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Mitochondrial dysfunction as a critical event in the pathophysiology of bipolar disorder

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Abstract

The understanding of the pathophysiology of bipolar disorder (BD) remains modest, despite recent advances in neurobiological research. The mitochondrial dysfunction hypothesis of bipolar disorder has been corroborated by several studies involving postmortem brain analysis, neuroimaging, and specific biomarkers in both rodent models and humans. Evidence suggests that BD might be related to abnormal mitochondrial morphology and dynamics, neuroimmune dysfunction, and atypical mitochondrial metabolism and oxidative stress pathways. Mitochondrial dysfunction in mood disorders is also associated with abnormal Ca²⁺ levels, glutamate excitotoxicity, an imbalance between pro- and antiapoptotic proteins towards apoptosis, abnormal gene expression of electron transport chain complexes, and decreased ATP synthesis. This paper aims to review and discuss the implications of mitochondrial dysfunction in BD etiology and to explore mitochondria as a potential target for novel therapeutic agents.

Keywords

Mitochondria; Bipolar disorder; Mania; Depression; Mitochondrial modulators

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating psychiatric illness characterized by episodes of mania or hypomania, depression, and mixed states, often accompanied by psychotic features and functional impairment (Cotrena et al., 2016; Grande et al., 2016; Zarate et al., 2000). Despite the advances in neurobiological research, comprehension of the pathophysiology of BD remains modest. Several studies have suggested that the pathophysiology of BD is orchestrated by several mechanisms synergistically involving complex interactions between genetic predisposition and exposure to different environmental risk factors and psychosocial stressors (Manji et al., 2011). Numerous research findings have proposed diverse mechanisms in the pathophysiology of BD, including neurotrophic factors, epigenetic mechanisms, mitochondrial dysfunction, oxidative stress, inflammation, circadian rhythm abnormalities, and biological aging acceleration (Scaini et al., 2020).

In the past few years, BD has been suggested to be a progressive condition, characterized by cognitive impairment and functional decline (Knezevic and Nedic, 2013; Leboyer and Kupfer, 2010; Muneer, 2016). Neuroprogression in BD may be considered pathological rewiring of the brain that occurs in parallel with the functional and clinical deterioration over the course of the disorder (Berk, 2009; Berk et al., 2014, 2011b; Fries et al., 2012; Gama et al., 2013; Schneider et al., 2012). Evidence from the literature demonstrates that structural brain changes and cognitive deficits are not consistently observed at early stages of BD, appearing to become more evident with chronicity and number of episodes (El-Badri et al., 2001; Lyoo et al., 2006; Robinson and Ferrier, 2006; Strakowski et al., 2002). In this context, neuroprogression seems to be related to the cumulative effects of immune dysfunction, enhanced oxidative stress, neurotrophic support breakdown, mitochondrial dysfunction, and impairment of cellular resilience (Berk et al., 2011b; Fries et al., 2012; Kapczinski et al., 2008; Post et al., 2012). Staging models of BD have suggested that multiple episodes may lead to permanent alterations, including significant systemic toxicity, cognitive and functional impairment, and biological changes, which may be transduced to greater liability to relapse and poorer treatment response (Gama et al., 2013; Kapczinski et al., 2010; Post et al., 2012). However, such a progressive feature does not seem to be present across all patients, with some not experiencing as much cognitive or functional impairment as others (Passos et al., 2016), suggesting the existence of subgroups within BD.

Mitochondria are unique intracellular organelles that contain their own DNA (mtDNA) and are composed of inner and outer membranes with an intermembrane space and an intracellular matrix (Velot and Srere, 2000). Mitochondria are classically described as the powerhouse of the cell, as they are the source of adenosine triphosphate (ATP) through the process of oxidative phosphorylation via the electron transport chain (ETC) (Briere et al., 2004; Fang et al., 2016). The ETC is composed of five multimeric protein complexes (I-IV and ATP-synthase or complex V) that are responsible for ATP production through oxidative phosphorylation. Complex I (NADH: ubiquinone oxidoreductase) and complex II (succinate dehydrogenase) begin the process of oxidative phosphorylation by catalyzing the transfer of electrons from NADH and FADH₂, respectively, to coenzyme Q (or ubiquinone). The transfer of electrons is serially conducted through complex III (ubiquinol: cytochrome

c oxidoreductase), cytochrome c, and complex IV (cytochrome c oxidase), to the terminal acceptor, generating an electrochemical proton gradient that enhances ATP production in complex V via oxidative phosphorylation (Lenaz and Genova, 2010; Velot and Srere, 2000).

In addition to ATP generation, mitochondria play an important role in other cellular functions, including reactive oxygen species (ROS) production, cell death pathways (apoptosis), and calcium (Ca^{2+}) homeostasis (Budd and Nicholls, 1998; Chakrabarty et al., 2018; Kadenbach et al., 2010). Mitochondria also modulate some of the effects of brain-derived neurotrophic factor (BDNF) in neurons and, therefore, exert an essential function regarding synaptic plasticity (Burkhalter et al., 2003). Multiple signaling pathways stimulate mitochondrial biogenesis, motility, shape, fusion and fission, and energy metabolism due to activation of neurotransmitters and growth factor receptors, which are ultimately related to memory and learning processes (Cheng et al., 2010; Ly and Verstreken, 2006). Moreover, mtDNA is associated with higher rates of damage compared to nuclear DNA due to exposure to ROS and insufficient repair mechanisms (Cuperfain et al., 2018).

Given the role of this organelle, it is not surprising that mitochondrial dysfunction has been implicated in a variety of neurological and psychiatric disorders, including BD (Cuperfain et al., 2018; Kim et al., 2019; Panchal and Tiwari, 2019; Pei and Wallace, 2018; Streck et al., 2014). The mitochondrial dysfunction hypothesis suggests that BD is triggered, in part, via mitochondria dysfunction, which is intimately linked to a wide range of processes associated with treatment outcomes and disease progression or severity, including inflammation, oxidative stress, stress response systems, and accelerated aging. Interestingly, studies in primary mitochondrial diseases have shown a high prevalence of self-reported affective syndromes, particularly BD (Colasanti et al., 2020; Koene et al., 2009; Morava et al., 2010). However, it remains unclear whether abnormal mitochondrial function is a cause or consequence (or even both) of BD. This paper aims to review and discuss, in more detail, the implications of mitochondrial dysfunction in the pathophysiology of BD and to explore the mitochondria as a potential target for novel therapeutic agents, providing an overview of recent findings on the mechanisms of mitochondrial dysfunction in BD (Fig. 1).

2. Changes in mitochondrial bioenergetics and morphology in bipolar disorder

Mitochondria are the primary source of ATP synthesis and the major intracellular source of vital energy production in the brain. As a direct by-product of this ATP production, mitochondria also produce reactive oxygen species (ROS) that play an important role in cell signaling and regulation (Rhee, 1999; Thannickal and Fanburg, 2000). However, under pathological conditions, when cellular production of ROS overwhelms antioxidant capacity, oxidative stress occurs, causing damage to lipids, proteins, and DNA (Rhoads et al., 2006).

