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Review paper

Mitochondria dysfunction and bipolar disorder: From pathology to therapy

Xin-Jieh Lam [a], Bingzhe Xu [b], Pei-Ling Yeo [c], Pike-See Cheah [a], King-Hwa Ling [d,*]

[a] Department of Human Anatomy, Faculty of Medicine and Health Sciences, Unversiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
[b] School of Biomedical Engineering, Sun Yat-sen University, 132 Daxuecheng Outer Ring E Rd, Panyu Qu, Guangzhou Shi, Guangdong 511434, People's Republic of China
[c] School of Postgraduate Studies and Research, International Medical University, 126, Jalan Jalil Perkasa 19, 57000 Bukit Jalil, Kuala Lumpur, Malaysia
[d] Department of Biomedical Science, Faculty of Medicine and Health Sciences, Unversiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

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ABSTRACT

Bipolar disorder (BD) is one of the major psychiatric diseases in which the impairment of mitochondrial functions has been closely connected or associated with the disease pathologies. Different lines of evidence of the close connection between mitochondria dysfunction and BD were discussed with a particular focus on (1) dysregulation of energy metabolism, (2) effect of genetic variants, (3) oxidative stress, cell death and apoptosis, (4) dysregulated calcium homeostasis and electrophysiology, and (5) current as well as potential treatments targeting at restoring mitochondrial functions. Currently, pharmacological interventions generally provide limited efficacy in preventing relapses or recovery from mania or depression episodes. Thus, understanding mitochondrial pathology in BD will lead to novel agents targeting mitochondrial dysfunction and formulating new effective therapy for BD.

Introduction

Bipolar disorder (BD) is a major psychiatric disease characterised by manic and depressive episodes. According to the World Health Organization, bipolar disorder is the sixth most common cause of disability worldwide, and it affects ~5% of the population with multiple dangerous impacts on their lives (Auerbach et al., 2019). The prevalence rate of bipolar disorder reaches 4.4%, considerably higher than other psychiatric disorders such as schizophrenia (at 1% prevalence). BD patients suffer severe disability and social impairment with unusual shifts in elevated and depressed "mood episodes", including unusual changes in mood, energy, activity levels and sleep patterns, which deprive them of the ability to carry out day-to-day tasks. It is reported that significant neurocognition disturbance occurs during different BD stages (Simonsen et al., 2008). In the depressive episodes, the apparent evidence is the deficits in attention and memory, impairment in verbal recall and fine motor skills. In mania episodes, complex processing, such as attention, memory, and emotional processing, is dysfunctional.

In recent years, the impairment of mitochondrial energy metabolism has gained increasing attention in many brain diseases and is closely related to BD. Compared with the general population, the prevalence of mitochondrial dysfunction is higher in people with BD (Kato, 2007; Manji et al., 2012). Based on structural and functional magnetic resonance imaging studies (MRI), specific brain areas, such as the frontal and prefrontal cortex and marginal areas, appear to show abnormal size and impaired function (Chen et al., 2011; Drevets et al., 2008). Different hallmarks of decreased energy metabolism have also been found, including decreased pH in specific brain regions, reduced levels of creatine phosphate and adenosine triphosphate (ATP), and increased lactate levels (Zuccoli et al., 2017). Mitochondrial damage, such as abnormal morphology and marginal distribution, has been discovered in brain imaging of BD patients (Gigante et al., 2011a). Postmortem staining of frontal and prefrontal samples from BD patients also revealed morphological abnormalities and marginal distribution of mitochondria (Ben-Shachar and Karry, 2008; Mattson et al., 2008; Mertens et al., 2015). Abnormal energy metabolism has also been found in functional measurements and magnetic resonance spectroscopy studies of BD patients (Hroudová et al., 2019; Kato and Kato, 2000). The detailed genetic analysis further showed that genes related to mitochondrial function are affected in BP. Transgenic mice with mitochondrial DNA polymerase

Abbreviations: DNA, deoxyribonucleic acid; ATP, adenosine triphosphate; ROS, reactive oxygen species; ETC, electron transport chain; ER, endoplasmic reticulum; TCA, tricarboxylic acid cycle; IP3, inositol triphosphate; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; GPCR, G protein-coupled receptor; VPA, valproic acid.

* Corresponding author.
E-mail address: lkh@upm.edu.my (K.-H. Ling).

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mutations provide genetic evidence for BD mitochondrial abnormalities (Kato et al., 2018). Gene and protein expression studies show reduced enzymes involved in ATP production and storage (Iwamoto et al., 2005). All these shreds of evidence indicate a strong connection between BD and mitochondrial dysfunction. Thus, a better understanding of perturbed mitochondrial function would provide therapeutic benefits to bipolar disorder.

This review will show different lines of evidence of the close connection between mitochondria dysfunction and BD. We will discuss the genetic and physiological evidence of BD mitochondrial abnormalities to elucidate the pathology of BD. For now, the current pharmacological treatments generally provide limited efficacy in preventing relapses or recovery from mania or depressed episodes. Thus, novel therapeutic techniques targeting mitochondrial dysfunction are urgently required.

Mitochondrial dysregulation and affected brain energy metabolism

Dysfunction in energy metabolism has been one of the most consistent findings related to BD. The human brain usually consumes about 27% of the body's total glucose consumption, and well-worked energy metabolism is believed to be a vital support for brain function. During brain energy metabolism, glucose serves as the essential energy source and undergoes many reactions in the cell in the production of some harmful byproducts, including reactive oxygen species (ROS). If the high level of ROS were not dealt appropriately by antioxidant enzymes, it would bring damage, functional defects or even cell death to brain cells. Glucose is also crucial for synthesising vital neural transmitters such as glutamic acid, acetylcholine, and gamma-aminobutyric acid (GABA). Therefore, metabolism dysfunction could trigger various abnormal brain functions involving calcium buffering and amino-acid metabolism.

