricarboxylic acid |

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## 1 Background

Psychiatric disorders represent a large class of medical disorders with unclear etiologies and limited effective treatments. A simple single gene or chromosomal abnormality has not been found to explain most psychiatric disorders. Although linkage studies have identified many candidate regions of certain chromosomes that could be associated with many psychiatric disorders, these findings have been inconsistent across studies. For example, recent studies have identified genetic polymorphisms associated with increased susceptibility to psychiatric disorders such as schizophrenia, but most polymorphisms identified are in the noncoding regions of the genome, making the understanding of how these genetic changes contribute to psychiatric disorders opaque (Harrison and Weinberger 2005; Kleinman et al. 2011). Some research studies have started to investigate gene-environment interactions and epigenetic factors in psychiatric disorders, rather than fixed genetic defects. These studies may lead to a better understanding of how interactions between genetic polymorphisms and the environment contribute to the development of psychiatric disorders and also provide a deeper understanding of the pathophysiological mechanisms that cause these disorders. Other research studies examining the etiology of psychiatric disorders have embraced the study of pathophysiological mechanisms that could more directly result in cellular dysfunction and the subsequent development of psychiatric disorders. Pathophysiological mechanisms identified in some psychiatric disorders include immune dysregulation, inflammation, impaired detoxification, environmental toxicant exposures, redox regulation/oxidative stress, and mitochondrial dysfunction (Burke and Miller 2011; Dantzer et al. 2008; Ng et al. 2008; Shao et al. 2008). The focus of this chapter is on mitochondrial dysfunction in common psychiatric disorders.

## 2 Mitochondria and Their Physiological Function

Mitochondria are distinct cellular organelles that generate adenosine triphosphate (ATP), the energy carrier in most mammalian cells, from adenosine diphosphate (ADP) by oxidizing glucose and fatty acids (Haas et al. 2007). Acetyl-CoA is a key intermediate generated from the oxidation of glucose and fatty acids that is further metabolized by the tricarboxylic acid (TCA) cycle. The TCA cycle produces flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH). NADH and $FADH_2$ transport energy to the mitochondrial electron transport chain (ETC), a series of reactions known as oxidative phosphorylation. Mitochondria contain two plasma membranes, an inner and an outer membrane. The ETC is located in the inner mitochondrial membrane and consists of five multi-subunit enzyme complexes (complexes I through V) and two electron carriers (ubiquinone, also known as coenzyme Q10, and cytochrome *c*) (Zeviani et al. 1996).

Mitochondria are the only organelle in mammalian cells with their own genome. The ETC is coded by both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) (Zeviani et al. 1996). mtDNA contains 37 genes that code for 13 subunits of complexes I, III, IV, and V, as well as the machinery required to translate and transcribe the mtDNA genes into ETC complex subunits. The rest of the ETC complex subunits are coded by over 850 nDNA genes (Cotter et al. 2004). nDNA also codes for mitochondrial enzymes that participate in carbohydrate and fatty-acid oxidation. Thus, mutations in either genome can impair mitochondrial function and cause ETC complex deficiencies (DiMauro and Schon 2003).

The ETC complexes, particular complexes I and III, are the source as well as the major target of reactive oxygen species (ROS) (Fernandez-Checa et al. 1998; Trushina and McMurray 2007). The ETC is protected from damage caused by ROS by a mitochondrial specific superoxide dismutase and by antioxidants such as glutathione (GSH) (Fernandez-Checa et al. 1998) as well as by uncoupling proteins (Lambert and Brand 2004). Mitochondria lack the enzymes to synthesize GSH and therefore are dependent on cytosolic GSH production (Enns 2003; James et al. 2009b). The depletion of GSH in mitochondria makes cells more vulnerable to oxidative stress and damage from ROS originating from the mitochondria (Fernandez-Checa et al. 1997). Additionally, factors that increase ROS production (such as environmental toxicants, infections, and autoimmune disease) can directly and indirectly lead to impairments in ETC activity (Anderson et al. 2008; Calabrese et al. 2005; Munnich and Rustin 2001), deplete GSH (Calabrese et al. 2005), and activate mitochondrial- and non-mitochondrial-dependent biochemical cascades that result in programmed cell death (apoptosis) (Roberts et al. 2009).