Over the past several decades, researchers have highlighted the role of this organelle in the pathophysiology of BD. A series of magnetic resonance spectroscopy (MRS) and phosphorus-31 MRS (^{31}P -MRS) studies, Kato and colleagues have shown that patients with BD exhibited alterations in neurometabolites, including high-energy compounds, all of which are hallmarks of a decrease in mitochondrial energy production (Kato, 2005; Kato

et al., 1998, 1992, 1994). In summary, patients with mood disorders present with lower levels of phosphocreatine (PCr), N-acetyl-aspartate (NAA), adenosine diphosphate (ADP), and ATP (Kato et al., 1992; Scaini et al., 2016). Moreover, studies have noted that negative correlations exist between NAA/Creatine + PCr or NAA levels and illness duration in BD (Chang et al., 2003; Deicken et al., 2003; Winsberg et al., 2000). Furthermore, some investigators have suggested that patients with BD exhibit an abnormality in enzymatic reaction rate in the creatine kinase (CK) system. These studies have shown a decrease in the forward rate constant of the CK enzyme without alterations in ATP or PCr levels, as well as downregulation of CK in postmortem brains of BD patients (Du et al., 2018; MacDonald et al., 2006). These findings are in line with a study indicating that individuals with BD maintain average brain concentrations of high-energy compounds at rest. However, when energy demand is increased, BD patients exhibited significant reductions in ATP but not in PCr, suggesting a failure to replenish ATP from PCr through CK enzyme catalysis during tissue activation (Yuksel et al., 2015).

Based on findings showing that BD patients present high lactate levels, a product of increased glycolysis, and reduced intracellular pH in the brain, studies have also suggested that in BD, during mitochondrial dysfunction, cells shift primarily to glycolytic metabolism to generate ATP (Dager et al., 2004; Dogan et al., 2018; Kato et al., 1998, 1992, 1994; Kuang et al., 2018). Supporting this hypothesis, several studies have reported mitochondrial-specific changes regarding the Krebs cycle and oxidative phosphorylation in BD. A metabolomics study showed that BD patients had higher serum levels of pyruvate, N-acetylglutamic acid, α -ketoglutarate, and arginine, whereas levels of β -alanine and serine were significantly lower (Yoshimi et al., 2016b). The same research group found evidence for abnormalities in the metabolism of isocitrate in cerebrospinal fluid (CSF) and postmortem brain tissue of BD patients. In line with these findings, Zverova et al. (2019) reported a significant decrease in citrate synthase (CS), complex II, and complex IV activities in platelets from BD patients during a depressive episode. In contrast, complex I activity and complex I/CS ratio were increased in these patients. Along the same lines, Valvassori et al. (2018) revealed that depressed BD patients present decreased complex II activity in peripheral blood mononuclear cells (PBMCs). On the other hand, studies on postmortem frontal cortex from patients with BD showed a decrease in complex I activity (Andreazza et al., 2010; Kim et al., 2015). Contrary to these reports, studies have reported that activity of complexes I, II-III and IV were unaltered in PBMCs and platelets from BD patients (Ben-Shachar et al., 1999; Gubert et al., 2013). Moreover, a study in drug naïve BD patients reported no significant alterations in citrate synthase, malate dehydrogenase, or succinate dehydrogenase (de Sousa et al., 2015).

Microarray and real-time quantitative polymerase chain reaction (qPCR) data revealed decreased expression of many messenger RNAs (mRNAs) encoding subunits of ETC complexes I to V in BD patients (Table 1). Studies have shown significant differences in mRNA levels for complex I subunits NDUFV1, NDUFV2, NDUFS1, NDUFS7 and NDUFS8 in patients with BD, yet a follow up study described no difference (Akarsu et al., 2015; Andreazza et al., 2010, 2013; Iwamoto et al., 2004; Konradi et al., 2004; Sun et al., 2006). In a re-analysis of microarray studies in postmortem brains, Scola et al. (2013) showed that subunits containing iron-sulfur clusters within the hydrophilic arm (NDUFV2,

NDUFS8, and NDUFS7) were downregulated in BD patients, suggesting dysfunction of the electron transfer process. Subunits associated with complex III (UQCRC2), complex V (COX7A2, COX7B, COX5A, COX6C, and COX15), and complex IV (ATP5C1, ATP5G3, ATP5H, ATP5J, ATP5J2, and ATP5O) have also been reported as decreased in the prefrontal cortex and hippocampus, while in blood, increases in subunits of the ETC were observed (Beech et al., 2010; Iwamoto et al., 2004; Konradi et al., 2004; Sun et al., 2006). Moreover, Naydenov et al. (2007) showed that during glucose deprivation, genes associated with complex III and IV were downregulated in lymphocytes from patients with BD. However, a recent multivariate meta-analysis of mitochondrial complexes I and IV revealed that alterations in these complexes are not always consistent, suggesting brain region- and tissue-specific heterogeneity. In summary, they found moderate effects on complex I and small effects in complex IV (Holper et al., 2019). In addition to the alterations in genes of the ETC, Yoshimi et al. (2016a) showed downregulation of isocitrate dehydrogenase genes (IDH3A and IDH3B) in BD patients. Considering these findings, we hypothesized that besides downregulation in subunits of the ETC complexes, alterations in Krebs cycle enzymes cause a decrease in its velocity, limiting NADH production for complex I, which might cause maximal reduction of the rate and efficiency of electron transfer.

In addition to alterations in energy metabolism, recent attention has focused on the role of the mitochondrial quality control system in BD. This system is sustained through synthesis of new mitochondria, the processes of fusion and fission, and elimination of damaged mitochondria (Kornmann, 2014), which is responsible for the maintenance of a healthy mitochondrial population that is fundamental to cell health and viability (Boveris et al., 1972; Fischer et al., 2012). Previous research findings into mitochondrial morphology have reported that postmortem prefrontal cortical neurons from patients with BD and their peripheral cells display morphological abnormalities (more mitochondria of smaller size). Moreover, the same authors showed an abnormal pattern of clumping and marginalization with respect to the intracellular distribution of mitochondria in peripheral cells and atypically shaped mitochondria (ring- or cup-shaped mitochondrial profiles), suggesting subtle changes in the critical network architecture of mitochondria in cells (Cataldo et al., 2010). In an elegant study using a BD neuronal model based on iPSC technology, Mertens et al. (2015) corroborated previous findings showing that iPSC-derived fibroblasts from patients with BD exhibited smaller mitochondria than those from iPSC-derived fibroblasts of HCs.

Following these findings, Scaini et al. showed that BD patients present alterations in the levels of proteins governing mitochondrial fission and fusion, causing an imbalance in mitochondrial fission and fusion towards fission. The same group also showed impairment in the removal of damaged mitochondria via the mitophagy pathway, followed by apoptosis activation in BD patients (Scaini et al., 2019, 2017b). In summary, these studies revealed downregulation of the mitochondrial fusion-related proteins Mfn-2 and Opa-1 and upregulation of the fission protein Fis-1 in PBMCs from BD patients, suggesting that the imbalance in mitochondrial dynamics might explain the abnormal mitochondrial morphology observed in patients with BD. Moreover, mRNA expression and protein levels of Parkin, p62, and LC3B, which are mitophagy-related proteins, were decreased in PBMCs from BD patients, followed by higher levels of activated caspase-3. Taken together, these

results suggest that in BD, the number of damaged mitochondria exceeds the capacity of mitophagy, causing apoptosis to become the dominant pathway to minimize tissue damage (Scaini et al., 2019, 2017b). The lack of mitophagy leads to a loss of mitochondrial quality control, resulting in a release of damage-associated molecular patterns (DAMPs) that induce sterile inflammation by interacting with Toll-like receptor 9 (TLR9) and promoting activation of NF- κ B and the NLRP3 inflammasome (Nakahira et al., 2011; Pinti et al., 2014; Wu et al., 2019; Yuzefovych et al., 2019). Not surprisingly, inflammation has been associated with BD by many studies and research groups (Fries et al., 2019b)

