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Targeting mitochondrially mediated plasticity to develop improved therapeutics for bipolar disorder

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Abstract

Introduction—Bipolar disorder (BPD) is a severe illness with few treatments available. Understanding BPD pathophysiology and identifying potential relevant targets could prove useful for developing new treatments. Remarkably, subtle impairments of mitochondrial function may play an important role in BPD pathophysiology.

Areas covered—This article focuses on human studies and reviews evidence of mitochondrial dysfunction in BPD as a promising target for the development of new, improved treatments. Mitochondria are crucial for energy production, generated mainly through the electron transport chain (ETC) and play an important role in regulating apoptosis and calcium (Ca²⁺) signaling as well as synaptic plasticity. Mitochondria move throughout the neurons to provide energy for

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Declaration of interest

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intracellular signaling. Studies showed polymorphisms of mitochondria-related genes as risk factors for BPD. Postmortem studies in BPD also show decreased ETC activity/expression and increased nitrosative and oxidative stress (OxS) in patient brains. BPD has been also associated with increased OxS, Ca^{2+} dysregulation and increased proapoptotic signaling in peripheral blood. Neuroimaging studies consistently show decreased energy levels and pH in brains of BPD patients.

Expert opinion—Targeting mitochondrial function, and their role in energy metabolism, synaptic plasticity and cell survival, may be an important avenue for development of new mood-stabilizing agents.

Keywords

apoptosis; bipolar disorder; calcium; mitochondria; mood stabilizer; oxidative stress

1. Introduction

Bipolar disorder (BPD) is a severe and chronic mental illness, affecting approximately 2% of the general population [1]. To date, available treatments have shown limited efficacy [2], especially for major depressive episodes and maintenance treatment. New treatments will be developed by gaining insight into the pathophysiological mechanisms underlying BPD to identify possible treatment targets. Research on the biological underpinnings of mood disorders has therefore moved away from focusing on absolute changes in neurochemicals such as monoamines and neuropeptides, and instead has begun highlighting the role of neural circuits and synapses, and the plastic processes controlling their function. Thus, these illnesses can best be conceptualized as genetically influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters.

1.1 Why consider mitochondrially mediated plasticity as playing a central role in the pathophysiology and treatment of BPD?

Plasticity, the ability to undergo and sustain change, is essential for the proper functioning of our nervous system. This capacity for change allows organisms to adapt to complex alterations in both their internal and external environments, a feature fundamentally important for survival and reproduction. Besides the evident need for significant adaptation mechanisms in learning and memory as well as physiological homeostasis, all complex behavioral phenomena – including mood and emotion – are dynamic processes that rely on plastic neural circuitry. The biological basis of this capacity to adapt encompasses a diverse set of cellular and molecular mechanisms that fall under the broad term of ‘synaptic plasticity’, and – more broadly – ‘neuroplasticity’.

Neuroplasticity is a broader term that encapsulates changes of synaptic number and strength, modeling of axonal and dendritic architecture, growth or atrophy of neuronal cell bodies and, in some areas of the CNS, the generation of new neurons. Modifications arising from neuroplastic mechanisms can be of short duration or long lasting, and this is determined by the qualitative, quantitative and temporal characteristics of the precipitating stimuli. Once again, as discussed later, mitochondrial function plays a critical role in regulating neural plasticity.

Synaptic plasticity is part of neuroplasticity and refers to the cellular process that results in lasting changes in the efficacy of neurotransmission. More specifically, the term synaptic plasticity refers to the variability of the strength of a signal transmitted through a synapse. The regulation of transmission at the synapse may be mediated by changes in neurotransmitter levels, receptor subunit phosphorylation, surface/cellular levels or receptors, and conductance changes, among others. As will be discussed, mitochondrial function plays a key role in mediating efficient synaptic plasticity.

Although mood disorders are not classic neurodegenerative disorders, there is a growing body of evidence to suggest that, in many patients, these disorders are associated with regional atrophic brain changes (discussed later). These changes, together with the changes in synaptic function seen in many mood disorders, may be closely associated with abnormalities in cellular plasticity, including the ability of neuronal and glial cells to resist or adapt to environmental stressors (cellular resilience) and the ability of these cells to undergo remodeling of synaptic connections.

Mitochondria have a pivotal role in cellular energy metabolism and are also involved in modulation of cellular calcium (Ca^{2+}) levels, production of free radicals and regulation of apoptosis. Thus, mitochondrial dysfunction not only impairs energy production but also affects other key neuronal processes. In this context, a growing body of evidence suggests that impaired mitochondrial function might lead to a disruption of normal neural plasticity and reduce cellular resilience, which might, in turn, promote the development or progression of mood disorders. It is not our contention that mood disorders are generally classic mitochondrial disorders. However, they are associated with impairments of mitochondrial function, and the emerging data support mitochondrial dysfunction research as an opportunity for novel therapeutic approaches.

In this review, we discuss the recent data from neuroimaging, postmortem brain, genetic, molecular and cell-biological studies in humans and rodents that strongly support the theory that mitochondrial dysfunction has an important role in mood disorders.

