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CANDIDATE REVIEWS

Mitochondrial Abnormalities in Bipolar Disorder

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Abstract
Bipolar disorder (BPD) is a common and severe mental illness that affects 3% of the population[1]. Although its disease mechanisms are poorly understood, several lines of evidence indicate that BPD involves genetic and functional mitochondrial disturbances. These studies include genetic linkage and gene expression studies, biochemical studies, and *in vivo* neuroimaging. Animal models indicate that mitochondrial perturbation can by itself produce mood disorder-like phenotypes. Additionally, the mood stabilizers used to treat BPD exert effects on mitochondria, enhancing mitochondrial-related gene expression and the functionality of mitochondrial enzymes, protecting cells from mitochondria-mediated cell death. This review discusses mitochondrial physiology and its links to BPD and the mechanisms of action of the mood stabilizers used in the treatment of BPD.

Key Words: *mitochondria, bipolar disorder, energy metabolism, mtDNA, gene expression, valproic acid, lithium*

Introduction

Bipolar disorder (BPD) is a common, severe mental illness in which patients suffer episodes of mania and depression[A]. The clinical presentation of BPD can vary among patients, but a common finding in genetic, biochemical, and neuroimaging studies is evidence of mitochondrial dysfunction. As a high-energy tissue, the brain relies heavily on energy production through mitochondria-mediated oxidative phosphorylation (OXPHOS)[2-3]. The brain, then, is particularly vulnerable to alterations in mitochondrial function, and mitochondria-related mutations often result in brain pathology, such as blindness or seizure[4-5]. Slight or major alterations in mitochondrial function—whether through mutation, alterations in levels of the mitochondrial genome (mtDNA), or reduced enzyme function—may play an important part in the pathophysiology of BPD. Accordingly, the mechanisms of action of the mood stabilizers[B] used to treat BPD may compensate for mitochondrial deficits by improving OXPHOS capacity or preventing mitochondria-mediated apoptosis. This review discusses mitochondrial genetics and physiology, the evidence for mitochondrial involvement in bipolar disorder, and the effects of mood stabilizers on mitochondrial function.

Mitochondria and mtDNA

Mitochondria are intracellular organelles with prominent roles in energy production through OXPHOS, intracellular calcium (Ca^{2+}) buffering, and regulation of apoptosis. Mitochondria possess outer and inner membranes, which are separated by the intermembrane space. The innermost space, the matrix, contains enzymes and metabolites needed for the Krebs cycle. The inner membrane is folded into cristae and houses the enzyme complexes used in electron-transport chain (ETC)-mediated energy production. Each mitochondrion contains multiple copies of a 16.6-kB circular genome (mtDNA) that encodes 37 genes: two rRNAs, 22 tRNAs, and 13 ETC genes[4-6]. The remainder of the 1000-plus genes required for mitochondrial function is encoded in the nuclear genome (nDNA)[4-5].

Most cells contain hundreds of mitochondria, and therefore also contain hundreds or thousands of mtDNAs, though cellular content varies with tissue type[2-4,7-9]. Typically, more mitochondria and mtDNA are found in high-energy tissues such as muscle and brain[2-3]. Because human cells are polyploid for mtDNA, different mtDNA genotypes can exist within the same cell, a state termed heteroplasmy. When mutant and wild-type mtDNAs exist within the same cell, the cell only becomes symptomatic of mitochondrial dysfunction when the proportion of mutant mtDNAs passes a threshold, typically 80-90% of the cell's mtDNA[5-7]. During cell division, mitochondria distribute randomly to daughter cells; in the event of heteroplasmy, some daughter cells may receive a higher proportion of mutant mtDNAs, resulting in tissue-specific variations in mitochondrial genotype, or mosaicism (Figure 1)[5,7].

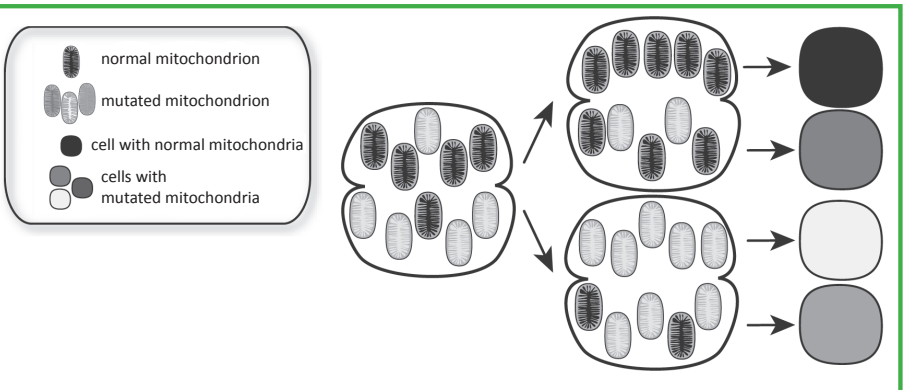

Figure 1. Heteroplasmy and mosaicism: Mitochondria containing both mutant and wild-type mtDNAs can divide such that some mitochondria become enriched for mutant mtDNAs. This is the basis for tissue-specific mitochondrial dysfunction.