The first clear evidence of disturbed metabolism in BD is a higher incidence of metabolic syndrome in individuals with BD than in the normal population (Bhowmik et al., 2015; Fagiolini et al., 2005). It is reported that the rate of metabolic syndrome could reach as high as 67% in BD patients, and various symptoms could be induced. These symptoms include hyperglycemia, type-2 diabetes mellitus and insulin resistance, which account for the prominent cause of mortality among individuals with BD (Brietzke et al., 2011; Vancampfort et al., 2013). Besides, changes in several markers related to metabolic dysfunction are identified in the serum of BD patients, such as reduced levels of glucagon, glucagon-like peptide-1 (GLP-1) and elevated levels of the glucose-dependent insulinotropic polypeptide (GIP) (Rosso et al., 2015). These markers are known to play vital roles in brain synaptic plasticity and neuroprotective mechanisms and are believed to be involved in mood and cognitive functions, such as psychological stress responses. Changes in metabolic markers in BD patients show a strong connection between BD and metabolic disease.

Mitochondria are a cellular powerhouse. The significant changes in size and intracellular distribution of mitochondria may have severe repercussions on the energy metabolism among BD subjects. Changes in mitochondrial morphology, number and cellular distribution were seen in the postmortem prefrontal cortex, primary fibroblasts and lymphocytes of BD individuals compared to controls (Cataldo et al., 2010). Significant alterations were seen in two peripheral cell types (lymphocytes and fibroblast) isolated from BD patients. Mitochondria from the BD group were found dense and bulky with perinuclear clustering, whereas an interconnected network of mitochondria that span across the cytoplasm between the nuclear and plasma membranes was observed in controls (Cataldo et al., 2010). An electron microscopy analysis of postmortem prefrontal cortex samples showed a significantly smaller mitochondrial area in individuals with BD (Cataldo et al., 2010). An independent study on hippocampal dentate gyrus-like neurons derived from iPSCs of BD patients also reported a significantly smaller mitochondrial size when compared to controls (Mertens et al., 2015).

Changes in energy metabolism in the brain of BD patients have been well reported, which directly and indirectly affected the homeostatic balance of glycolysis, tricarboxylic acid, oxidative phosphorylation (including electron transport chain/ETC system) and phosphagen pathways (Fig. 1). Lactate, a byproduct of the anaerobic glycolysis pathway, was increased in the grey matter of medication-free BD individuals (Dager et al., 2004). Magnetic resonance spectroscopy (MRS) analysis detected increased lactate in several brain regions of BD subjects, most prominently within the anterior cingulate and caudate regions (Chu et al., 2013). The total metabolite concentration in the ratio of lactate/N-acetylaspartate (Lac/NAA) and lactate/total creatine (Lac/Cr) were significantly higher in BD subjects (by 58–59%) when compared to controls (Chu et al., 2013). Similarly, adjusted lactate concentration was approximately 34% higher in the cerebrospinal fluid of BD subjects versus controls (Regenold et al., 2009). Using MRS, significantly decreased intracellular pH in the frontal lobe (Shi et al., 2015) and basal ganglia of BD subjects (MacDonald et al., 2006) were detected, a phenomenon often correlating with increasing lactate levels. In addition, lower levels of adenosine triphosphate (ATP) and phosphocreatine were also reported in the brain of BD subjects (Shi et al., 2015). MacDonald and colleagues (2006) reported a decrease in the creatine kinase mRNA level in the hippocampus and prefrontal cortex in BD individuals (MacDonald et al., 2006), suggesting that reduced ATP/phosphocreatine in BD could be related to the perturbed creatine kinase-mediated phosphagen pathway. The phosphagen pathway is an important mechanism not only involved in refuelling adenosine diphosphate into ATP but storing phosphate groups in the form of phosphocreatine. The changes in the levels of lactate, pH, ATP and phosphocreatine in the brain indicate a possible mitochondrial dysfunction-related shift from the energy-efficient tricarboxylic acid/-oxidative phosphorylation pathway to the inefficient anaerobic glycolysis pathway in the brain of BD individuals.

Concurring with the notion of shifted energy metabolism to glycolysis, disturbances to the aerobic respiration process involving the tricarboxylic acid cycle and oxidative phosphorylation pathway have been documented in BD. The glycolysis pathway produces pyruvate, an essential substrate for the TCA cycle that occurs within the mitochondrial matrix. Besides lactate, pyruvate, along with other intermediates of the TCA cycle (citrate, isocitrate and *cis*-aconitate α-ketoglutarate), was found significantly increased in the cerebrospinal fluid of BD subjects based on a metabolomic study using the capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) (Yoshimi et al., 2016). Increased levels of these intermediates may imply perturbed pyruvate metabolism in the early chain of reactions of the TCA cycle. Yoshimi and colleagues (2016) detected a significant reduction of *IDH3A* (~44%) and *IDH3B* (~25%) mRNAs that encode for isocitrate dehydrogenase (IDH) in the postmortem dorsolateral cortex of BD subjects. IDH3 catalyses D-isocitrate into α-ketoglutarate via the oxidative decarboxylation process in the mitochondrial matrix to generate NADH. Interestingly, *IDH1* and *IDH2* genes that encode for IDH isoforms that catalyse isocitrate in the cytoplasm were not differentially expressed, suggesting that the perturbation could be mitochondrial-specific. Also, the IDH3A subunit of the enzyme was found to be significantly lower in the cerebellum but not the parietal cortex of the BD subjects (Yoshimi et al., 2016). The study, however, failed to correlate the mRNA expression with the enzyme level in the same brain region. It is unclear how the reduced IDH3 enzyme in the specific brain region could lead to the dysregulated CSF metabolomic profile among BD subjects. Nevertheless, the dysregulation of isocitrate metabolism is intriguing and provides a fresh perspective on mitochondrial dysfunction in BD.