2. Mitochondria

2.1 Mitochondrial genetics and physiology

Mitochondria are organelles composed of an internal and an external membrane, delimiting the intermembrane space. The inner membrane envelops the mitochondrial matrix, where the energy-generating citric acid cycle occurs. Mitochondria are unique organelles with their own DNA: mitochondrial DNA (mtDNA). mtDNA codifies 37 genes linked to the production of tRNA, rRNA and electron transport chain (ETC) proteins. However, the nuclear DNA codifies the largest part of the mitochondrial proteins.

mtDNA is normally uniformly distributed in eukaryotic cells. However, heteroplasmy results when mutations in the mtDNA occur so that one cell contains more than one type of mtDNA. The prevalence of this mutant mtDNA can vary across tissues and relate to disease severity and organ involvement. For example, mitochondrial dysfunction may present in a specific or regional pattern that impacts only the CNS [3]. The number of mtDNA molecules

(mtDNA content) normally varies among the tissues, but its regulation is essential for good cell functioning [4]. mtDNA content reflects mitochondrial gene stability and mitochondrial number [5].

Mitochondria move through the cell according to neuronal requirements such as Ca^{2+} -buffering or a higher energy demand [6]. Mitochondrial transport occurs via microtubules. Anterograde transport (toward the periphery) utilizes two kinesins, KIF1B α and KIF5, which tether to the mitochondria. In addition, diverse adaptor proteins and accessory factors, such as disrupted in schizophrenia-1 (DISC1), Syntabulin, FEZ1, RanBP2, Miro, Milton and TRAK 1 and 2 [6–9], are important for the kinesin-mediated transport. DISC1 is thought to have an essential role in directing mitochondrial transport in neuronal cells. Mitochondria also constantly change their morphology through fissions and fusions, the balance of which is essential for mitochondrial physiology and traffic [10].

While increased fusion produces elongated, interconnected mitochondria, elevated fission results in fragmentation of mitochondria. Mitochondrial fusion is mediated by three GTPases: the mitofusins (Mfns) Mfn1 and Mfn2, and the protein (optic atrophy 1) [11] another GTPase, (dynamin-related protein 1) is involved in the process of mitochondrial fission [12].

2.2 Mitochondria produce energy mainly through oxidative phosphorylation

One of the most important mitochondrial functions is energy generation. Mitochondria are the main agents to convert sugars into ATPs, which are the cellular form of energy that fuel essential neuronal processes. The brain consumes 20% of resting body energy, although it accounts for only 2% of the body mass [10]. This makes the brain particularly sensitive to alterations in energy production and then vulnerable to subtle mitochondrial abnormalities.

In neuronal cells, ATPs are produced from oxygen and glucose through a cascade of events depicted in Figure 1: glycolysis $\rightarrow$ pyruvate decarboxylation $\rightarrow$ citric-acid cycle (tricarboxylic acid or Krebs cycle) $\rightarrow$ oxidative phosphorylation. Glycolysis occurs in the cytosol while the other processes take place in the mitochondria. During glycolysis, glucose is broken down into pyruvate. In the anaerobic pathway, pyruvate is converted into lactate, in a process with low-energy production. In contrast, in the high-energy production aerobic pathway, pyruvate is converted to acetyl-coenzyme A, which enters the citric acid cycle, leading to the production of substrates to oxidative phosphorylation. The oxidative phosphorylation occurs in the ETC and is the process with highest energy production in mitochondria.

The activity of ETC in oxidative phosphorylation generates reactive oxygen species (ROS). ETC complexes I and III activities generate superoxide (O_2^-), a highly toxic ROS. Superoxide dismutase (SOD) in mitochondria then converts O_2^- to oxygen (O_2) and hydrogen peroxide (H_2O_2). H_2O_2 diffuses to the cytosol, where it can be converted to H_2O through the action of glutathione peroxidase (GPx) and catalase (CAT). H_2O_2 can also interact with Fe^{2+} or Cu^+ to generate hydroxyl radicals (OH^-) that are ROS with powerful oxidative properties. If ROS production is excessive or their scavenging is insufficient, ROS will cause oxidative stress (OxS).

OxS is harmful for the cell and can affect signal transduction, structural plasticity and resilience [13]. Antioxidant protective molecules such as coenzyme Q10, creatine (Cr) and glutathione are involved in protecting mitochondria against OxS. In addition, the interaction of nitric oxide with O_2^- results in the formation of peroxynitrite, a reactive molecule that is a highly oxidant and nitrating agent. Peroxynitrite nitration of tyrosine on proteins impairs their enzymatic function in the production of monoaminergic neurotransmitters. ROS are also produced during the metabolism of monoamines by monoamine oxidases A and B, located on the outer mitochondrial membrane (Figure 2).

Exposure to stress and hypercortisolemia may also be sources of mitochondrial dysfunction. In a culture of cortical neurons, long-term exposure to high doses of corticosterone increased toxicity and apoptosis of the cells [14]. Also, corticosterone treatment for longer periods reduced B-cell lymphoma protein 2 (BCL-2) levels, impaired mitochondrial oxidation, decreased membrane potential, and disrupted Ca^{2+} homeostasis in cortical neurons [14]. In rat models, chronic unpredictable mild stress and corticosterone treatment lead to mitochondrial function impairment and/or decreased expressions of mitofusion and antioxidant enzymes [15]. Taken together, these findings suggest possible mechanisms for hypercortisolemia/hypothalamic–pituitary–adrenal axis dysfunction impairing mitochondrial function.

2.3 Mitochondrial role in Ca^{2+} homeostasis

In cases when mitochondrial oxidative phosphorylation is inadequate, it leads to deficient ATP production, which can result in an impaired action of ATP-dependent Ca^{2+} transporters and a consequent imbalance of Ca^{2+} homeostasis. Besides regulating Ca^{2+} homeostasis through ATP generation, mitochondria can function as both a Ca^{2+} high-capacity sequester and a releaser of cytosolic Ca^{2+} [16].