The number of mitochondria in each cell depends on the cellular energy demands. For example, low-energy cells, such as skin cells, have fewer mitochondria, while cells that require high energy demands, such as muscle, liver, brain, cerebrovascular endothelium, and GI cells, have many mitochondria. Neural synapses are areas of high energy consumption (Ames 2000) and are therefore especially dependent on mitochondrial function (Mattson and Liu 2002). Mitochondria are concentrated in the dendritic and axonal termini where they play an important role in ATP production, calcium homeostasis, synaptic plasticity (Chen and Chan 2009; Li et al. 2004), as well as neurotransmitter release (Vos et al. 2010). Mitochondria help to regulate neuroplasticity, and abnormalities in mitochondrial function can play a role in psychiatric and neurodegenerative disorders (Mattson 2007). Therefore, central nervous system (CNS) manifestations are common in patients with mitochondrial disorders (MD) (Finsterer 2006).

Studies of healthy individuals have revealed a decrease in brain mitochondrial function associated with healthy aging (Forester et al. 2010) and brain mtDNA mutations are generally more common in elderly subjects compared to younger individuals (Lin et al. 2002). Mitochondrial dysfunction is particularly interesting to study as it has been implicated in a wide variety of diseases including psychiatric disorders (Anglin et al. 2012b; Jou et al. 2009; Manji et al. 2012; Marazziti et al. 2011, 2012; Rezin et al. 2009; Scaglia 2010; Shao et al. 2008) such as schizophrenia

(Clay et al. 2011; Kato et al. 2011; Scaglia 2010; Verge et al. 2011), bipolar disorder (Clay et al. 2011; Kato et al. 2011; Scaglia 2010), depression (Kato et al. 2010; Scaglia 2010), and autism spectrum disorder (Frye and Rossignol 2011; Rossignol and Bradstreet 2008; Rossignol and Frye 2011) as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (Federico et al. 2012). Mitochondrial dysfunction has also been reported in genetic syndromes associated with neurodevelopmental delays such as Rett syndrome (Condie et al. 2010; Gibson et al. 2010; Grosser et al. 2012), PTEN abnormalities (Napoli et al. 2012), Phelan-McDermid syndrome (Frye 2012a), 15q11-q13 duplication syndrome (Filipek et al. 2003; Frye 2009), Angelman syndrome (Su et al. 2011), Septo-optic dysplasia (Schuelke et al. 2002), and Down syndrome (Pagano and Castello 2012; Pallardo et al. 2010) along with a wide variety of medical disorders such as persistent systemic inflammation (Cox 2012), cardiac disease (Dai et al. 2012), and diabetes (Naudi et al. 2012). Mitochondria are also intimately involved in programmed cell death (apoptosis), calcium homeostasis, synaptic plasticity, and neurotransmitter release (Anderson et al. 2008; Roberts et al. 2009). In fact, mitochondrial dysfunction may be one of the common pathways in the development of pathology associated with a wide variety of diseases, especially since mitochondrial dysfunction can cause profound dysfunction in many organ systems, particularly high-energy organs such as the nervous and immune systems and the gastrointestinal tract (Rossignol and Frye 2011). The identification of mitochondrial dysfunction in psychiatric conditions could lead to the development of better medications for these conditions (Manji et al. 2012). Given the importance of mitochondria in CNS function, we review the involvement of mitochondria and MD in patients with psychiatric disorders.

## 3 Psychiatric Disorders in Patients with Mitochondrial Disease

Psychiatric disorders appear to be relatively common in patients with MD. For example, in a study of 36 adults with MD, 54 % had major depression, 17 % had bipolar disorder, and 11 % had a panic disorder (Fattal et al. 2007). In one study of 24 Italian patients with MD, psychiatric conditions were more common (60 %) than in the general population and included agoraphobia, panic disorder, anxiety disorders, and psychotic syndromes (Mancuso et al. 2013). As a group, fourteen adolescents and young adults with MD self-reported significant depression and anxiety on the Behavior Assessment System for Children (Schreiber 2012) and in another study, 14 % of children with MD developed symptoms of major depression before the MD diagnosis (Koene et al. 2009). Dementia has also been reported in multiple types of MD (Finsterer 2009).

Some patients with mtDNA mutations have been reported to have psychiatric symptoms. For example, one study reported that 19 adults with mtDNA mutations had more depressive symptoms and mood disorders compared to 10 controls (Inczedy-Farkas et al. 2012). Progressive psychiatric disturbance and dementia

along with neurological disturbances have been reported in a 57-year-old woman (Young et al. 2010) and a 27-year-old man (Salsano et al. 2011) with mitochondrial transfer RNA mutations. One study reported on a family with multiple deletions in mtDNA; this family contained multiple generations of psychiatric problems, including bipolar disorder, schizophrenia, and depression (Mancuso et al. 2008). Dementia (Hopkins et al. 2010) and psychiatric problems (Komulainen et al. 2010) have also been reported in the polymerase gamma-1 (POLG1) mutation. In one study of 50 patients with MD, of whom 52 % had mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), the most common psychiatric diagnoses were mood disorders, psychosis, cognitive deterioration, and anxiety (Anglin et al. 2012a). Confusion, aggressive behaviors, hallucinations, and paranoid delusions can also occur along with nonconvulsive status epilepticus and recurrent complex partial seizures in MELAS (Kaufman et al. 2010). In addition, MELAS has been associated with depression (Ju Seok et al. 2009) and obsessive-compulsive disorder (Lacey and Salzberg 2008).