Disturbances of the ETC system have been implicated in the brain of BD individuals. A significant decreased (~53%) in mitochondrial complex I activity was observed in the brain of BD subjects (Andreazza et al., 2010). In addition, microarray experiments detected a significant reduction of complexes I-V encoding mRNAs levels in the postmortem hippocampus (Konradi et al., 2004) and complexes I, IV and V in the

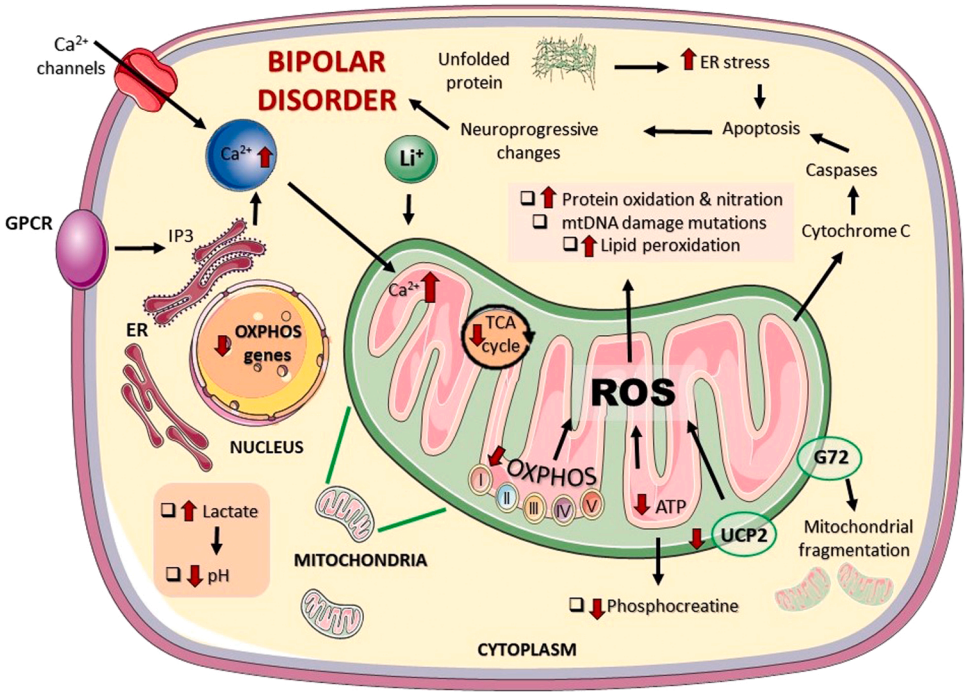

Fig. 1. Overview of mitochondrial dysfunction in bipolar disorder.
In BD cells, TCA (or Kreb cycle) is disturbed, and its metabolic profile switches from OXPHOS to aerobic glycolysis and lactate production, with a concomitant decreased intracellular pH level. Decreased OXPHOS and reduced UCP2 also induce ROS accumulation leading to subcellular changes and apoptosis. Accumulation of unfolded proteins causes ER stress that subsequently can induce apoptosis. Excess calcium influx leads to high levels of intracellular calcium concentration. Lithium attenuates neuronal Ca^{2+} entry and subsequently normalises the hyperexcitable neurones. ROS - reactive oxygen species; UCPs - uncoupling proteins; ER – endoplasmic reticulum; OXPHOS – oxidative phosphorylation; mtDNA – mitochondrial DNA; TCA - tricarboxylic acid cycle; GPCR – G protein-coupled receptor; IP3 – inositol triphosphate. The organelles within the cell image were created using Servier Medical Art templates at https://smart.servier.com, which are licensed under a Creative Commons Attribution 3.0 Unported License.

frontal cortex of BD subjects (Sun et al., 2006a). Mitochondrial ETC complexes are involved in the oxygen-dependent transportation of electrons from the matrix to intermembrane space. Reduction of mitochondrial ETC complexes activity may disrupt the establishment of electron gradient, thus affecting the oxidative phosphorylation pathway. In a different study, the mitochondrial complex I genes (*NDUFV1, NDUFV2, and NDUFS1*) were significantly higher in the peripheral blood sample during the manic episodes of BD patients compared to controls (Akarsu et al., 2015). Likewise, citrate synthase, ETC complexes II and IV activities were decreased, but ETC complex I was increased in the platelets of bipolar affective disorder subjects (Hroudová et al., 2019). Contrary to these reports, Rosenfeld and colleagues (2011) did not find any differences in the lymphoblastoid mitochondrial dynamics and respiration between the BD and control groups (Rosenfeld et al., 2011 May 15). The inconsistencies between the brain and peripheral blood profiles suggest that the brain bioenergetics among BD individuals may not be directly correlated. Nevertheless, various studies have repeatedly demonstrated the dysregulation of ETC in both the brain and peripheral blood in BD, implicating mitochondrial dysfunction in the shift of energy metabolism proposed earlier.

Genetic variants, mitochondrial dysfunction and bipolar disorder

The heritability of BD is estimated at 0.7–0.8, with a child of an affected parent having approximately a 10-fold higher risk of developing the disorder (Craddock and Sklar, 2013). Many genetic loci, genes or single nucleotide polymorphisms (SNPs) have been found to be significantly associated with BD. Nuclear and mitochondrial DNA mutations have been implicated in the abnormal or impaired level of expression of activities of mitochondrial ETC complexes required for oxidative phosphorylation among BD individuals (Iwamoto et al., 2005; Konradi et al., 2004; Sun et al., 2006b). Mitochondria are maternally inherited. Not all cells or brain regions are similarly affected by the mitochondrial gene variants (Scaini et al., 2016), and the percentage of accumulated mutations over time or heteroplasmy affects the disease outcome. Decreased mitochondrial function in BD patients due to mutations in the mitochondrial or the nuclear genomes has been postulated as a genetic risk in BD development and progression.