MtDNA copy number regulation is important for the maintenance of mitochondrial function[10-14]. MtDNA depletion produces respiratory deficiencies inversely proportional to mtDNA levels[10-13]. MtDNA is packaged into protein-DNA complexes termed nucleoids, which house an average

[A] **Mania and Depression.** Affective states that define BPD. Mania involves elevated or irritable mood and hyperactivity, while depression is marked by sad mood and loss of pleasure, among other symptoms.
[B] **Mood Stabilizers.** Medications used to prevent episodes of mania and depression in BPD.

of eight mtDNA molecules[15], mitochondrial transcription factor A (TFAM), mitochondrial DNA polymerase γ (POLG), the helicase Twinkle, and mitochondrial single-strand binding protein (mtSSBP)[6,16]. Each nucleoid protein is nDNA-encoded. These proteins work together in mtDNA replication, and mutation or knockdown of POLG or TFAM can result in mtDNA depletion and subsequent respiratory deficiency[10-13]. In fact, mice with neuronal TFAM knockout exhibited neurodegeneration and increased apoptosis concomitant with reductions in mtDNA14. Loss of mtDNA also correlated with decreased functioning of the ETC complexes that contain mtDNA-encoded subunits[14]. Overexpression of TFAM in mice increased expression of some mitochondrial genes, but did not increase respiratory capacity beyond that of control[17].

Mitochondrial physiology

Mitochondria are important for producing energy in the form of ATP. This process begins in the cytosol with glycolysis, which breaks down glucose into pyruvate. In the mitochondrial matrix, the Krebs cycle further metabolizes pyruvate to produce electron donors NADH+H+ and FADH. NADH+H+ donates electrons to complex I of the ETC (NADH dehydrogenase). FADH donates electrons to complex II (succinate dehydrogenase)[4]. Electrons move from complexes I and II to coenzyme Q, then to complex III (ubiquinol:cytochrome c oxidoreductase), cytochrome c, then complex IV (cytochrome c oxidase), where the electrons combine with O_2 to form H_2O[4,7]. As electrons move along the ETC, they release energy, which is coupled to the pumping of protons from the matrix to the intermembrane space. The protons create an electrochemical gradient across the inner membrane[4-5,7]. The energy stored in this gradient is released as protons pass through complex V (ATP synthase), back into the matrix. Complex V uses energy released from protons to condense ADP and inorganic phosphate (Pi) into ATP (Figure 2)[5,7].

ETC inhibition or dysfunction can lead to production of reactive oxygen species (ROS), which damage proteins, lipids, and nucleic acids. ROS form when electrons prematurely release from the ETC and combine with O_2 to produce the superoxide anion (O_2•-)[4]. Because mtDNA lies close to ROS production sites, mtDNA has a higher mutation rate than nDNA, acquiring both single nucleotide polymorphisms (SNPs) and large-scale deletions[4,7]. The most prevalent mtDNA deletion, the common deletion, is nearly 5 kB long[4]. Cells containing a very high percentage of deletion-type mtDNAs exhibit higher ROS production rates and increased susceptibility to apoptosis[18-19].

Mitochondria provide Ca^{2+} buffering for the cell. Stimulation of receptors such as those for N-methyl-D-aspartate (NMDA) or inositol triphosphate (IP_3) elevates cytosolic Ca^{2+} levels[20]. Mitochondria take up Ca^{2+} but release it slowly, preventing Ca^{2+} overload and excitotoxicity[20].

Mitochondria also participate in the regulation of apoptosis. Exposure to cytotoxic stimuli such as high Ca^{2+} levels, excess ROS, or loss of the mitochondrial membrane potential triggers the opening of the mitochondrial permeability transition pore (mPTP). While not yet fully characterized, the mPTP is thought to contain several mitochondrial proteins, including cyclophilin D, the voltage-dependent anion channel (VDAC), and the adenine nucleotide translocase (ANT)[21]. Opening of the mPTP results in loss of the mitochondrial membrane potential and release of pro-apoptosis proteins such as cytochrome c and procaspases[21]. Cytochrome c, apoptotic protease activating factor 1 (Apaf1), and ATP work together to activate procaspase-9. Caspase-9 activates procaspase-3, which, in turn, promotes disassembly of the cytoskeleton, degradation of the nuclear genome, and apoptotic cell death[22].