Ca^{2+} is a chief second messenger that is involved in the regulation of both neurotransmission and short- and long-term neural brain plasticity. Increase in Ca^{2+} levels may reduce post-tetanic potentiation, impairing synaptic signaling (Figure 3) [17]. High cytosol Ca^{2+} levels induce stress and excitotoxicity that can be prevented by mitochondrial buffering [18,19]. However, cellular injury triggered by excess Ca^{2+} influx can lead to increased mitochondrial membrane permeability, which is often triggered by the opening of the mitochondrial permeability transition pore, a protein complex that unites its membrane's inner and outer spaces. When opened, the mitochondrial permeability transition pore releases mitochondrial proteins such as cytochrome C and procaspases, which induce apoptosis [20,21].

2.4 Mitochondrial role in synaptic and neural apoptosis

Neural apoptosis is physiological and part of normal brain development, occurring even in the normal adult brain, especially during neurogenesis [22,23]. However, dysregulation of apoptotic mechanisms can also lead to 'synaptic apoptosis,' a selective atrophy of synapses or neurites [24].

Mitochondria have a regulatory role in apoptosis via pathways both intrinsic and extrinsic to the cell. In the intrinsic mitochondrial-mediated pathway, stimuli such as high levels of

cytoplasmic Ca^{2+} or ROS, or the activation of proapoptotic BCL-2 family proteins trigger a cascade of processes that activate caspases, ultimately leading to apoptosis (Figure 4) [25,26]. In the extrinsic pathway, activation of extracellular death receptors leads to a series of events that alter membrane permeability, resulting in leakage of proapoptotic factors and, eventually apoptosis [25,26]. It is noteworthy that the mood stabilizers lithium and valproate can have neuroprotective effects, at least to some extent, through the upregulation of antiapoptotic BCL-2 family proteins [27,28].

2.5 The role of mitochondria in synaptic plasticity

Mitochondria regulate synaptic activity, as well as learning and memory, mainly through actions on long-term potentiation (LTP) [29–32]. Moreover, long-term depression (LTD) is prevented through both the inhibition of caspase-3 and -9 and the overexpression of the antiapoptotic proteins X-linked inhibitor of apoptosis protein and BCL-2 family member B-cell lymphoma-extra large (BCL-XL) [31]. Caspase-3 activation is mediated by the BCL-2 antagonist of cell death (BAD)–BCL-2-associated X protein (BAX) cascade; caspase-3 activation is required for NMDA-receptor-dependent LTD [32]. Also, BCL-2 and BCL-XL facilitate axonal regeneration, neurite growth, neuronal survival and neurogenesis [33,34].

Synapses are dynamic, thus inducing ongoing mitochondrial movement within axons and dendrites, and mitochondrial division and fusion [35,36]. Mitochondrial movement is important in providing energy for synaptic signaling and plasticity, while mitochondria division and fusion control mitochondria number [36,37]. Disruption in synaptic modeling and connectivity may contribute to the pathophysiology of certain diseases. The mood stabilizers lithium and valproate may regulate mitochondria movement through phosphorylation of cytoskeletal and mitochondrial proteins, as observed in preparations of rat prefrontal cortex [38].

Importantly, increased OxS parameters have been associated with cessation of mitochondrial movement and pathological fission, ultimately leading to cell apoptosis or necrosis [39]. Because mitochondrial movement is necessary for synaptic signaling and plasticity [40], alterations in OxS might impair mitochondrial function through alterations in movement.

3. Mitochondrial dysfunction in BPD

3.1 Genetic evidence of mitochondrial dysfunction in BPD

Mitochondrial dysfunction in BPD is supported by genetic findings. It should be emphasized that although BPD may act as a mitochondrial disease in selected families (that is, the disorder arises from the inheritance of mtDNA), it is not a classic mitochondrial disorder. Rather, that BPD generally arises from the inheritance of nuclear-encoded genes that converge to regulate mitochondrial function, and ultimately cellular resilience. McMahon *et al.* [41] found increased prevalence of mood disorders in maternal versus paternal relatives of patients with BPD. The mtDNA is inherited only through the maternal line, which could suggest a greater vulnerability to BPD through mtDNA genes. However, contrary to this finding, no BPD-related mtDNA mutations were found in BPD families with predominant maternal transmission [41,42].

A rare gene variant of mtDNA, 3644T>C, was found to be associated with BPD. Patients with BPD showed 1.43% prevalence of the gene variant (against 0.13% in controls) [43]. Patients with the 3644T>C mutation had comorbid somatic symptoms suggestive of mitochondrial disorders. However, a later study suggested that 3644T>C might not be pathogenic [44].

An analysis of mtDNA sequence showed no specific mutations associated with BPD, also challenging the role of mtDNA in BPD [45]. However, some mtDNA haplogroups (U, K and UK) showed significantly lower cerebellar pH, leading to the speculation that pH alterations could be inherited through mtDNA and constitute a risk factor for BPD [45]. In addition, other studies with smaller sample sizes have shown an association of nuclear-encoded mitochondrial genes and mtDNA polymorphisms with BPD [46,47].