Biomarkers of MD have been found to be abnormal in some patients with psychiatric disorders. For example, some hospitalized psychiatric patients have been reported to have low carnitine levels (Cuturic et al. 2011). Treatment with vitamins and minerals which improve mitochondrial function might help with certain psychiatric symptoms. One case report revealed that coenzyme Q10 improved psychiatric symptoms in a patient with MELAS (Shinkai et al. 2000). Another case report demonstrated that riboflavin treatment normalized behavior in a patient with MD and psychiatric illness (Triggs et al. 1992).

## 4 Schizophrenia

Several studies have reported genetic findings that might affect mitochondrial function in patients with schizophrenia. For example, one study reported that postmortem analysis of brains in patients with schizophrenia revealed a global downregulation of genes encoding mitochondrial elements, such as the electron transport chain (Iwamoto et al. 2005). Another study reported that postmortem brain samples from the dorsolateral prefrontal cortex revealed base pair substitutions in the mtDNA genome that was more common in individuals with schizophrenia compared to controls (Rollins et al. 2009). Finally, one study of 100 patients with schizophrenia found evidence of mtDNA inheritance (Verge et al. 2012).

Several studies have examined mitochondrial function in patients with schizophrenia. One postmortem study reported a 63 % reduction in complex IV activity in the nucleus caudatus and a 43 % reduction in the cortex gyrus frontalis in patients with schizophrenia compared to controls (Cavelier et al. 1995). Decreased hippocampal neuron gene expression affecting mitochondrial function was reported in 22 patients with schizophrenia compared to 24 controls (Altar et al. 2005). One study reported a patient with MELAS who had paranoid delusions, confusion, hallucinations, and aggressive behaviors (Kaufman et al. 2010). Finally, one study reported

improvements in 15 patients with schizophrenia using normobaric hyperoxia (40 % inspired oxygen) compared to room air; the investigators suggested that the increased oxygen may have improved mitochondrial function by augmenting oxygen delivery to mitochondria (Bloch et al. 2012).

## 5 Major Depression

One case reported discussed a 17-year-old girl with MELAS and reported depressed mood, loss of interest, and catatonia that improved with medication (Ju Seok et al. 2009). Another study reported on 35 children with MD; five of these children had major depression prior to the diagnosis of MD (Koene et al. 2009). Finally, one study reported symptoms of depression and anxiety in students with MD (Schreiber 2012).

## 6 Bipolar Disorder

Several studies have reported genetic findings in individuals with MD that might contribute to bipolar disorder. For example, one study reported that postmortem analysis of brains in patients with bipolar disorder revealed a global downregulation of genes encoding mitochondrial elements, such as the electron transport chain (Iwamoto et al. 2005). Another study reported that 2 of 35 patients had a mitochondrial DNA deletion which was not found in any of 29 normal controls (Kato and Takahashi 1996). Finally, one study reported an increased level of common deletions in mtDNA in the dorsolateral prefrontal cortex in patients with bipolar disorder compared to controls (Sequeira et al. 2012).

Some studies have also reported depressed mitochondrial function in patients with bipolar disorder. In one postmortem study of 15 patients with bipolar disorder, complex I activity in the prefrontal cortex was significantly depressed compared to 15 patients with depression and 15 patients with schizophrenia (Andreazza et al. 2010). In another study, 32 patients with bipolar disorder exhibited gray matter increases in lactic acid levels on brain spectroscopy imaging compared to controls, suggesting mitochondrial dysfunction (Dager et al. 2004). Finally, one study of 10 older adults with bipolar disorder reported a decrease in depressive symptoms with coenzyme Q10 (400–1,200 mg/day) in an open-label study (Forester et al. 2012).