As mentioned above, defects in the ETC result in increased ROS production, culminating in oxidative stress and changes in energy production that lead to a vicious cycle of cellular dysfunction and death (Ott et al., 2007; Sanz et al., 2006). In fact, oxidative stress has been implicated in BD, being explored as an agent of accelerated aging in BD (Fries et al., 2020). Several markers of oxidative stress were found to be altered in patients with BD, including glutathione peroxidase, 8-oxo-2'-deoxyguanosine (8-oxodG), 8-oxo-7,8-dihydroguanosine (8-oxoGuo), lipid peroxidation hydroperoxides, glutathione S-transferase, glutathione reductase, 3-nitrotyrosine, protein carbonyl, and thiobarbituric acid reactive substances (Andreazza et al., 2013; Ceylan et al., 2018; de Sousa et al., 2014; Gubert et al., 2013; Raffa et al., 2012; Rosa et al., 2014). A meta-analysis of studies that measured oxidative stress markers in BD patients compared to healthy controls showed that lipid peroxidation, DNA/RNA damage, and nitric oxide were significantly increased in BD patients (Brown et al., 2014). Another study demonstrated a significant increase in GSH concentrations in the anterior cingulate cortex (ACC) of BD patients (Das et al., 2019). Moreover, a recently published study focusing on cerebral spinal fluid revealed that 8-oxoGuo is statistically significantly higher at baseline and follow-up in BD, suggesting that CSF oxidative stress may represent state and trait markers in BD and may reflect neurobiological correlates of illness progression and sensitization (Knorr et al., 2019).

3. Bipolar disorder and changes in calcium and apoptosis

As mentioned above, mitochondria are the primary source of cellular energy. However, they are also responsible for other crucial processes for cellular function and survival, such as apoptosis and Ca²⁺ homeostasis (Zavodnik, 2016). Mitochondria play a part in intracellular Ca²⁺ signaling as modulators, buffers and sensors (Rizzuto et al., 2012). Ca²⁺ influx and efflux through the outer mitochondrial membrane occurs by the voltage-dependent anion channel (VDAC), the principal metabolite transport system across the outer mitochondrial membrane. While mitochondrial Ca²⁺ uniporter (MCU), mitochondrial ryanodine receptor (mRyR), and rapid mode of Ca²⁺ uptake (RaM) are responsible for Ca²⁺ influx through the inner mitochondrial membrane (IMM) (Bravo-Sagua et al., 2017). Ca²⁺ uptake in the mitochondrion has essential roles such as spatially remodeling intracellular Ca²⁺ signaling, controlling the rate of energy production, being conducive to cellular death, and neuronal excitability (Belosludtsev et al., 2019; Giorgi et al., 2018; Gorlach et al., 2015). On the other hand, Ca²⁺ overload causes endoplasmic reticulum stress and Ca²⁺ leakage, which affects mitochondrial uptake, causing an excessive Ca²⁺ taken up into mitochondria, resulting in a collapse of the mitochondrial membrane potential, termination of oxidative phosphorylation processes, osmotic changes, mitochondrial swelling, and inner membrane remodeling,

mitochondrial permeability transition pore (mPTP) opening, cytochrome c release, activation of caspases and apoptosis, and subsequently cell death (Belosludtsev et al., 2019; Bravo-Sagua et al., 2017; Giorgio et al., 2018; Marchi et al., 2018).

Altered intracellular Ca^{2+} levels are a consistent finding in BD patients, and many studies point to the role of mitochondrial dysfunction, indicating the possibility that mitochondrial Ca^{2+} dysregulation is involved in the pathophysiology of BD (Kato, 2008). Several studies have investigated intracellular Ca^{2+} dynamics and alterations in the pathophysiology of BD. Most of these studies consistently found elevated basal (Ca^{2+B}) and agonist-stimulated (Ca^{2+S}) intracellular Ca^{2+} levels in the platelets, lymphocytes, B lymphoblast cell lines (BLCLs) and olfactory neurons of BD patients compared with healthy subjects (Corson et al., 2001; Dubovsky et al., 2014; Emamghoreishi et al., 1997; Hahn et al., 2005; Hough et al., 1999; Perova et al., 2008). Moreover, postmortem brain studies have also found altered mRNA expression of inositol monophosphate type II (IMPase) and a transient receptor potential channel (TRPM2), proteins that are involved in the Ca^{2+} homeostasis (Yoon et al., 2001a, 2001b). In fact, a recently systematic review and meta-analysis of studies of cellular calcium levels in BD found a robust, medium effect size elevation of basal and stimulated free intracellular Ca^{2+} , suggesting altered Ca^{2+} functioning in the disorder (Harrison et al., 2019). In line with this, studies have proposed that chronic lithium at therapeutic doses blocks the increase in Ca^{2+} concentration, attenuating agonist-stimulated intracellular Ca^{2+} responses (Gould and Manji, 2005; Gurvich and Klein, 2002; Hashimoto et al., 2002; Li et al., 2002). Wasserman et al. (2004) showed that lithium exerts significant modulatory effects on intracellular Ca^{2+} dynamics in BLCLs from BD-I patients through the attenuation of receptor-G-protein coupled agonist (lysophosphatidic acid (LPA)) stimulation of Ca^{2+} mobilization (a G-protein-coupled receptor activated signaling pathway), and TG-evoked store-depletion-induced Ca^{2+} influx (a measure of SOCE).

More recently, Mertens et al. (2015) demonstrated that young hippocampal dentate gyrus-like neurons derived from iPSCs of patients with BD had smaller mitochondria than controls, as well as changes on the gene expression of pathways involving Ca^{2+} signaling, neuroactive ligand-receptor interaction, and protein kinase PKA/PKC signaling, in addition to changes in the action potential firing system. Moreover, using neuronal hyperactivity and lithium responsiveness as two indices, the same authors detected correlated changes in the PKA/PKC/AP and mitochondria genes in the BD neurons, indicating that these pathways might be related to neuronal hyperexcitability. Indeed, excess Ca^{2+} affects both neuronal excitability and signaling cascades regulating gene expression, leading to perturbation of multiple neuronal processes, such as dendrite development, synaptic plasticity, and excitatory/inhibitory balance (Greer and Greenberg, 2008). Therefore, these changes in Ca^{2+} dynamics described in patients with BD might be related to disturbances in homeostatic cellular physiology control.

Another fascinating aspect of Ca^{2+} signaling is its capacity to regulate cell death. One of the most well-studied Ca^{2+} -induced cell death pathways is the cross-talk between the endoplasmic reticulum and mitochondria. As described above, mitochondrial Ca^{2+} overload induces several changes that culminate by mitochondrial outer membrane permeabilization (MOMP) and the release of cytochrome c, which is an inducer of apoptosis

and modulator of other proapoptotic factors, such as Smac/DIABLO, HtrA2/Omi, AIF and EndoG. Moreover, it is proposed that VDAC1, play crucial role in apoptosis activation mediated by cytochrome c release through transfers of apoptotic Ca²⁺ signals from the endoplasmic reticulum to mitochondria, as well as by the interaction with the Bcl-2 family of proteins (Shimizu et al., 2000b, 2001; Tsujimoto and Shimizu, 2000; Azoulay-Zohar et al., 2004).