DISC1 is a gene that encodes a protein involved in mitochondrial dynamics and trafficking [48]. Initially, *DISC1* was studied in a Scottish pedigree, segregating with schizophrenia and BPD [49]. Subsequently, further studies supported an association of both *DISC1* polymorphisms and haplotypes with BPD [50–55]. Another gene thought to be associated with risk for BPD is *G72* [56], which is involved in mitochondrial fission–fusion [57], thus impacting on oxidative phosphorylation and mitochondrial transport [58]. Ca^{2+} abnormalities have been also supported by genetic studies. A polymorphism of the gene *CACNA1C* encoding a subunit of the L-type Ca^{2+} channel was identified as a risk factor for BPD [59]. The finding was confirmed by a meta-analysis of around 12,000 cases with BPD and 50,000 controls [60].

Not only polymorphisms, but also mtDNA deletions could be associated with BPD. mtDNA deletions were found increased in frontal cortex of BPD patients [61] and in dorsolateral prefrontal cortex of BPD patients (compared to controls) [62,63]. However, other studies did not replicate the findings in frontal cortex [64–66] or in cerebral cortex [67]. The discrepancy of the findings may be due to the use of different methodologies and brain regions studied. Also, analyzed samples from three of the negative studies were from the same source [64–66], the Stanley Foundation Brain Bank, warranting confirmation in independent samples.

The number of mtDNA molecules, mtDNA content, is a marker of mitochondria number [5] and is associated with cellular viability [4]. mtDNA content (as measured in leukocytes) has been shown to be decreased in euthymic patients with BPD [68] and slightly decreased in depressed patients with BPD [69]. Studies in postmortem brains of BPD were conflicting. One study showed mtDNA to be slightly increased in the dorsolateral prefrontal cortex [70], while other studies that involved samples from the Stanley Foundation Brain Bank showed no alterations in either occipital [71] or frontal cortices [65,66]. An age-dependent decrease in mtDNA content has been observed in one study in leukocytes of BPD patients [69] and in another study in frontal cortex of BPD patients [64].

3.2 Increased OxS in BPD

Increased OxS leads to deleterious consequences on signal transduction, cellular resilience and synaptic plasticity, through alterations in lipids, proteins and DNA [72–74], involving

mitochondrial dysfunction. Damage to DNA was found to be correlated with the severity of depressive and manic symptoms in BPD [75]. A direct index of cell lipid peroxidation and indicative of enhanced OxS are the levels of thiobarbituric acid reactive substances (TBARS).

Increased peripheral TBARS levels in BPD have been reported in recent studies [76–78] and a meta-analysis [79]. However, some studies did not show increased TBARS in BPD [80]; most of those included young or recent-onset BPD patients [81,82]. The lack of increase in TBARS levels in BPD patients with a short length of illness may be explained by compensatory antioxidant mechanisms present in initial phases of BPD that prevent oxidative damage [82,83].

The antioxidant system consists of coordinated effects of antioxidant enzymes SOD, CAT, and GPx [84]. Imbalance of antioxidant enzymes is consistently associated with increased OxS and has been reported in several studies [79].

SOD activity in peripheral blood was found to be increased in most studies in BPD [78,85–90], although a previous meta-analysis did not find the increase to be significant [79] and some studies have found unaltered [91–93] or decreased SOD in BPD [94,95]. The increase in SOD activity in BPD is consistent with a deleterious role of the enzyme leading to impairment of LTP (discussed above). Also, consistent with a potential harmful role for SOD increase, after short-term lithium treatment SOD activity decreased in healthy controls [96] and in BPD patients [82]. SOD catalyzes a reaction that converts superoxide to H_2O_2 ; SOD decrease could potentially reduce H_2O_2 formation and OxS [97].

CAT activity in peripheral blood was increased in studies analyzing patients during mania and depression with short history of BPD [82,87]. The increase could be attributed to a compensatory mechanism present early in the course of BPD. Noteworthy, in mitochondria isolated from rat brain and in SH-SY5Y neuroblastoma human cells, CAT has shown to be effective against OxS [98,99]. Results for other studies in patients with chronic BPD, which evaluated CAT activity in diverse phases, have shown it to be decreased [86,91–93] or unaltered [85,86].

While some results show GPx activity is increased in peripheral blood of BPD patients during euthymia [86] and depression [82], other results did not show significant alterations in GPx across different mood states [88,89,91,92,100]. The drug *N*-acetyl cysteine, a glutathione byproduct, showed efficacy as adjunctive antidepressant therapy in BPD [101], suggesting a potential role for glutathione in BPD depression. However, there was quite a lag period until the onset of antidepressant effects after starting *N*-acetyl cysteine.

Reduced glutathione is used as an electron donor for GPx action, leading to the production of oxidized glutathione; the oxidized glutathione is recycled to glutathione through the action of glutathione S-transferase. Both reduced glutathione and glutathione S-transferase were found increased among patients with late-stage BPD (as compared with healthy controls) and both were positively correlated with illness duration [100]. Such increase in reduced glutathione and glutathione S-transferase could be a mechanism present in late-stage BPD to help GPx in the scavenging of ROS [100].

Several different factors might contribute to the heterogeneity of results observed in antioxidant enzymes studies in BPD [88,102]. Nevertheless, it has been suggested that an imbalance of enzymes rather than a single enzyme alteration is more likely associated with increased OxS [82,86,103].

SOD and CAT act sequentially to eliminate ROS and imbalances in SOD/CAT ratio [104]. Importantly, lithium treatment decreased the SOD/CAT ratio in BPD patients [87] and in healthy volunteers [96]. Consistently, BPD patients with a short duration of illness showed a decreased SOD/CAT ratio in comparison with healthy controls, which could be a compensatory antioxidant mechanism [82].