## 7 Personality/Mood Disorders

One study of 238 healthy Japanese volunteers reported that a mitochondrial DNA polymorphism (C5178A) was associated with increased extraversion compared to those with the 5178C polymorphism (Kato et al. 2004). Another study reported two

individuals with obsessive-compulsive disorder who also had MELAS; the response to standard treatments was relatively poor (Lacey and Salzberg 2008). Finally, one study reported that genetic variants in mitochondrial proteins were associated with oxidative stress in patients with obsessive-compulsive disorder (OCD) (Orhan et al. 2012).

## 8 Alzheimer's Disease

In an animal model of Alzheimer's disease, decreased activity of complex IV was observed compared to control mice and was related to the production of beta-amyloid (Manczak et al. 2006). Two studies reported changes in TCA cycle enzyme activities in postmortem brain samples in patients with Alzheimer's disease which were consistent with mitochondrial dysfunction (Bubber et al. 2005, 2011). A study of 17 patients with Alzheimer's disease reported increased free radical production and decreased ATP production in brain samples compared to controls (Lin et al. 2002). Beta-amyloid production was associated with changes in mitochondrial structure including fragmentation in another study (Wang et al. 2008). Finally, in one study, relatives of patients who had Alzheimer's disease and who were at increased risk for Alzheimer's disease had evidence of reduced cerebral metabolism (Small et al. 1995).

## 9 Autism

Several review articles have reported mitochondrial dysfunction in individuals with autism (Frye and Rossignol 2011; Haas 2010; Rossignol and Frye 2011). Autism spectrum disorder (ASD) has also been reported in 120 cases of MD in 21 studies (Castro-Gago et al. 2008; Chauhan et al. 2010; Correia et al. 2006; Ezugha et al. 2010; Filiano et al. 2002; Filipek et al. 2003; Frye 2012a, b; Frye and Naviaux 2011; Gargus and Imtiaz 2008; Graf et al. 2000; Laszlo et al. 1994; Marin-Garcia et al. 1999; Nissenkorn et al. 2000; Oliveira et al. 2005, 2007; Pancrudo et al. 2007; Poling et al. 2006; Pons et al. 2004; Scaglia et al. 2009; Shoffner et al. 2010; Tsao and Mendell 2007; Weissman et al. 2008). One article reported that out of 153 studies examining various aspects of mitochondrial dysfunction in individuals with autism, 145 (95 %) implicated mitochondrial dysfunction in ASD (Rossignol and Frye 2012).

Several studies have suggested that treatment with mitochondrial cofactor supplementation, including antioxidants, coenzyme Q10, carnitine, and B vitamins, may improve mitochondrial function and behavior in some children with ASD (Rossignol and Frye 2011). L-carnitine may be particularly helpful in children with ASD since carnitine deficiency has been implicated in ASD (Filipek et al. 2004; Mostafa et al. 2005) and some studies have reported improvements with the use of L-carnitine in ASD (Ezugha et al. 2010; Filipek et al. 2003; Gargus and Imtiaz 2008; Gargus and Lerner 1997; Pastural et al. 2009; Poling et al. 2006). One double-blind, placebo-controlled study reported improvements in children with ASD using L-carnitine

(50 mg/kg/day), including hand muscle strength and cognition (Geier et al. 2011). A second double-blind, placebo-controlled study of L-carnitine (100 mg/kg/day) reported significant improvements over 6 months of treatment in ASD symptoms compared to placebo (Fahmy et al. 2013). Two double-blind, placebo-controlled studies using a multivitamin containing B vitamins, antioxidants, vitamin E, and coenzyme Q10 reported various improvements in ASD symptoms compared to placebo (Adams et al. 2011; Adams and Holloway 2004). Treatments for oxidative stress have also been shown to be beneficial for some children with ASD. For example, methylcobalamin and folinic acid have been reported to significantly increase glutathione concentrations in children with ASD and appear to improve certain autistic behaviors (James et al. 2004, 2009a). A recent study has demonstrated that *N*-acetylcysteine (NAC) improves irritability in children with ASD compared to placebo (Hardan et al. 2012). Several other antioxidants (Rossignol 2009), including vitamin C (Dolske et al. 1993) and carnosine (Chez et al. 2002), have also been reported to significantly improve autistic behaviors. Finally, one study reported improvements in ASD symptoms using NADH and D-ribose (Freedenfeld et al. 2011).

## 10 Conclusions

Evidence has started to accumulate that mitochondrial dysfunction plays a role in the development of many psychiatric disorders. The number of studies published to date which have examined mitochondrial function in these disorders is small. Additional studies are needed to evaluate mitochondrial function in psychiatric disorder in order to identify the burden that mitochondrial dysfunction plays. Studies examining prevalence, severity, laboratory testing, and treatments of mitochondrial dysfunction in psychiatric disorders are warranted.

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