Mutations or polymorphisms in mitochondrial DNA (mtDNA) have been controversially associated with calcium buffering deficiency, glutamate-mediated excitotoxicity, and differential response to treatment (Kato, 2008). Analysis of 16 major mtDNA haplogroups in a Japanese cohort indicated mtDNA N9a haplogroup as over-represented in the BD group (Kazuno et al., 2009). The N9a haplogroup consists of several variants, such as 5231 G>A, 12358 A>G, and 12372 G>A, that are protective against metabolic syndrome among Japanese women (Tanaka et al., 2007, 2004), an observation that contradicts dysfunctional mitochondrial bioenergetic profiles seen in the BD brain. The mtDNA 3644 T > C mutation (valine to alanine conversion) at the region encoding for subunit 1 of NADH dehydrogenase (ubiquinone) is associated with BD. The mutation leads to reduced complex I activity and decreased MMP in cell lines transfected with mutant mitochondria, known as cybrids (Munakata et al., 2004). Using the same cybrids model, another susceptible mtDNA 3243 A>G mutation was shown to cause increased expression of LARS2 (mitochondrial leucyl-tRNA synthetase) expression, which was subsequently validated in human postmortem brain samples (Munakata et al., 2005). LARS2 catalyses the aminoacylation of $tRNA^{Leu}$, and the mtDNA 3243 A>G mutation causes decreased efficiency of LARS2 as well as mitochondrial diseases such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) (Li and Guan, 2010) that has coincidental comorbidities such as mood disorders and psychosis. This suggests that the mutation could lead to some overlapping phenotypes observed in MELAS and BD, whereas increased LARS2 expression in mtDNA 3243 A>G mutation in the BD brain is most likely a compensatory mechanism that failed to restore LARS2 function. In a different study involving 224 BD patients, mtDNA U haplogroup and various mtDNA gene variants of tRNA (rs2853498), *ND5* (rs2853499), *ND4* (rs2853493, rs2853495), *CYB* (rs527236041) and *CO1* (rs2015062) were found significantly associated with a higher risk of psychosis based on an uncorrected analysis (Frye et al., 2017). The implicated mtDNA gene variants are essential components of ETC energy regulation. In addition, BD patients with mtDNA 5178 A>C variant have lowered frontal lobe pH when assayed by MRS (Kato and Kato, 2000; Kato et al., 2000). In contrast, mtDNA 10398 A>G variant is associated with decreased

mitochondrial matrix pH, higher fasting glucose and lower glucose utilisation in the prefrontal cortex (Li et al., 2015) and higher baseline and poststimulation mitochondrial Ca^{2+} levels (Kato et al., 2000, 2003; Kazuno et al., 2006; Washizuka et al., 2003a). MtDNA 10398 A variant was also associated with a better response to lithium treatment in BD patients (Li et al., 2015), whereas the mtDNA 10398 G variant prevailed more among lithium non-responder (Washizuka et al., 2003a). Cybrids with the mtDNA 10398 A variant responded better to valproate (VPA, mood stabiliser) when compared to the mtDNA 10398 G variant in stabilising the intracellular Ca^{2+} level (Kazuno et al., 2008). Although many mtDNA gene variants have been associated with BD and mitochondrial dysfunction, their overall effects on functional perturbations may vary from one to another.

Reduction in the levels of nuclear gene expression for ETC complex I subunits, such as *NDUFV1*, *NDUFS8*, and *NDUFS7*, have been reported in the BD postmortem prefrontal cortex and hippocampus. At the protein level, NDUFS7 was reduced in the BD prefrontal cortex and was correlated with decreased complex I activity (Andreazza et al., 2010). Reduced complex I function may lead to an increased rate of electron leakage hence elevated reactive oxygen species. In non-BD subjects, *NDUFV1* gene mutation (1268 C.T) resulted in a significant reduction of NDUFV1 protein, subsequently severe phenotypes or death in early postnatal development (Schuelke et al., 1999). A few polymorphisms within *NDUFV2* are significantly associated with BD in Japanese (Washizuka et al., 2003b), European Caucasians (Xu et al., 2008) and Chinese Han (Zhang et al., 2009), but the observations were not reproducible in another study on the Caucasian population (Doyle et al., 2011). Another nuclear gene, *POLG1*, which encodes for mitochondrial polymerase, was reported to be significantly enriched with deleterious variants in BD subjects compared to controls. POLG1 with deleterious variants were also biochemically less active (Kasahara et al., 2017). While there is no direct evidence indicating that the deleterious variants of *POLG1* are involved in the neuropathology of BD, mice with an exonuclease-deficient mutant of POLG1 (D198A in human POLG1) expressed explicitly at the paraventricular nucleus of thalamus exhibit recurrent depression-like behavioural changes (Kasahara et al., 2016). In addition to these gene variants, *DISC1*, has been proposed as a potential candidate susceptible gene for BD (Brandon and Sawa, 2011). A family-based association study involving 57 BD pedigrees showed over-transmission of risk haplotype (HP1) to BD subjects, and the haplotype was associated with reduced DISC1 mRNA expression in the lymphoblasts (Maeda et al., 2006). DISC1 is localised to the inside of the mitochondria to interact with mitofilin, a mitochondrial inner membrane protein (Park et al., 2010). When one or both DISC1 and mitofilin were knockdown in mice, NADH dehydrogenase and ATP levels were significantly reduced, whereas Ca^{2+} buffering was affected, indicating the relevance of DISC1/mitofilin in mitochondrial bioenergetic function as well as calcium homeostasis and dynamics (Park et al., 2010). Although many genetic variants of *DISC1* were implicated in various neuropsychiatric disorders, including BD, the levels of *DISC1* mRNA or protein have never been different between the BD and control brains (Chubb et al., 2008). While DISC1 deficiencies could be caused by post-translational modifications or differential localisation of the protein, there is no direct evidence indicating the loss of DISC1 function in the brain of BD subjects and neuropathologies associated with DISC1-perturbed mitochondrial function. Taken together, the functional consequences of the said polymorphisms or susceptible genes on mitochondrial function have not been well-established in BD development or progression and warrant further investigations.

Oxidative stress, DNA damage, dysregulated apoptosis and cell death

It is well documented that BD patients have significantly increased oxidative stress, which is thought to mediate the neuropathological processes of BD. During an oxidative stress state, a cell has a disturbed cellular function when the production of reactive oxygen species (ROS) supersedes antioxidant activities leading to an increase in ROS levels. Oxidative stress can cause subcellular changes and direct damage to nucleic acids, lipids (increased lipid peroxidation) and proteins (increased protein oxidation and nitration). Oxidative phosphorylation is an essential and major energy provider for the cell. This mechanism declines when an electron leaks from the ETC, which subsequently increases the intracellular superoxide production leading to oxidative stress that can cause damage to neurons (Wang et al., 2009). Catalase and antioxidant enzymes such as peroxidase, glutathione S-transferase, and superoxide dismutase were dysfunctional in BD, confirming the effects of potential oxidative stress in BD as evidenced by postmortem brain tissue analysis (Andreazza et al., 2008, 2010; Che et al., 2010; Soeiro-De-Souza et al., 2013).