The widely described presence of apoptosis in cells from BD patients occurs through several mechanisms, including Ca²⁺-mediated excitotoxicity, as mentioned above, increased oxidative stress parameters, and profound changes in mitochondrial structure and function (Giorgi et al., 2008). A postmortem brain study in BD patients revealed a significant decrease in levels of Bcl-2 and brain-derived neurotrophic factor (BDNF), whereas Bax, Bad and caspase-3 and -9 levels were significantly increased (Kim et al., 2010). The changes observed in postmortem brain studies parallel changes observed in peripheral cells of patients with BD. Bei et al. (2009) observed decreased cytosolic Bax, suggesting an increase in Bax activation and translocation to mitochondria to activate apoptosis, as well as decreased expression of HSP70, an antiapoptotic factor. In agreement with these findings, Moutsatsou et al. (2014) showed an increase in the BAX/Bcl2 ratio, cytochrome c release, and caspase-3 activity in manic and depressed patients compared to healthy controls. Likewise, higher levels of antiapoptotic proteins, Bcl-xL, survivin, and the Bcl-xL/Bak dimer, were significantly decreased in PBMCs from patients with BD, while active caspase-3 levels were significantly increased (Scaini et al., 2017a). The same authors showed that BD patients present higher levels of VDAC1 and TSPO (Scaini et al., 2019). Another study showed that in depressed patients, S100B levels correlated with cytochrome c release (Paraskevi et al., 2014). Furthermore, the percentage of cells in early apoptosis was higher in PMBCs from BD patients compared to controls (Fries et al., 2014). Taken together, could be hypothesized that in patients with BD, the selective placement of VDAC channels at ER/mitochondria contact sites facilitates mitochondrial Ca²⁺ accumulation leading to cell death. However, further experimental investigations are needed to estimate the functional relevance of the crosstalk between VDAC, mitochondrial Ca²⁺ dynamics, and ROS metabolism to the apoptosis activation in BD patients.

4. Mitochondria, redox system and circadian rhythmicity in bipolar Disorder. How do these Interrelate?

Several studies have demonstrate that, at the cellular level, mitochondrial oxidative phosphorylation and redox states are regulated in a circadian manner, and also signal back to the core clock, suggesting a regulation loop exists between clock machinery and metabolism (de Goede et al., 2018; Peek et al., 2013; Schmitt et al., 2018). Several studies have shown that suprachiasmatic nucleus neurons and astrocytes exhibit daily rhythms in cytochrome c oxidase activity, mitochondrial membrane potential and calcium release from mitochondria (Burkeen et al., 2011; Isobe et al., 2011; Marpegan et al., 2011). In fact, studies have described that metabolic byproducts (e.g.: NAD⁺, ATP) display 24 h oscillation and can in turn regulate the clock. The rhythms of these byproducts are believed to be dependent on the molecular clockwork because the activity of the rate-limiting enzyme nicotinamide

phosphoribosyltransferase (NAMPT) is controlled by CLOCK–BMAL1 activator complex in conjunction with NAD⁺-dependent deacetylase sirtuin 3 (SIRT3) (Nakahata et al., 2009; Ramsey et al., 2009; Sahar et al., 2011). Moreover, it was shown that the transcriptional coactivator PGC-1 α , which is the master regulator of mitochondrial biogenesis and energy metabolism, is an essential component of the circadian clock in the liver and muscle (Liu et al., 2007). In the same line, studies have also suggest that the activation of AMPK (adenosine monophosphate-dependent protein kinase), can directly modulate the core clock machinery by phosphorylation of the clock repressor proteins CRY and PER, targeting them for proteasomal (Jordan and Lamia, 2013). Of the note, evidence has also shown that alterations in mitochondrial morphology (i.e., fusion and fission) and mitochondrial abundance are under circadian clock control (Jacobi et al., 2015; Schmitt et al., 2018). These cycles of fission and fusion and, consequently, the rhythms of energy production are regulated by phosphorylation and activity of dynamin-related protein 1 (DRP1), which occurs in a circadian manner to drive mitochondrial network fragmentation (Schmitt et al., 2018).

So given the intimate connection between the circadian system and redox sensing, it seems reasonable to suspect that a disruption in metabolic/clock cross talk might lead to poor cellular health. At this point to be remember that mitochondrial dysfunction is a key element in the pathophysiology of BD. Moreover, the role of SIRT3 and PGC-1 α in the context of BD phenotypes and treatments has been suggested but not studied in depth. A study using PGC-1 α null mice showed that the lack of PGC-1 α in GABAergic neurons causes an increase in the activity across tests that might be related to a mania-like phenotype. Geoffroy et al. (2016) performed a pharmacogenetic study and found an association between PGC-1 α and lithium response in BD patients, but this association did not survive Bonferroni correction, requiring additional studies to provide more functional/biological data supporting these preliminary finding. Of the first consideration, BD are associated with major disruptions in circadian rhythms. Studies have demonstrate that genes such as Clock, Bmal1, and Per, which are intimately involved in the generation and regulation of circadian rhythms, have been linked to BD, as well as illness severity (Geoffroy, 2018; Maciukiewicz et al., 2014; McCarthy et al., 2012, 2013; Milhiet et al., 2014; Shi et al., 2008; Yang et al., 2009)

Taking together the evidence of the correlation between mitochondrial and circadian clock dysfunction, and the fact the cross-sectional research design of most studies precludes establishing a cause/effect relationship between mitochondrial dysfunction, circadian disruption, and BD, it remains undetermined what comes first. Of note, given that mitochondrial metabolism is connected, on the one hand, with circadian rhythms and, on the other hand with the pathogenesis of BD, it would be a thrilling challenge to highlight the impending interplay between mitochondrial network, the circadian rhythm in both physiological systems.

5. Genetic evidence for mitochondrial dysfunction in bipolar disorder

As mentioned above, mitochondria are organelles that contain their own DNA, which is responsible for encoding genes that include proteins involved in oxidative phosphorylation,

as well as some unique transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) (Calvo et al., 2016; Taanman, 1999). Although mitochondria have their own DNA, cellular metabolism and mitochondrial function require a combination of proteins that are also encoded in the nucleus (Cuperfain et al., 2018). Thus, both nuclear DNA (nDNA) and mtDNA must be analyzed in a genetic investigation of mitochondrial dysfunction.

Several studies suggest that BD possesses an important genetic component, with twin studies showing heritability rates as high as 70–80% (Edvardsen et al., 2008; McGuffin et al., 2003). The high genetic component is also shown by the increased risk of BD in first-degree relatives of patients (Gottesman et al., 2010). Accordingly, children of parents diagnosed with BD have been shown to have a significantly increased risk to develop the disorder compared to offspring of control parents (Duffy et al., 2019; Rasic et al., 2014) and often present signs and symptoms that may accompany familial risk in the absence of a BD diagnosis (Axelson et al., 2015; Diler et al., 2017; Dong et al., 2019; Levenson et al., 2015; Manelis et al., 2016).