3.3 Postmortem brain evidence of mitochondrial dysfunction in BPD

Postmortem brain studies are an important avenue toward the understanding of BPD pathophysiology and establishing mitochondrial role in BPD. Study results have shown mitochondria-related genes are downregulated in postmortem brains of BPD patients. The expression of mRNA encoding mitochondrial proteins of ETC complexes I, III, IV and V was decreased in postmortem brains of BPD patients as compared to healthy controls [105–107]. The observed downregulation of genes was suggested to be the effect of the medication used [107] or the low pH [70]. However, an alteration in pH might be associated to the mitochondrial dysfunction itself [105], which is suggested by a study in lymphocytes showing deficiency in upregulating mitochondrial genes in response to agonal factors in BPD (compared to controls) [108].

Importantly, postmortem prefrontal tissue of BPD patients showed decreased levels of subunits of complex I, reduced complex I activity, and increased oxidative and nitrosative damage [109,110]. In line with these findings, patients who were under lithium treatment showed an increase in ETC complex I expression in a postmortem brain study, suggesting a neuroprotective effect of the drug by improving energy parameters [105,106]. Lithium has consistently been shown to increase ETC complex I activity in postmortem brains of healthy subjects [111] and decrease OxS in BPD [77,82,87].

An impaired mitochondrial energy production by ETC could manifest as reduced levels of phosphocreatine (PCr), a high-energy phosphate. PCr metabolism and synthesis involve the enzyme Cr kinase, which was found to be downregulated in the dorsolateral prefrontal cortex of postmortem brains of BPD patients compared to controls [112].

Consistent with the findings of mitochondrial impairment and cellular damage, in the cerebral cortex of BPD patients gene and protein expression of the antiapoptotic BCL-2 were downregulated, while mRNA levels of BAX and BAD were upregulated [113]. Finally, patients with BPD exhibited smaller mitochondrial size in cells of postmortem prefrontal cortex [114].

3.4 Neuroimaging evidence of mitochondrial dysfunction in BPD

Methodologies to investigate structural and functional deficits within the human brain have exponentially increased in recent years, allowing for a more complete and intensive analysis of potential regional dysfunction in the brains of patients suffering from mood disorders.

Thus, it is possible now to discern relatively small differences in cerebral blood flow, receptor density or in macroscopic brain structure. Using magnetic resonance spectroscopy (MRS), it is now possible to ascertain certain aspects of neuronal function, including those related to neuronal energetics (e.g., pH, high-energy phosphates and *N*-acetyl aspartate [NAA], formed in mitochondria and presumed to represent a marker of neuronal viability). Likewise, postmortem studies are relying upon methodologies, which, while not perfect, allow for relatively unbiased observations of cell density, morphology and size. These postmortem brain studies can thus add independent, corroborative evidence to the brain imaging studies.

Proton (¹H) MRS studies in BPD patients showed changes in cerebral concentrations of NAA and lactate, while studies using phosphorus (³¹P) MRS have found abnormalities in levels of PCr and intracellular pH. Energy is stored in cells in the form of PCr, a high-energy compound synthesized from ATP and Cr. Lower levels of PCr in the frontal lobe were observed in bipolar depression [115,116]; in the left frontal lobe, Cr + PCr was decreased in bipolar depression compared with euthymic patients with BPD [117]. However, other studies evaluating PCr levels did not replicate the findings [113].

MRS studies also have evaluated pH in brains *in vivo* of patients with BPD. Several studies have found a lower pH in BPD [115,118–121]. Treatment with triacetylrudine, a prodrug of uridine that enhances mitochondrial function, increased the pH in bipolar depression [122]; patients who responded to treatment showed increased pH (in comparison to baseline pH), suggesting a role for triacetylrudine in improving mitochondrial function in BPD [122].

Consistent with a decreased pH, elevations in lactate were observed in BPD [123–125]. Also, lactate levels have shown to be positively correlated with manic symptoms [123]. Significant increases of lactate have also been found in cerebrospinal fluid of BPD patients, reinforcing the validity of neuroimaging findings [126]. Quetiapine reduces lactate levels in patients with bipolar mania, with a more prominent decrease of lactate in responders than in nonresponders [123].

NAA is synthesized in mitochondria in adult brains [127] and reflects neuronal viability [128]. NAA levels were found to be decreased in several studies evaluating BPD patients [129–136]. A recent meta-analysis revealed decreased NAA in the basal ganglia of BPD patients compared to controls [137]. However, some studies did not show a decrease in NAA levels [137–139]. Differences in findings may correspond to different brain regions analyzed [137] or disease characteristics of the sample population such as short length of illness [140]. Several studies have shown negative correlations between NAA and illness duration [129,132,141] suggesting that reductions in NAA levels may become more pronounced with the progression of BPD.

Another explanation for the variability of findings in NAA levels is the use of medications. Some studies in BPD have shown lithium to increase cerebral NAA [142–144] levels, while other studies did not [145,146]. In BPD patients, quetiapine treatment was associated with increased NAA levels in anterior cingulate cortex [147], and both quetiapine and valproate

increased hippocampal NAA [148]. However, another study showed no effect of quetiapine treatment on brain NAA levels [123].

Interestingly, the presence of metabolic disturbance in mitochondrial ETC was suggested to decrease NAA levels. BPD patients with diabetes had lower NAA levels when compared to BPD patients without diabetes [149]; inhibitors of the mitochondrial ETC reduced NAA concentrations [150].