Contradictory findings have been reported on the antioxidant enzymatic activities of superoxide dismutase, catalase and glutathione peroxidase in BD patients. A meta-analysis involving 226 studies on eight oxidative stress markers indicated that lipid peroxidation, nitric oxide, and DNA/RNA damage levels were significantly increased in BD patients compared to healthy controls (Brown et al., 2014). The heterogeneity of the studies involving different tissues, age of onset, treatment given at the time of sample collections, duration of the disorder and the number of manic/depression episodes could contribute to the differences in the study outcome.

Using ^{1}H-MRS, no diminution of glutathione (GSH) baseline levels in the anterior cingulate cortex (ACC) between BD patients and matched healthy controls was observed (Lagopoulos et al., 2013). When the same brain region was assessed in BD and control young adults who consumed alcohol, the level of GSH decreased significantly in both groups. However, alcohol consumption was negatively correlated with GSH levels in the BD group, suggesting alcohol consumption may increase oxidative stress and serve as a risk factor in the onset of BD among high-risk BD individuals (Chitty et al., 2013). The notion was supported by an independent study involving the blood chemistry of BD patients with different disease onset ages. GSH level was lower in BD patients and negatively correlated with the disease onset age (Rosa et al., 2014). A significantly higher protein carbonyl and lipid hydroperoxide content was observed in adults compared to adolescents with BD (Hatch et al., 2015), suggesting that the cumulative cellular effects of oxidative stress are expected to worsen with time as adults BD patients suffered from more manic episodes than adolescent patients. In addition, the antioxidant defences behave differently at different phases of the disorder. For example, the serum superoxide dismutase activity was higher during the manic and depressive phases among BD patients than in euthymic patients and controls (Andreazza et al., 2007a).

Magnetic resonance spectroscopy (MRS) is a non-invasive in vivo imaging tool designed to visualise energy-related metabolites levels in the brain, such as high-energy phosphates ATP and phosphocreatine (PCr). Shi and colleagues (2015) observed an inverse correlation in BD characterised by decreased PCr and increased depression severity. Inefficient OXPHOS leads to the accumulation of lactic acid from glycolysis and acidification of the tissue, as well as the depletion of high-energy phosphates in BD (Regenold et al., 2009; Clay et al., 2011). Phosphomonoesters (PMEs) are membrane precursors for synthesising membrane lipids such as phosphoethanolamine and phosphocholine, the most abundant phospholipids in the neuronal membrane. The breakdown of these phospholipids releases phosphodiester (PDE). MRS is useful to measure levels of PME and PDE to detect abnormal membrane phospholipid metabolism in BD. Decreased PME/PDE (phosphodiesters) in subjects with bipolar depression was consistent with differences in membrane turnover rates indicating alterations in phospholipid metabolism and mitochondrial function (Shi et al., 2015).

The primary function of the endoplasmic reticulum (ER) in the cell is to serve as the plant for protein synthesis, folding and post-translational modifications. Disrupted protein folding or post-translational modifications, alterations in ionic calcium levels, redox imbalance and

inflammatory signalling can cause accumulation of unfolded or misfolded proteins and subsequently causes ER stress. Mitochondria respond to ER stress to restore cell homeostasis, which failure will lead to cells undergoing apoptosis or cell death (Kim et al., 2017; Malhotra and Kaufman, 2011). Impaired ER stress response has been documented in BD patient-derived lymphoblastoid cell lines or blood cells. When challenged with ER stressors such as thapsigargin or tunicamycin, the induction ER stress-related genes or proteins such as spliced forms of X-box binding protein 1 (*XBP1*), total *XBP1*, heat shock protein 90 beta family member 1 (*HSP90B1 a.k.a. GRP94*), C/EBP homologous protein (CHOP), eukaryotic initiation factor 2 (eIF2a-P) and chaperone heat shock protein family A (Hsp70) member 5 (HSPA5 a.k.a. GRP78) were attenuated in BD but not control samples suggesting an impaired ER stress response in BD patients (Hayashi et al., 2009; Pfaffenseller et al., 2014; So et al., 2007). The primary cause of impaired or altered ER stress response is not well-defined. One of the many speculations is the perturbed Ca^{2+} gradient within the ER that leads to increased misfolded protein. Unfolded protein response (UPR), a highly regulated signalling pathway, will be activated to prevent intolerable accumulation of misfolded protein through XBP1-, ATF6 p50- and ATF4-mediated ER-associated degradation process (ERAD) (Kim et al., 2017; Malhotra and Kaufman, 2011). In a chronic misadventure of protein misfolding, UPR may fail to restore ER-homeostasis of protein folding and modifications for the fundamental cellular process. Ultimately, UPR will activate apoptotic response leading to cellular demise.

On the other hand, the excessive production of ROS has been blamed as the culprit that leads to mitochondria or ER membrane turnover. Given the vast ER network and membrane contacts with mitochondria, prolonged oxidative stress may lead to alteration of MMP, structural changes or redistribution of the ER-mitochondrial network within the cell. These mitochondrial changes compromise the Ca^{2+} buffering capacity leading to disrupted Ca^{2+} signalling that affects protein misfolding. The multitude of intrinsic dysregulations both at mitochondria and ER organelles contributed to the molecular pathophysiology seen in BD.

Mitochondria are highly dynamic organelles that divide and fuse continually, forming changing interconnecting tubular networks to maintain cellular function. Deviations in either fusion or fission can compromise cellular function, which may lead to apoptosis and cell death. Apoptosis is thought to contribute to neuronal loss in patients with BD, and the hallmark feature of apoptosis is the presence of DNA fragmentation. Expression of G72 (also known as DAOA/D-amino acid oxidase activator) promotes DNA fragmentation (Kvajo et al., 2008) (Kvajo et al., 2008) and is a strong candidate susceptibility gene for BD patients (Bass et al., 2009). The single-cell gel electrophoresis comet assay and silver nitrate staining on peripheral blood BD patients and matched controls showed that an increased frequency of DNA damage was associated with the severity of manic and depressive symptoms of BD patients (Andreazza et al., 2007b). Consistent with the finding, Buttner and coworkers (2007) observed a significant increase of apoptotic activity (DNA damage) in the postmortem ACC of BD patients, subsequently causing loss of non-GABAergic cells in that region (Buttner et al., 2007). Mitochondrial complex I expression is decreased in BD patients (AC Andreazza et al., 2010) in association with increased protein oxidation and nitration, predisposing neuronal cells to mitochondrial-dependent apoptosis. Complex I deficiency leads to the release of cytochrome c and pro-caspases (intra-mitochondrial proteins) and consequent activation of programmed cell death through caspase 3 (Hotchkiss et al., 2009). Microarray analysis of postmortem hippocampal extracts showed that multiple proapoptotic genes (*FAS*, *c-MYC* and *APAF-1*) were upregulated (Benes et al., 2006). Mitochondrial uncoupling protein 2 (UCP2) are anion-carrier proteins anchored in the inner membrane of the mitochondria. The mRNA levels of UCP2 were significantly lower in the dorsolateral prefrontal cortex of subjects with BD (Gigante et al., 2011b), suggesting that this protein reduces the ROS production in BD by lowering proton leak in the mitochondrial inner membrane and consequently decreases cell death.