Recent studies have investigated specific mutations related to mitochondrial function in mtDNA and nDNA, such as single nucleotide polymorphisms (SNPs), deletions, copy number variations, as well as epigenetics and haplogroups, which may be correlated with the pathophysiology of psychiatric disorders, including BD (Cuperfain et al., 2018; Kasahara and Kato, 2018; Schulmann et al., 2019). Munakata et al. (2004) suggested that the 3644C mutation is associated with increased risk for BD, by decreasing mitochondrial membrane potential and complex I activity, due to a 3644 T → C that causes a V113A amino acid substitution in NADH-ubiquinone dehydrogenase subunit I (ND1). It was also identified that in postmortem brains of BD patients, there was increased gene expression of mitochondrial leucyl-tRNA synthetase, which is related to the accumulation of 3243A → G in mtDNA (Munakata et al., 2005). Moreover, different amino acid substitutions in specific candidate genes and haplogroups in BD patients have been reported (Kato and Kato, 2000; Kato et al., 2001; Kazuno et al., 2009).

Genome-wide association studies (GWAS) have showed that genes encoding ankyrin 3 (ANK3) and the α -calcium channel subunit (CAC-NA1C) are considerable genetic risk factors for the development of BD (Fiorentino et al., 2014). In line with this, Michels et al., 2018 showed that downregulation of CACNA1C expression protected cells from oxidative stress by inhibiting excessive mitochondrial ROS generation and Ca^{2+} influx in mouse hippocampal cells. Recently, a trio-based WES study for BD published by Kataoka et al. (2016) identified potential roles of *de novo* protein-altering mutations and calcium-related genes in the disease etiology most of which create non-functioning proteins, predominantly in genes for calcium-binding proteins. The same authors described that earlier age at onset in carriers of protein-altering *de novo* mutations, and the rate of *de novo* mutations was higher in BD-I, suggesting a role for these mutations in BD (Kataoka et al., 2016). Schulmann et al. (2019) demonstrated that the odds ratios for BD risk decreased from 1.1 to 0.38 by adding a mtSNP minor allele compared to the mtSNP major allele for the nuclear gene AK5, a brain-specific gene involved in the synthesis of ADP and the cytochrome B oxidase gene (CYTB), suggesting. These findings suggest that both genomes jointly determine the

cellular energy production requirements, impairment of which is associated with risk for BD (Schulmann et al., 2019).

Recently Fries et al. (2017) showed that BD patients may display accelerated epigenetic aging, most likely due to high mtDNA copy number (mtDNAcn), although no association with telomere shortening was observed (Fries et al., 2017). The same group also demonstrated a reduction in mtDNA copy number and an epigenetic aging acceleration in postmortem hippocampus from BD patients compared to controls among older subjects (Fries et al., 2019a). However, a meta-analysis identified no significant differences between mtDNA copy numbers in BD patients. Another meta-analysis, including a low level of heterogeneity, revealed significantly lower mtDNAcn in patients (Yamaki et al., 2018). Recent studies have also described a downregulation of DNA polymerase gamma (POLG) and 8-oxoguanine-DNA glycosylase 1 (OGG1), a DNA repair enzyme, in patients with BD, suggesting that this may be one of the mechanisms responsible for reduced mtDNA copy number (Ceylan et al., 2018; Munkholm et al., 2015).

6. Effects of mood stabilizers on mitochondria

Multiple drugs, such as lithium, some anticonvulsants and antipsychotics, have been shown to be effective in treating or preventing manic and depressive episodes; however, full comprehension of their precise mechanisms of action in BD remains unknown with little progress being made in developing novel medications. It has been postulated that mood stabilizers likely enhance energy metabolism by changing intracellular signaling pathways (Hroudova and Fisar, 2011), and there are several explanations for their neuroprotective properties. Among mood stabilizers, lithium seems to be the most investigated compound.

In vitro studies showed that lithium might stabilize mitochondrial membrane potential and reduce DNA damaging effects. Lithium may also delay Ca²⁺-induced apoptosis by antagonizing the mPTP, as demonstrated in isolated rat mitochondria (Shalbuyeva et al., 2007). Findings of increased grey matter in BD subjects following lithium treatment is congruent with its antiapoptotic properties (Moore et al., 2000). Lithium also decreased levels of DNA methylation in BD patients (Huzayyin et al., 2014), increased levels of glutathione transferase (Clay et al., 2011; Cui et al., 2007; Shao et al., 2005), reduced apoptosis and enhanced catalase activity (Machado-Vieira et al., 2007).

Impairment of complex I function is related to increased generation of ROS (Sharma et al., 2011), and lithium stimulates the activity of this complex in the prefrontal cortex (Valvassori et al., 2010). Another study by Scola et al. (2014) demonstrated that lithium attenuated complex I dysfunction on DNA methylation and hydroxymethylation induced by rotenone in rat primary cortical neurons. In addition to complex I, lithium has also been observed to increase the activity of mitochondrial chain enzyme complexes II and III in human frontal cortex (Maurer et al., 2009). In addition to the numerous benefits related to lithium use, this medication is also associated with several side effects, and some studies have reported negative outcomes involving lithium and mitochondrial function. For example, one study reported reduced synthesis of antioxidants and decreased mitochondrial membrane potential in rat hepatocytes (Eskandari et al., 2012). The cardiotoxic adverse effects of lithium may be

partially explained by inhibition of complex II activity and ATP formation, enhanced ROS generation and increased activity of proapoptotic caspase-3 (Salimi et al., 2017).

Valproate and lithium seem to increase the expression of the antiapoptotic Bcl-2, which leads to the inhibition of proapoptotic enzymes, such as caspase 3 (Chen et al., 1999). In addition, both drugs are related to inhibition of glycogen synthase kinase-3 (GSK-3) enzyme activity, which is responsible for modulating gene expression of proteins involved in apoptosis, synaptic plasticity and cellular resilience (Bachmann et al., 2009; Kato, 2011; Kazuno et al., 2008; Zarate et al., 2006). Lithium and valproate were found to increase production of BDNF, decrease glutamate-induced excitotoxicity and inhibit NMDA receptor-mediated Ca²⁺ influx (Hashimoto et al., 2002; Nonaka et al., 1998). Valproate also seems to influence mitochondrial epigenetics due to its potent inhibition of histone deacetylase (Chen et al., 2012).

Platelets and lymphocytes from BD subjects have been associated with increased levels of intracellular Ca²⁺. In this context, valproate and carbamazepine seem to contribute to the regulation of intracellular Ca²⁺ levels by enhancing expression of ER stress proteins, which potentiates neuronal resistance to lethal fluctuations in intracellular Ca²⁺ and cytotoxic insults (Cikankova et al., 2019, 2017). Other studies have demonstrated that pretreatment with valproate prevented amphetamine-induced citrate synthase and succinate dehydrogenase inhibition in the brain of rats (Correa et al., 2007; Feier et al., 2013). Another study reported that valproate reversed metabolic alterations induced by ouabain administration in a model of mania (Lopes-Borges et al., 2015).

Some researchers suggest that mitochondria may also play a role in the side effects related to the use of mood stabilizers. The toxicity of valproate can be partially explained by several different mechanisms. An investigation of the effects of valproate on isolated rat mitochondria demonstrated that it might induce oxidative stress as a result of decreased mitochondrial respiratory chain complex II. Additionally, valproate induces the opening of mitochondrial ion channels and membrane pores, with consequent release of cytochrome *c* and induction of apoptosis (Jafarian et al., 2013). A recent study involving isolated pig brain mitochondria showed that complex I activity was significantly inhibited in response to lithium and carbamazepine, while activity of complex IV was decreased after exposure to carbamazepine. The activities of complex II and III were unaffected by any tested drug (Cikankova et al., 2019). Furthermore, carbamazepine may reduce mitochondrial ATP production and inhibit Ca²⁺-induced cellular swelling in rat liver cells (Finsterer and Scorza, 2017). Moreover, lamotrigine seems to prevent opening of the mPTP and increase levels of glutathione (Kim et al., 2007).