In addition to cytochrome c and procaspases, mitochondrial outer membranes house members of the Bcl-2 protein family, which are important in apoptosis regulation[21,23]. Pro-apoptosis Bcl-2 proteins such as Bax and Bid promote the opening of the mPTP, while anti-apoptosis proteins such as Bcl-2 and Bcl-xL bind and inhibit pro-apoptosis Bcl-2 proteins[21,23]. The balance of pro- and anti-apoptosis Bcl-2 family proteins determines cell survival. As such, o IN- expression of Bcl-2 enhar TER- mitochondrial respiration and resilience against Ca^{2+}-mediated stress, but Bcl-2 knockout results in premature death[24-25].

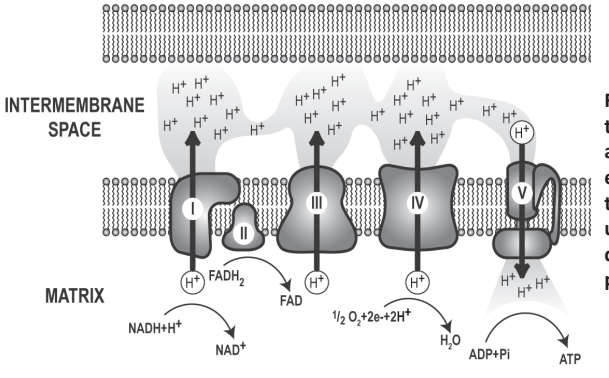

Figure 2. The electron transport chain (ETC): Electrons donated from NADH⁺H⁺ and FADH are passed along the five ETC complexes, releasing energy with each step. This energy is used to pump protons from the matrix to the intermembrane space. Complex V uses the energy stored in the electrochemical gradient across the inner mitochondrial membrane to produce ATP from ADP and P_i.

Mitochondrial disease

Mutations in mtDNA- or nDNA-encoded mitochondrial genes can result in mitochondrial disease. Because oocytes contain vastly more mitochondria than sperm, diseases stemming from mtDNA mutations or deletions exhibit a maternal inheritance pattern[5,7,26]. Alteration of OXPHOS genes impairs ETC function, and mutations in mitochondrial tRNAs inhibit mitochondrial protein synthesis. Also, POLG or TFAM mutations can prevent mtDNA replication, resulting in mitochondrial depletion syndrome[C,5-6]. Any of these alterations results in mitochondrial dysfunction and impaired energy production. Mitochondrial diseases commonly affect OXPHOS-reliant tissues such as muscle, brain, and pancreas, and involve symptoms like muscle weakness, blindness, seizure, and diabetes[4-6].

In addition to somatic symptoms, mitochondrial diseases are often comorbid with affective disorders and psychosis[5,27-30]. Inversely, BPD patients have increased rates of diabetes and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)[26,28]. As in BPD, mitochondrial diseases commonly do not appear until adulthood, and symptoms tend to worsen with time[1,7].

Mitochondrial abnormalities in BPD

Family studies have found a genetic contribution to BPD with an excess of maternal transmission, suggesting mitochondrial inheritance[31-35]. BPD-associated SNPs have been found across the mitochondrial genome[36-41], as well as in the nDNA-encoded complex I gene NDUFV2[42-44]. In addition to mitochondria-related SNPs, the common deletion may be more prevalent in the brains of BPD patients[45], though some have failed to replicate this finding[46].

Expression of mitochondria-related genes is altered in BPD. Lymphoblastoid cell lines (BLCLs) derived from BPD patients had reduced mRNA expression of complex I and III subunits[42,47-48]. Glycolysis and OXPHOS genes were downregulated in the prefrontal cortex (PFC) of BPD patients[49-51]. Mitochondria-related gene expression was also reduced in the hippocampus[52], nucleus accumbens, and cerebellum in BPD[53]. In hippocampus, 43% of all downregulated genes in BPD were mitochondria-related[52].

Alterations in gene expression could stem from abnormal mitochondrial gene regulation. Lymphocytes from BPD patients were unable to respond normally to mitochondrial stress, failing to upregulate mitochondrial genes in response to low-glucose stress[54]. Altered mitochondrial mRNA levels were associated with reduced protein expression and mitochondrial enzyme activity, as well as increased oxidative damage in the PFC[55].

Mitochondrial Ca^{2+} buffering is also abnormal in BPD. Baseline Ca^{2+} levels were elevated in lymphocytes, platelets, and BLCLs of BPD patients[56-57]. Both platelets and BLCLs exhibited increased Ca^{2+} responses to stimulation[58-60], indicating increased mitochondrial Ca^{2+} content, possibly placing cells at a greater risk for apoptosis.