Findings of both decreased pH and increased lactate in BPD led to the very recent proposal that BPD patients exhibit a shift away from oxidative phosphorylation toward anaerobic glycolysis, thus reducing efficiency and total energy output [151] in their brains. This suggests that impairment in mitochondrial functioning, which is normally responsible for the oxidative phosphorylation process, might cause the changes observed in BPD. In addition, if the respiratory chain of cellular metabolism were less available, the energy production would be displaced toward anaerobic glycolysis, consequently increasing lactate production [151]. Notably, mitochondrial dysfunction is associated with reduced pH and lactate level increases. Thus, the seemingly distinct neuroimaging findings in BPD (reduced pH, increased lactate, reduced high-energy phosphates, reduced NAA and regional volumetric reductions) may all be linked by mitochondrial dysfunction as the more proximal cause (Figure 5) [151].

3.5 Cellular evidence of mitochondrial dysfunction in BPD

Peripheral cells from patients with BPD have shown altered mitochondrial function when compared with controls. Ca^{2+} signaling is usually enhanced in cells of BPD patients [152], although the molecular mechanisms of the abnormalities are not clear. Endoplasmic reticulum, store-operated Ca^{2+} channel and mitochondria were all involved in altered Ca^{2+} signaling when lymphoblastoid cells of patients with BPD were challenged with drugs and then compared with controls [153]. The mtDNA A10398G polymorphism was associated with higher levels of intramitochondrial Ca^{2+} and lower pH in the matrix observed in transmitochondrial cybrids with A-type polymorphism compared to G-type cybrids [154]. This polymorphism encodes an amino acid change in a subunit of ETC complex I, NADH ubiquinone oxidoreductase chain 3, and is associated with BPD diagnosis [46,155].

The exposition of lymphocytes from BPD patients and controls to low-glucose medium induced upregulation of mitochondrial genes in cells of controls, but downregulated the same genes in lymphocytes of patients with BPD; the findings suggest a lack of adaptation to energy stress in BPD [108]. Patients with BPD exhibited altered distribution of mitochondria in fibroblasts when compared to healthy controls [114]; the observed changes in mitochondrial morphology highlight a possible role of mitochondrial fusion–fission in BPD and may correspond to altered energy metabolism [156].

A polymorphism of *BCL-2* antiapoptotic gene (rs956572) was associated with decreased expression of *BCL-2* mRNA and proteins and dysfunctional Ca^{2+} homeostasis in lymphoblastoid cells from patients with BPD, suggesting that altered Ca^{2+} signaling is at least partly mediated by *BCL-2* [157]. Noteworthy, the Ca^{2+} alteration occurred through an inositol triphosphate receptor-dependent mechanism; lithium could increase *BCL-2* and

reverse Ca^{2+} abnormalities [157]. The same polymorphism of *BCL-2* was also associated with increased levels of glutamate in anterior cingulate cortex of patients with BPD [158].

In lymphocytes, BAX/Bcl2 ratio, cytochrome c release and caspase-3 activity were increased in manic and depressed patients with BPD compared with controls [159].

4. Conclusion

Mitochondria are important organelles, being responsible for cell energy production, Ca^{2+} homeostasis and apoptosis regulation. Neuronal cells depend almost exclusively on mitochondria for energy production. To attend to neuronal demands, mitochondria move along the axon and undergo fission and fusion. Normal mitochondrial functioning is important for cell resilience, being integral to synaptic signaling and plasticity.

Different lines of evidence suggest mitochondrial impairment in BPD. Mitochondrial dysfunction was observed in patients with BPD based on brain MRS studies showing energy shortage and low intracellular pH in those patients.

Consistent with the reduced energy production, a decreased activity or expression of ETC complex I was found in patients with BPD. Impairment in ETC activity could increase OxS and generate imbalance of antioxidant enzymes, both of which were observed in patients with BPD. In addition, mitochondria-related genes were found to be associated with BPD. Synaptic plasticity could be affected by abnormalities in mitochondrial transport, apoptotic mechanisms and Ca^{2+} dysregulation, all of which have genetic evidence of being altered in patients with BPD. ETC complex I, OxS, mitochondrial transport, apoptotic mechanisms and Ca^{2+} regulation are potential mitochondrial targets in the development of novel drugs (Figure 2).

Reinforcing the importance of these pathophysiological findings in therapeutics, mood stabilizers and atypical anti-psychotics used in BPD treatment regulates some of these targets. Lithium, for example, is associated with increases in energy production, decreased OxS, and regulation of both Ca^{2+} signaling and apoptosis in BPD.

In brief, mitochondrial function is essential to many aspects of BPD. Several abnormalities of mitochondrial function have been identified in BPD, opening an avenue for a better comprehension of BPD pathophysiology and the identification of targets for mood stabilization.

5. Expert opinion

BPD is a complex illness involving multiple systems and different clinical presentations. Thus, it is improbable that a single gene, protein or cascade can completely explain the pathophysiology of BPD. Neuronal function depends on the energy produced by mitochondria, which is likely involved in the pathophysiology of BPD, with abnormalities possibly more evident in patients with chronic illness.

Data presented in this review might allow a focus on BPD as a disease involving mitochondrial impairment – one in which metabolic abnormalities take place, leading to

subtler neuronal damage, synaptic loss and cell atrophy. New therapeutic strategies targeting crucial aspects of neuronal plasticity mediated by mitochondria might therefore offer promising avenues for treatment of BPD. Mood stabilizers might ultimately increase energy metabolism and reduce the damage caused by OxS.