7. Mitochondria as a therapeutic target in BD

In addition to the impact of mood stabilizers on cellular metabolism, the mitochondrial dysfunction hypothesis of BD has been contributing to recent clinical trials involving mitochondrial modulators. However, there are some limitations for the use of mitochondrial modulators in the clinical practice. Most of the clinical trials, as described in Table 2, recruited an insufficient number of participants. Therefore, the questionable power of these

studies could partially explain some of the intriguing results about the effectiveness of mitochondrial agents. Another hypothesis for the limited use of mitochondrial modulators is that mitochondrial dysfunction may be only present in a fraction of BD patients, which corresponds to a mitochondrial endophenotype subgroup of the illness. This may explain the insufficient effectiveness of therapeutic agents when used in a broader patient population. In addition, it remains unclear if mitochondrial dysfunction is a consequence of bipolar disorder, instead of its cause, which could theoretically explain the fair effect of mitochondrial agents described in clinical trials. Ultimately, it is possible that mitochondrial modulators interact with different psychotropic drugs, such as mood stabilizers and antipsychotics, with a consequent insufficient bioavailability of mitochondrial agents in the central nervous system.

As described below, several metabolic antioxidants have been tested as potential add-on treatments in BD, including N-acetylcysteine (NAC), acetyl-L-carnitine (ALCAR), alpha-lipoic acid (ALA), creatine monohydrate, omega-3 fatty acids, and ketogenic diet.

7.1. N-Acetylcysteine

NAC is known for its beneficial properties, such as participation in glutathione production, anti-inflammatory effects, neurogenesis enhancement, as well as modulation of apoptosis and glutamate pathways (Samuni et al., 2013). According to Fernandes et al. (2016), adjuvant NAC treatment seems beneficial for bipolar depression. It was also found that a 24-week administration of NAC, as an adjuvant treatment, decreased depressive symptoms in BD patients, with more pronounced effects after 20 weeks of administration, suggesting long-term NAC treatment (Berk et al., 2008). An open label study investigating the efficacy of maintenance treatment with NAC in BD patients with depressive episodes reported a statistically significant reduction in the severity of depressive symptoms at the end of the 8-week treatment (Berk et al., 2011a). The same authors conducted a double-blind randomized placebo trial investigating the efficacy of adjuvant NAC in the maintenance treatment of bipolar depression and found no significant differences in recurrence or symptomatic outcomes during the maintenance phase of the trial (Berk et al., 2012). In contrast, Magalhaes et al. (2011) reported that NAC resulted in significant improvement in symptom severity, function and quality of life, and depressive symptoms after 24 weeks of treatment in patients with type-II BD in a randomized placebo-controlled trial. Another placebo-controlled, randomized clinical trial concluded that administration of NAC for 24 weeks resulted in attenuated manic symptoms in the NAC group and worsening depressive symptoms in the placebo group at endpoint (Magalhaes et al., 2013). On the other hand, there are recent negative trials showing no significant differences between groups with respect to primary outcomes (Berk et al., 2012, 2019; Ellegaard et al., 2019).

7.2. Acetyl-L-Carnitine and Alpha-Lipoic acid

ALCAR and ALA are compounds that play critical roles in modulating the cellular stress response by improving mitochondrial function and reducing mitochondrial free-radical production and inflammation, exhibiting antioxidant and anti-inflammatory properties (Liu, 2008; Liu et al., 1993; Scafidi et al., 2010a, 2010b). Overall, ALCAR and ALA are promising agents for the treatment and/or prevention of neurodegenerative disorders (Dos

Santos et al., 2019; Hager et al., 2007; Molz and Schroder, 2017; Palacios et al., 2011; Soczynska et al., 2008).

In BD, several early clinical trials suggest the ALCAR has significantly greater efficacy than placebo as an augmentation treatment for depressive disorders (Pettegrew et al., 2002; Zanardi and Smeraldi, 2006), while a randomized placebo-controlled trial using ALCAR and ALA concluded that there was no statistically significant difference between ALCAR/ALA compared to placebo groups with respect to changes in the Montgomery-Asberg Depression Rating Scale (MADRS) scores (Brennan et al., 2013).

7.3. Creatine

It has been proposed that oral intake of creatine may provide substrate to produce ATP by increasing brain concentrations of creatine and PCr (Lyo et al., 2003). Creatine also attenuates decreases in N-acetylaspartate (NAA), a marker of impaired mitochondrial function, and inhibits activation of the mitochondrial permeability transition, suggesting neuroprotective effects (Ferrante et al., 2000; Hemmer and Wallimann, 1993; O’Gorman et al., 1996). Despite limited evidence in mood disorders, Roitman et al. (2007) showed that creatine supplementation was associated with a significant reduction in depressive symptoms in unipolar depression, but in two bipolar depression patients, its supplementation precipitated manic episodes. Similarly, a randomized, double-blind, placebo-controlled trial demonstrated significant superiority of creatine add-on vs. placebo on the rates of remission in the completers and of partial response and remission, but two patients transitioned to hypomania/mania early during the trial. Thus, the authors suggested that creatine supplementation may have a role in treatment of the depressive phase of the illness (Toniolo et al., 2018). However, further investigation with larger sample sizes should be conducted to verify the efficacy of creatine add-on to standard pharmacotherapy and to determine in which mood state and dosage it might ideally exert its neuroprotective effects.

7.4. Omega-3 fatty acids

Evidence suggests that erythrocytes from BD patients exhibit decreased levels of omega-3 fatty acids, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and α -linolenic acid compared to healthy controls (Balanza-Martinez et al., 2011). Moreover, Sobczak et al. (2004) showed a trend towards lower levels of omega-3 fatty acids in first-degree relatives of BD patients. A double-blind randomized trial using supplementation with omega-3 fatty acids also reported longer remission and improvements of depressive symptoms, bipolar symptoms and global functioning compared to the placebo group (Stoll et al., 1999). Furthermore, a 12-week, double-blind study reported that ethyl-EPA is an effective adjuvant treatment in bipolar depression (Frangou et al., 2006). More recently, however, Murphy et al. (2012) reported that omega-3 fatty acids did not mediate a significant improvement in mood symptoms over an extended period of treatment.

A systematic review on clinical trials assessing nutraceuticals confirmed that omega-3 fatty acids may be useful in the treatment of depressive symptoms of BD (Fusar-Poli et al., 2019). However, sample sizes were small, reducing the chance of positive results (Sarris et al., 2011). Previous evidence suggests that supplementation or increased consumption

of omega-3 fatty acids may be beneficial in mood disorders, but additional studies are necessary to more accurately define their clinical efficacy.

7.5. Ketogenic diet

The ketogenic diet is known for its low carbohydrate and high-fat components, which forces the body to use fatty acids as the primary source of energy (DeVivo et al., 1978). Alternatively, the administration of ketone supplements, such as ketone salts or ketone esters, generates rapid and sustained nutritional ketosis (Kovacs et al., 2019). The effects of ketogenic diet or supplements on CNS diseases have not been thoroughly investigated, but ketosis seems to modulate different pathways implicated in psychiatric disorders, including BD (Bostock et al., 2017; Kovacs et al., 2019).