Reduced cellular resilience in BD is associated with defective mitochondrial metabolism and oxidative stress. Consequently, the protective cellular mechanisms become less efficient with the neuroprogression of BD. These targets in mitochondrial biology represent an attractive and promising target for therapeutic purposes, to make the modulation of cell survival possible and, ultimately, to reduce the biological impact of BD illness progression.

Affected calcium homeostasis and electrophysiology

For a long time, calcium signalling has been associated with BD, especially reports of changes in intracellular calcium ion concentrations. Researchers compared a series of Ca^{2+} parameters between BD and controls and found significant increases in the basal and stimulated free intracellular calcium concentrations in BD. Various explanations have been made for the increased calcium concentration in BD (Berridge, 2014; Warsh et al., 2004), including an excess of intracellular calcium influx, reduced efflux, or compartmental change. Cytosolic Ca^{2+} released from the endoplasmic reticulum and external Ca^{2+} sources (e.g. NMDA receptors) are taken up by mitochondria to buffer the internal Ca^{2+} level to prevent the cell from Ca^{2+}-induced stress or excitotoxicity (Baron et al., 2003; Rizzuto and Pozzan, 2006). The influx of Ca^{2+} requires ATP, and as a consequence, the TCA cycle is triggered to produce more ATP via $NADH+H^{+}$ production. In the absence or deprivation of glucose, the ATP production is affected; thus, the Ca^{2+} compartmentalisation within the cell will change, disrupting intracellular Ca^{2+} buffering, stress induction and cell death (Isaev et al., 2008; Orrenius et al., 2003; Stelmashook et al., 2009). Some studies have shown the disrupted expression or abnormal function of molecules involved in calcium flux and buffering in BD (Emamghoreishi et al., 2000; Hayashi et al., 2015; Roedding et al., 2012). For example, the trait disturbances in regulating β-adrenergic receptor sensitivity and G protein-mediated cAMP signal transduction are related to changes in calcium influx in BD patients; In addition, there is evidence implicating the disrupted function in calcium-permeable nonselective ion channels transient receptor potential (TRP) melastatin subtype 2 (TRPM2) and canonical subtype 3 (TRPC3), which is believed to be involved in abnormal calcium influx in the pathogenesis of BD. The shift of energy metabolism from the more efficient TCA cycle to the less efficient anaerobic glycolysis seen in the BD brain could further aggravate the situation by creating a pseudo-glucose-deprived environment leading to dysregulation of Ca^{2+} fluxes.

Other essential calcium-related functions were also believed to play roles in BD pathology, including neuronal excitation, transmitter synthesis and release, synaptic function and plasticity (Bading, 2013; Baker et al., 2013; Dittman and Ryan, 2019; Greer and Greenberg, 2008; Nanou and Catterall, 2018). Some believe disturbed calcium homeostasis is related to the mitochondrial and endoplasmic reticulum defects in the disease, as these organelles are essential for regulating the concentration of calcium in cells (Quiroz et al., 2008; Mekahli et al., 2011). Calcium levels were also considered to have effects on mood (such as hyperparathyroidism); thus, some researchers insist lithium and some other psychotropic classes help the patient by altering calcium function (Dubovsky and Franks, 1983; Glen, 1985; Helmeste and Tang, 1998). Lithium, the most effective drug for bipolar disorder, down-regulates ANK3 and CaV1.2 channels in mouse brains (McQuillin et al., 2007). Genomic data suggest that the voltage-gated calcium channel (VGCC) is a part of the genetic risk structure of BD, which further confirm the role of calcium signalling in the disease (Harrison et al., 2018, 2020; Heyes et al., 2015). These findings have recently prompted a renewed interest in calcium in bipolar disorder by using iPSCs from BD patients. Compared with the normal group, the neural network derived from iPSCs of BD patients showed a higher incidence of Ca^{2+} events. Lithium treatment can effectively lead to a significant reduction in the frequency of Ca^{2+} events and the percentage of active neurons. In addition, it has

been observed that this hyperexcitability is relieved as diseased neurons age, which may indicate early signs of loss of mature active neurons in the BD brain. Overall, these findings strongly support affected calcium homeostasis in bipolar disorder.

Electrophysiological studies can be used to study abnormal neurological functions in the BD brain. The mediated calcium change could also generate electrophysiology changes for the BD neural networks, such as a decreased high-frequency gamma-band activity. In the EEG / ERP signal of bipolar disorder, tons of electrophysiological evidence was found to suggest attention deficit. EEG patterns recorded from BD patients showed insufficient sleep, increased rapid eye movement (REM), decreased slow-wave sleep (SWS), and insomnia in manic and depressive states. During a click train paradigm of the manic state, the auditory EEG synchronisation in the β / γ band (20–50 Hz) is reduced, which is believed to play an essential role in cognitive and executive dysfunctions (Gray and Singer, 1989; Harrison et al., 2020; Phillips and Takeda, 2009; Singer, 1993), including abnormalities in sensory perception, motor behaviour, and memory formation (Kann et al., 2014). Consistent with calcium-related data, the following report indicates increased expression of neuronal calcium sensor protein 1 (NCS-1) in the brain of some BD patients (Stern et al., 2018). The overexpression of NCS-1 could be responsible for the decreased activity of the gamma-band present. The hyperactive action-potential firing was observed in the young neurons of BD patients by using both patch-clamp recordings, which disappear during neuronal cell ageing. Therefore, excessive excitement is an early phenotype of bipolar disorder. Compared with control neurons, BD neurons were characterised by greater sodium channel activation, a lower threshold of action potentials, more induced action potentials, higher AP amplitudes, and higher spontaneous AP frequencies. These observations are consistent with RNA-seq and qRT-PCR results (Mertens et al., 2015). Scientists found that lithium treatment selectively reverses this hyperexcitability phenotype in some BD lines; however, the other lines seem to have no response to the treatment. BD neurons were then classified into two subpopulations as lithium (Li) -responsive (LR) and Li-non-responsive (NR) subgroups, which are also intrinsically different from each other. Interestingly, the LR neurons exhibited phenotypic behaviour similar to rapidly spiked intermediate neurons—high amplitude, narrow spikes, indicating their excessive excitability. Moreover, the NR neurons showed a decrease in sodium current by nearly 50% and a higher threshold for depolarisation. The significant differences between the two subgroups make it possible to predict the lithium response of patients by electrophysiological tests (Stern et al., 2018).