In addition to biochemical data, neuroimaging studies have provided *in vivo* evidence for abnormalities in the brains of BPD patients. In magnetic resonance spectroscopy (MRS) studies, patients exhibited reduced pH, ATP, and phosphocreatine (PCr) levels in the frontal cortex, indicating impairments in OXPHOS and a subsequent reduction in high-energy phosphate levels[27,28,61-62]. These changes may be state-dependent, as white matter PCr levels were found to inversely relate to depressive symptoms[63], and pH levels increased during mania compared to euthymia within individual patients[62].

Animal models have likewise provided links between mitochondrial abnormalities and psychiatric symptoms. Bcl-2 knockdown mice displayed increased anxiety-related behaviors[25]. Mice expressing neuron-specific POLG mutations exhibited increased startle amplitude and freezing, as well as altered circadian rhythms[64]. Treatment with the mood stabilizer lithium (Li) or electroconvulsive shock normalized the behaviors of POLG mutant mice[64-65]. The phenotypes seen in these animal models indicate that mitochondria-related mutations are sufficient to produce behaviors similar to those of BPD.

Mood stabilizers affect mitochondrial physiology and apoptosis

Valproic acid (VPA) and Li are two of the most common mood stabilizers used to treat BPD. The exact mechanisms of action of these drugs have not yet been fully elucidated, but both VPA and Li exert several different mitochondria-related effects.

Treatment with VPA or Li increased expression of mRNAs for nDNA- and mtDNA-encoded OXPHOS genes[66], and Li treatment prevented methamphetamine-induced reductions of complex IV expression[67]. Additionally, VPA and Li treatment increased expression of the transcription factors that regulate expression of mitochondria-related genes in both nDNA and mtDNA[66], opening the potential for VPA- or Li-mediated changes in mtDNA copy number.

VPA and Li treatment enhanced O_2 consumption and mitochondrial membrane potential in the SH-SY5Y neuroblastoma cell line[67]. In rats, VPA and Li exerted at least partial protection against amphetamine-mediated reductions in OXPHOS enzyme activities in the PFC, striatum, and hippocampus[67-68]. Additionally, Li treatment in postmortem human PFC enhanced the activities of OXPHOS complexes I-IV, indicating that mood stabilizers could directly promote mitochondrial function in human brain areas affected by BPD[69].

BPD patients often have elevated cytosolic Ca^{2+}, both at baseline and after stimulation. VPA and Li exert opposite effects on baseline Ca^{2+} levels[60,70], but both caused reduced Ca^{2+} spikes after stimulation with histamine or lysophosphatidic acid[60,70]. In mice, Li treatment reduced ROS levels and increased Ca^{2+} uptake capacity after Ca^{2+} exposure[71]. In addition, these mice contained mitochondria that were less swollen than those of non-Li controls[71].

VPA and Li reduced apoptosis rates after stressors such as serum deprivation and glutamate exposure[72-73]. Additionally, VPA and Li prevented cytochrome c release, caspase-3 activation, poly (ADP-ribose) polymerase cleavage, and excitotoxicity in ROS-exposed SH-SY5Ys[74-75]. VPA and Li not only prevented apoptosis, but also actively promoted survival through upregulation of the antioxidant enzyme glutathione-S-transferase, and increased protein and phosphorylation levels of Bcl-2[67,73-74,76-77]. VPA and Li also downregulated the pro-apoptosis genes Bax and p53[72,74]. Enhancing cellular resilience could translate to the reversal of gray matter loss that has been found in BPD[61,78]. Magnetic resonance imaging (MRI) studies of BPD patients on and off Li treatment showed that those taking Li had elevated gray matter levels in areas related to mood regulation, such as the hippocampus, anterior cingulate gyrus, and amygdala[76]. These data indicate that both VPA and Li improve mitochondrial health, and so may be a common mechanism of action toward mood stabilization.

Conclusion

Energy availability and mitochondrial health are crucial for proper brain function. In a tissue as OXPHOS-reliant as the brain, even a small perturbation in mitochondrial function could have detrimental effects. BPD is not a classical mitochondrial disease, as most BPD patients do not experience the symptoms of primary mitochondrial dysfunction. However, the pathophysiology of some or all BPD cases may receive significant contribution from mitochondrial abnormalities. The heterogeneity of mitochondria-related genetic susceptibility loci indicates that a number of abnormalities could result in similar symptoms, such as those seen in biochemical and spectroscopic studies. Animal models strengthen the link between mitochondrial dysfunction and psychiatric phenotype. VPA and Li at least partially reverse mitochondrial deficits, enhancing mitochondrial function and resilience by increasing OXPHOS-related gene expression and enzyme activity. The full scope of mitochondrial involvement in BPD is not yet known. Characterizing the exact contributions of mitochondrial dysfunction in BPD pathophysiology, however, will enhance overall understanding of the disorder and could help direct the development of more targeted and effective therapeutics.

[C] **Mitochondrial Depletion Syndrome**. A mitochondrial disease in which symptoms stem from a loss of mtDNA.

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