Taken together, the evidence presented in this review suggest that the modulation of mitochondrial function might have an important role for the regulation of cellular resilience and synapses in neuronal pathways that control high-order functions of the brain such as cognition, mood, perception and behavior. However, the findings described here suggest that the development of mitochondrially targeted therapies still requires much work. Ideally, this work would involve testing drugs with good CNS penetration and compounds with a more incisive action than simple antioxidants.

We described a possible efficient and cost-effective way to test new potential treatments in a previous paper [160]. The strategy consists in initially focusing the trials on disorders that are essentially mitochondrial such as Leigh's syndrome, Leber's hereditary optic neuropathy and Huntington's disease. This approach involves a proof-of-concept therapy for such disorders. Subsequently, disorders with more subtler mitochondrial deficits would be studied (e.g., BPD and other complex psychiatric disorders). Any drug being considered to treat BPD and that target mitochondria would first need to be tested in classic mitochondrial diseases.

The proposed approach brings several advantages. Classic mitochondrial diseases usually have very high morbidity and mortality with no effective treatments. In this context, the studies would require fewer patients, might exempt placebo controls and take less time to complete. These trials could involve the study and validation of biomarkers that provide an early readout of pharmacodynamic effects of the drug tested, which would result in a faster market availability of the compound when compared to agents used for other diseases.

Another good opportunity for developing effective treatments might be in a framework of early intervention, when the biological abnormalities might be less severe. Some studies suggest that mitochondrial dysfunction may be present only in later stages of BPD [82,87]. Identifying targets that could lead to mitochondrial impairment may be an effective strategy for early intervention. However, careful selection of the patients who might benefit from early intervention and even of subjects at ultra-high-risk of developing BPD are necessary. Moreover, appropriate study designs for a correct evaluation of the outcome are needed; the identification of biomarkers holds a promise to help stratifying patients according to the neurobiological severity in stages. Furthermore, biomarkers might be helpful in finding specific neurobiological profiles to refine diagnostic accuracy; the use of biomarkers could allow clinical trials with enriched samples, in a more cost-effective way. Both proposals would allow more specific interventions. The suggestion involves translating basic neuroscience research in order to enhance the classification of BPD based on pathophysiologic processes.

There has, unfortunately, been little progress in developing truly novel medications specifically for the treatment of BPD, and most recent additions to the pharmacopeia are

brain-penetrant drugs developed for the treatment of epilepsy or schizophrenia. The next generation of drugs, in addition to treating the core symptoms of BPD, might be able to target other important aspects of the illness. These include enhancing cognition independent of any improvement in mood symptoms, and preventing or reversing epigenetic factors that may have long-term negative impacts on the course of the illness.

We are optimistic that the advances in mitochondrially mediated plasticity outlined here will ultimately lead to the discovery of new approaches for the prevention and treatment of some of mankind's most devastating and least understood illnesses.

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Article highlights

- Mitochondria are crucial for apoptosis regulation, calcium (Ca^{2+}) signaling and energy production, which are mainly generated through the electron transport chain (ETC).
- Synaptic plasticity is modulated by energy metabolism, apoptotic factors, Ca^{2+} regulation and mitochondrial movement.
- Postmortem brains of patients with bipolar disorder (BPD) show decreased ETC activity and expression, and increased oxidative stress (OxS).
- Evidence from peripheral blood suggests that BPD is associated with increased OxS, Ca^{2+} dysregulation and increased proapoptotic signaling.
- Neuroimaging studies suggest an energy shortage and impaired metabolism in patients with BPD.
- Targeting mitochondrial function may be an important avenue for developing mood-stabilizing agents.

This box summarizes key points contained in the article.

Figure 1. Energy production in the mitochondrion

The energy is produced in mitochondria from oxygen and glucose through a cascade of events: glycolysis → pyruvate decarboxylation → citric-acid cycle → oxidative phosphorylation. During glycolysis, glucose in the cytosol is broken down into pyruvate. In the anaerobic pathway, pyruvate is converted into lactate, while in the high-energy production aerobic pathway, pyruvate is converted to acetyl-coenzyme A, which enters the citric acid cycle. Acetyl-coenzyme A is first converted to citrate, then to α-ketoglutarate; α-ketoglutarate converts to succinyl-coenzyme A, and then succinate; succinate is transformed to fumarate, and then malate; malate is converted to oxaloacetate. The process of oxidative phosphorylation uses NADH₂ and FADH₂, produced in the glycolysis and in the acid citric cycle. NADH₂ and FADH₂ transfer electrons to the ETC, where oxidative phosphorylation occurs. NADH+H transfers the electrons to the complex I of ETC, while the FADH₂ produced in mitochondrial matrix carries electrons to ETC complex II. The electrons pass from ETC complex I and complex II to coenzyme Q, and then to ETC complex III, and eventually to complex IV, where they are combined with O₂ to generate H₂O. In each electron passage, there is energy production and hydrogen ions are transported to the intermembrane space, generating an electrochemical gradient. Through ETC complex V the hydrogen ions go back to matrix using the electrochemical gradient to produce ATPs. ETC: Electron transport chain.