Current treatments targetting mitochondrial and future therapeutic potentials

The involvement of mitochondrial dysfunction has been widely implicated in the pathogenesis of various brain diseases, such as Alzheimer disease (Misrani et al., 2021), Parkinson disease (Hattori and Mizuno, 2022), Huntington disease (Carmo et al., 2022), Down syndrome (Izzo et al., 2022), autism (Giulivi et al., 2010) and epilepsy (Folbergrová and Kunz, 2022). In clinical settings, mitochondrial impairment in these diseases can be detected via molecular testing such as mitochondrial DNA (mtDNA) sequencing, non-invasive biochemical screening (blood and urine metabolic screening tests), minimally-invasive tissue testing (including OXPHOS and ETC testing through a skin biopsy and buccal sample), and invasive tissue testing (such as skeletal muscle biopsy) (Murаresku et al., 2018).

Furthermore, scientists have been actively researching to discover biomarkers to detect mitochondrial dysfunction in several brain diseases. For instance, the cell-free circulating-mitochondrial DNA (ccf-mtDNA) is a promising biomarker for mitochondrial diseases, which has been widely investigated in various diseases, including neurodegenerative diseases (Podlesniy et al., 2013; Pyle et al., 2015). The mitochondrial damage-associated molecular patterns (DAMPs) such as low levels of ccf-mtDNA in the cerebrospinal fluid (CSF) of Alzheimer and Parkinson diseases patients could be attributed to neuronal cell loss through the depletion of mtDNA (Podlesniy et al., 2013; Pyle et al., 2015). A recent study has proven the strong association between ccf-mtDNA and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes or MELAS (Maresca et al., 2020). High levels of ccf-mtDNA and elevated inflammatory cells in the plasma indicate acute neuronal cell death that enhanced the extracellular release of mtDNA that triggered an inflammatory response towards the injury (Maresca et al., 2020; Zhang et al., 2022). The study shed light on the potential of ccf-mtDNA in evaluating the efficacy of anti-inflammatory therapies. In fact, the implication of ccf-mtDNA in BD patients has been investigated in a previous study that compared the levels of serum lactate and ccf-mtDNA between 64 BD and 41 healthy adolescents aged 13–21 years. A semi-structured diagnostic interview was also conducted to accurately evaluate the BD progression in the diseased group, and to confirm the absence of manic and depressive symptoms in the healthy control group (Jeong et al., 2020). A significant positive correlation was evident between lactate and ccf-mtDNA levels in the BD group but not in the healthy control group, suggesting that BD patients are indeed more prone to perturbation leading to mitochondrial dysfunction (Jeong et al., 2020). Unfortunately, the study failed to show a definite correlation between ccf-mtDNA and BD in a small population of BD patients. Hence, future studies are warranted to explore further the use of ccf-mtDNA as a biomarker of mitochondrial dysfunction in BD patients.

An in-depth understanding of the biological basis of BD has revealed complex disturbed networks and various genetic risks that provide the potential for targeted interventions. However, the number and scope of conventional treatments for BD are still limited. Most conventional drugs currently used to treat BD were initially used to treat other diseases, such as anticonvulsants for controlling seizures and antipsychotics for treating psychosis. These drugs are grouped into two categories, presenting an overlapping action mechanism. First, mood stabilisers like anticonvulsants block voltage-sensitive sodium and calcium channels and have side effects on monoamine regulation. The second option is to use antipsychotics, common medications for acute manic episodes. Some atypical antipsychotics are also used for the depression of the disease. These agents bind a range of receptors and affect multiple downstream mechanisms. Although the clinical effects of these drugs have been studied and reported, in most cases, the underlying mechanism of these mood stabilisers in manic or depressive episodes is not fully understood and was reviewed in this section and summarised in Fig. 2.

Lithium

Lithium is the gold standard pharmacological treatment to date for BD. Lithium effectively treated acute manic and depressive episodes, decreasing recurrence and lowering suicidal thoughts (Baldessarini et al., 2006; Goodwin et al., 2003) in BD patients. Lithium exhibits molecular effects by modulating oxidative stress, apoptosis, inflammation, and mitochondrial and endoplasmic reticulum (ER) dysfunction (De Sousa et al., 2015; Li et al., 2010; McColl et al., 2008; Valvassori et al., 2019). A preliminary study involved a small number of subjects who reported acute treatment with lithium in manic patients reduced superoxide dismutase/catalase (SOD/CAT) ratio and thiobarbituric acid reactive substances (TBARAS) levels when compared to untreated manic patients (Machado-Vieira et al., 2007; de Sousa et al., 2014). A similar finding in the context of oxidative stress parameters reported a significant decrease in the SOD/CAT ratio following lithium treatment in healthy volunteers (Khairova et al., 2012). The SOD/CAT ratio reduction was associated with hydrogen peroxide levels. The present findings reinforce the potential antioxidative properties of lithium.