As previously discussed, BD seems to be related to an impaired ability to utilize pyruvate in the oxidative phosphorylation and the Krebs cycle, which results in high levels of pyruvate, derived from glycolysis (Yoshimi et al., 2016b). The increased plasma levels of ketones play an essential role as an alternative energy source by providing acetyl coenzyme A (acetyl-CoA) to the Krebs cycle, and therefore, bypasses the traditional pathway through glycolysis, which seems to be related to its mood stabilization properties (Campbell and Campbell, 2019). Newell et al. (2016) demonstrated that higher levels of ketone bodies, such as beta-hydroxybutyrate, increased the number of mitochondria and the electron transport chain proteins in this organelle, with consequently increased ATP synthesis. Marosi et al. (2016) showed that ketone 3-hydroxybutyrate metabolism increases mitochondrial respiration which drives changes in expression of brain-derived neurotrophic factor (BDNF) in cultured cerebral cortical neurons.

Moreover, ketosis seems to have anti-inflammatory properties and optimizes the cellular antioxidant system by activating nuclear factor erythroid-derived 2-related factor 2 (Nrf2) (Pinto et al., 2018). Furthermore, it has been postulated that the ketogenic diet may regulate neurotransmitters' function, such as monoamine modulation and enhancement of GABAergic transmission, with consequent anxiolytic effects (Brietze et al., 2018; Kashiwaya et al., 2013; Rogawski et al., 2016). In addition, some ketone bodies seem to inhibit the vesicular glutamate transporters (Danial et al., 2013), which can act as a buffer under conditions of excess of glutamate, such as acute mood episodes (Jaso et al., 2017). Although ketosis may be a promising treatment for BD, the availability of studies involving the ketogenic diet and BD is limited, and to date, there are no randomized controlled trials published.

8. Conclusion and future directions

Several studies in rodent models and humans suggest and reinforce the mitochondrial dysfunction hypothesis in BD. Mitochondria may present altered morphology and dynamics, as well as decreased metabolism and oxidative stress. Moreover, altered Ca^{2+} homeostasis and glutamate excitotoxicity likely play a crucial role in apoptosis. Taking together the findings reviewed above it is tempting to suggest that mitochondrial dysfunction is a critical pathological factor in BD that can be intimately linked to a wide range of processes associated with treatment outcomes and disease progression or severity (Fig. 1). The

pathophysiology of BD is quite complex and involves several factors, besides mitochondrial dysfunction. Nevertheless, it is worth noting that the mitochondrial hypothesis must be interpreted in light of some limitations since the majority of studies are cross-sectional, which can identify associations but not causal relationships or longitudinal patterns of development, leading to a significant gap in the understanding of the specific role played by mitochondria in the etiology of BD, and whether an abnormal mitochondrial function is a cause or consequence (or even both) of BD subtypes. Furthermore, it is not yet completely understood which mitochondrial mechanism was altered first in addition to the chance that more than one mechanism occurs concurrently during the development of the disease.

9. Literature search strategy

A systematic literature search was performed using databases of Scopus, Embase, PubMed, Cochrane Library, and ISI web of Science from inception to September 2020. Moreover, a hand search was performed on three pre-print databases (medRxiv, bioRxiv, PsyArXiv) in order to find additional articles. Searches were restricted to English language. Results from the databases were merged using EndNote to facilitate the removal of duplicates. Reference lists of studies, review articles and systematic reviews were manually reviewed to identify any additional studies. Key words were grouped using the following Boolean expression and adjusted according to each database: “(bipolar disorder OR bipolar depression OR mood disorders OR mania OR depression) AND (mitochondria OR mitochondrial dysfunction OR energy homeostasis OR cerebral bioenergetics OR mitochondrial DNA OR oxidative stress OR calcium OR redox signaling OR mood stabilizers OR lithium OR mitochondrial agents OR complimentary therapies)”.

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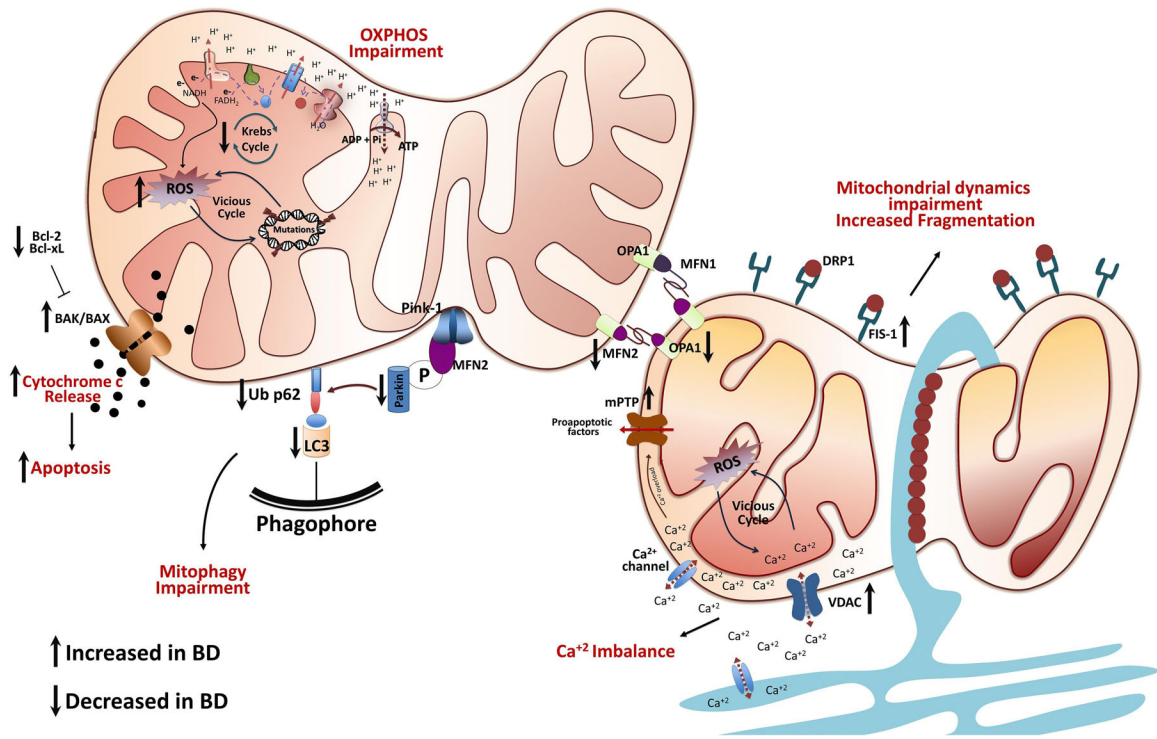


Fig. 1. Schematic representation of mitochondrial dysfunction in bipolar disorder.

Several mitochondrial pathways, not all of which are shown here, interact simultaneously to cause cellular damage. Mitochondrial dysfunction in the pathophysiology of BD is based on oxidative phosphorylation impairment, a decrease in energy production, ROS production, mtDNA damage, Ca²⁺ imbalance, cytochrome *c* release, and mitochondrial dynamics and mitophagy impairment. Thus, mitochondrial dysfunction could initiate a vicious cycle where numerous systems and mechanisms intensify and accelerate cellular damage, that with time exacerbates the disease process, and could independently determine the course of the disease, progression, functional outcomes and premature aging.