Figure 2. Possible targets for improving mitochondrial function in BPD are electron transport chain (especially complex I), oxidative stress, monoamine oxidases, apoptotic mechanisms, calcium homeostasis and mitochondrial movement

Monoamines (MA) are metabolized by monoamine oxidase A (MAO-A) and MAO-B, generating reactive oxygen species (ROS).

BCL-2: B-cell lymphoma protein-2; BPD: Bipolar disorder; DISC1: Disrupted in schizophrenia-1.

Figure 3. The putative role of mitochondria in synaptic plasticity and possible consequences of mitochondrial pathology and/or treatment

Under healthy conditions (left side), the mitochondrion exerts several effects on presynaptic neurotransmitter release. The surge in intracellular calcium during an individual action potential is rapidly buffered by MMP-driven mitochondrial calcium uptake (1). The slow release of calcium back into the cytoplasm is thought to allow for post-tetanic potentiation (2). The continuous production of ATP and removal of ADP are essential for the energy-demanding processes of vesicle docking, fusion and endocytosis (3). Under pathological conditions (right side), many of these processes may be disrupted. Failure of the MMP reduces the calcium uptake affinity, thereby resulting in more pronounced calcium spikes and chaotic, desynchronized release (4). The return of mitochondrial calcium to the cytoplasm is subsequently impaired, possibly resulting in deficient posttetanic potentiation (5). Failure of the MMP would also lead to a reduction in ATP production, resulting in more rapid fatigue of energy-dependant processes (6). Finally, abnormally elevated cytosolic calcium may inhibit the efficiency of endocytosis, further impairing subsequent release (7). Reproduced with permission from Quiroz *et al.* Mitochondrially mediated plasticity in the pathophysiology and treatment of bipolar disorder [3].

ADP/ATP: Adenosine di-/triphosphate; ANT: Adenine nucleotide translocase; BCL-2: B-cell lymphoma protein-2; CU: Calcium uniporter; MMP: Mitochondrial membrane potential; VDCC: Voltage-dependant calcium channel.

Figure 4. Cellular resiliency signaling pathways in mood disorders. (Left panel) *Neurotrophic factor signaling*

BDNF activates TrkB receptors; phosphorylation can then activate either the ERK signaling cascade, PI3K, or PLC-γ. Ultimately, these independent pathways converge to enhance plasticity and cell survival. (Center panel) *Antiapoptotic signaling*. Following activation of procaspases (e.g., Caspase 8), proapoptotic factors are activated (BH3-only proteins), which in turn inhibit antiapoptotic proteins such as Bcl-2. This enables proapoptotic members to form pores on the outer mitochondrial membrane, ultimately leading to the release of cytochrome C, activation of effector caspases (e.g., Caspase 3) and, eventually, impaired plasticity and cell death. (Right panel) *Glucocorticoid receptor signaling*. Following a stress response, glucocorticoids (GC) are released and downregulate the HPA axis, turning off the stress response after a period of time. At the cellular level, GCs bind to their receptor (GR), whereby different co-chaperones can modulate GR nuclear trafficking. FKBP5 and BAG-1 are two such co-chaperones that have opposing roles in either attenuating or enhancing GR nuclear trafficking, respectively. Once inside the nucleus, GRs bind to GC responsive elements (GRE) and turn on downstream gene targets (e.g., SGK-1 and MKP-1), leading to enhanced survival and plasticity mechanisms. Alternatively, the GRs can associate with Bcl-2 (dashed line) following acute doses of corticosterone. This complex translocates (dotted line) to the mitochondria to enhance survival, leading to enhanced cellular plasticity and resiliency. Mood stabilizer targets are depicted in red.

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APAF: Apoptotic protease activating factor; BAG-1: BCL2-associated athanogene; BCL-2: B-cell lymphoma protein-2; BDNF: Brain derived neurotropic factor; CREB: cAMP response element-binding protein; CHIP: Carboxyl terminus of the Hsc70-interacting protein; DAG: Diacylglycerol; ER: Endoplasmic reticulum; ERK: Extracellular-signal-regulated kinase; FKBP5: FK506 binding protein; GR: Glucocorticoid receptor; HIP: Hsc70-interacting protein; HOP: Hsp70-Hsp90 organizing protein; HPA: Hypothalamic-pituitary-adrenal axis; Hsp 40: Heat shock protein 40; Hsp 70: Heat shock protein 70; Hsp 90: Heat shock protein 90; IP: Interacting partners; MEK: Mitogen-activated protein kinase/ERK kinase; MKP-1: Mitogen associated protein kinase phosphatase 1; PLC- γ : Phospholipase C-gamma; SGK-1: Serum/glucocorticoid regulated kinase 1; TATA: TATA box DNA sequence; TrkB: Tyrosine Kinase Receptor B; TRPC3: Transient receptor potential cation channel, subfamily C, member 3.

Figure 5. A model integrating neuroimaging findings with the involvement of mitochondrial dysfunction in bipolar disorder (BPD) was proposed by Stork and Renshaw

The reduced cerebral *N*-acetyl aspartate (NAA) in BPD suggests decreased mitochondrial activity (a), that leads to a shift from the impaired oxidative phosphorylation (b) toward glycolytic inefficient energy production (c), consistent with the increased lactate (d) and reduced intracellular pH (e) found in patients with BPD. Pyruvate does not enter in mitochondria to integrate oxidative phosphorylation, but is converted into lactate, which raises pH. The energy shift leading to reduced ATP output would reflect in the decreased energy storage in the form of phosphocreatine (PCr) (f), dashed lines indicate an impaired pathway.

Adapted from [151].