Table 1

Summary of mitochondrial complex gene alterations in bipolar disorder.

Reference	Gene	Description	Sample	Expression
Iwamoto et al. (2004)	NDUFS1	Complex I NADH dehydrogenase (ubiquinone) Fe-S protein 1	Prefrontal cortex	↓
	UQCRC2	Complex III Ubiquinol-cytochrome <i>c</i> reductase core protein II		
	COX15	Complex IV Cytochrome <i>c</i> oxidase assembly homolog 15		
Konradi et al. (2004)	NDUFAB1	Complex I NADH dehydrogenase (ubiquinone) 1, α/β subcomplex 1	Hippocampus	↓
	COX7A2	Complex IV Cytochrome- <i>c</i> oxidase, subunit VIIa, polypeptide 2		
	COX7B	Cytochrome- <i>c</i> oxidase, subunit VIIb		
	ATP5G3	Complex V ATP synthase, mitochondrial Fo complex, subunit C3		
	ATP5H	ATP synthase, mitochondrial Fo complex, subunit d		
	ATP5J2	ATP synthase, mitochondrial Fo complex, subunit F2		
	ATP5C1	ATP synthase, mitochondrial F1 complex, γ polypeptide 1		
	ATP5O	ATP synthase, mitochondrial F1 complex, O subunit		
Sun et al. (2006)	NDUFS7	Complex I NADH dehydrogenase (ubiquinone) Fe-S protein 7	Prefrontal cortex	↓
	NDUFS8	NADH dehydrogenase (ubiquinone) Fe-S protein 8		
	UQCRC2	Complex III ubiquinol-cytochrome <i>c</i> reductase core protein II		
	COX5A	Complex IV cytochrome <i>c</i> oxidase subunit Va		
	COX6C	cytochrome <i>c</i> oxidase subunit V _{ic}		
	ATP5C1	Complex V ATP synthase, mitochondrial F1 complex, γ polypeptide 1		
	ATP5J	ATP synthase, mitochondrial Fo complex, subunit F6		
	ATP5G3	ATP synthase, mitochondrial Fo complex, subunit C3		
Andreazza et al. (2010)	NDUFS7	Complex I NADH dehydrogenase (ubiquinone) Fe-S protein 7	Prefrontal cortex	↓
Akatsu 2015	NDUFV1/NDUFV2/NDUFS1		Peripheral blood samples	↑

Table 2

Clinical and preclinical trials of mitochondrial modulators in Bipolar Disorder.

Author(Year)	N	Sample	Design	Duration	Assessments	Main findings
Berk et al. (2008)	75	Patients with bipolar disorder	Double-blind randomized placebo controlled	6 months	MADRS, BDRS, YMRS, CGI-BP, GAF, SOFAS, SLICE/LIFE, LIFE-RIFT, Q-LES-Q	Positive results showed improvements on most rating scales in NAC group compared with placebo group
Berk et al. (2011)	149	Patients with moderate depression	Open-label study	2 months	MADRS, BDRS, YMRS, CGI, CGI-BP, GAF, SOFAS, SLICE/LIFE, LIFE-RIFT, Q-LES-Q	Significant reduction in depressive symptoms in patients with bipolar depression
Berk et al. (2012)	149	Patients with bipolar disorder	Double-blind randomized placebo-controlled trial	8 weeks	MADRS, BDRS, YMRS, CGI, CGI-BD, PGI, GAF, SOFAS, SLICE/LIFE, LIFE-RIFT, Q-LES-Q	No significant differences in recurrence, symptomatic outcomes, quality of life measures during the maintenance phase of the trial between the groups receiving adjunctive NAC or placebo in addition to treatment as usual.
Magalhaes et al. (2011)	14	Patients with bipolar disorder type II	Double-blind randomized placebo-controlled	24 weeks	BDRS, MADRS, YMRS, CGI, GAF, SOFAS, SLICE-LIFE, LIFE-RIFT, Q-LES-Q	NAC group showed significant improvement on measures of symptom severity, functioning and quality of life and depressive symptoms
Magalhaes et al. (2013)	15	Patients with bipolar disorder in (mania or hypomania)	Double-blind randomized placebo-controlled	24 weeks	BDRS, MADRS, YMRS, CGI, GAF, SOFAS, SLICE-LIFE, LIFE-RIFT, Q-LES-Q	NAC tended to have less manic symptoms at endpoint
Pettegrew et al. (2002)	2	Mildly depressed elderly subjects	Open-label study	12 weeks	HDRS, MMSE, CIRS, CIRS and UKU	After 12 weeks of ALCAR treatment, subjects show remission, normalization of PME and elevation of PCr levels
Zanardi and Smeraldi (2006)	193	Patients with dysthymic disorder	Double-blind randomized parallel-group	12 weeks	HAM-D, CDRS, MADRS, CGI, CGI-S, CGI-I	Treatment with ALCAR for 12 weeks was associated with improvements of depressive symptoms
Brennan et al. (2013)	40	Patients with bipolar depression	Double-blind randomized placebo-controlled	12 weeks	MADRS, HAM-D, CGI-S, YMRS, 31P-MRS scan	ALCAR and ALA does not have antidepressant effects in depressed bipolar patients
Forester et al. (2012)	10	Older Patients (>55 years old) with bipolar depression	Open-label study	2 weeks	MADRS, YMRS, CGI, GDS, Rate constant of creatine kinase	CoQ10 improvements depression symptom severity in BD patients, but not demonstrate significant differences in the rate constant of creatine kinase
Stoll et al. (1999)	30	Patients with bipolar disorder	Double-blind randomized placebo-controlled	4 months	Kaplan-Meier survival, YMRS, HAM-D, CGI, GAS	Omega-3 group showed longer remission and improvements of depressive symptoms, bipolar symptoms and global functioning
Frangou et al. (2006)	25	Patients with bipolar depression	Double-blind placebo-controlled trial	12 weeks	HAM-D, YMRS, CGI	Treatment with ethyl-EPA over a 12 week period was associated with increased NAA levels
Murphy et al. (2012)	45	Outpatients with bipolar disorder type I Clinical Trial	Double-blind, randomized add-on	4 months	MADRS, YMRS, GAF	Supplementation with omega-3 did not produce a significant improvement in mood symptoms over an extended period of treatment
Roitman et al. (2007)	10	Patients with resistant depression	Open-label	4 weeks	HAM-D, HAS, CGI	Creatine supplementation causes a significant reduction in depressive symptoms in unipolar depression, but precipitated manic episodes bipolar patients Patients with bipolar disorder type II

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ALCAR: Acetyl-L-carnitine; ALA: Alpha-lipoic acid; BDRS: Bipolar Depression Rating Scale; CGI: Clinical Global Impression; CGI-BP: CGI-Improvement scale for bipolar disorder; CoQ10: Coenzyme Q10; GAF: Global Assessment of Functioning Scale; GAS: Global Assessment Scale; Ethyl-EPA: Ethyl-eicosapentanoic acid; HAM-D: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Scale; LIFE-RIFT: Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS: Montgomery Åsberg Depression Rating Scale; NAC: N-acetyl-cysteine; NAA: N-acetyl-aspartate; PGI: Patient Global Impression; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SLICE/LIFE: Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; SOFAS: Social and Occupational Functioning Assessment Scale; YMRS: Young Mania Rating Scale.