In addition, lithium exhibit antimanic and antidepressant through apoptosis modulation (O'Brien et al., 2004). Chronic administration of lithium has been shown to inhibit GSK-3β in various studies (Gould et al., 2004a; Jope and Bijur, 2002; Klein and Melton, 1996). GSK-3β

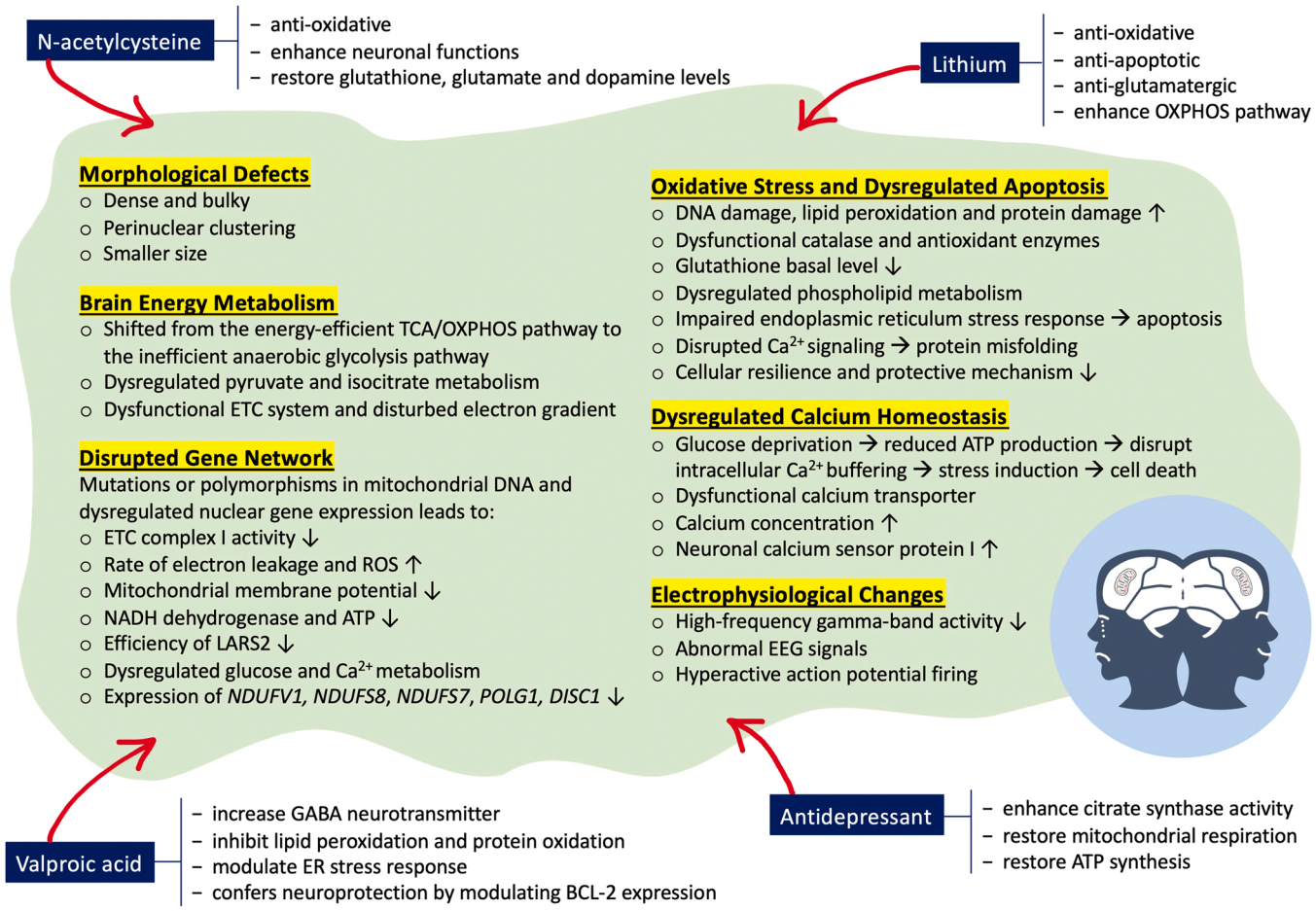

Fig. 2. A summary of mitochondrial dysfunctions in bipolar disorder and the potential therapeutic options.

induces neuronal cell death via phosphorylation of Bax (a component of the intrinsic apoptotic cascade) that stimulates the intrinsic mitochondrial death pathway by eliciting cytochrome c release from mitochondria (Linseman et al., 2004). Therefore, inhibition of GSK-3β can lead to an anti-apoptotic effect and improved mitochondrial stability. Aside from that, lithium reduces the expression of GSK3β mRNA levels in in vitro and in vivo Alzheimer disease rat models (Mendes et al., 2009). This finding suggests that lithium, directly and indirectly, modulates apoptosis via the GSK3β pathway (Beaulieu et al., 2004; Gould et al., 2004b).

Lithium is also anti-glutamatergic and decreases the excitatory transmission of glutamate. Glutamate excitotoxicity has been well-documented in BD postmortem frontal cortex (Rao et al., 2010), and glutamate signalling in synaptogenesis and NMDA receptors were proposed as a potential therapeutic target for BD (Ohgi et al., 2015). Chronic administration of the therapeutic dose of lithium reduces the excitotoxicity of glutamate in rats treated with a sub-convulsive injection of NMDA (Kim et al., 2016). NMDA decreases the level of mitochondrial ETC components complex I, III and V in the frontal cortex of the rat. Decreased mitochondrial ETC components increased oxidative stress (dysfunction of complex I and III) and decreased ATP production (dysfunction of complex V). Dysregulation of complex I and III, and possibly excessive ROS may have caused glutamate excitotoxicity in BD (Kim et al., 2016). Therefore, lithium potency in ameliorating BD progression could partly happen via the suppression of glutamate excitotoxicity.

Other therapeutic potentials of lithium include the enhancement of the respiratory oxidative pathway in mitochondria in BD. Studies in human frontal cortex brain tissue revealed lithium stimulates complex I+III and complex II+III activities of the mitochondria respiratory chain. The study suggested that lithium efficacy in treating BD because of its capability to increase mitochondria respiratory chain enzyme activity (Maurer et al., 2009). Another study reported that pre-treatment of lithium protected human neuroblastoma cells against 1-methyl-4-phenylpyridinium (MPP+) and rotenone-induced apoptosis. MPP+ and rotenone caused apoptosis and led to Parkinson disease-like symptoms in human and primate models, a mechanism most probably mediated by mitochondria complex I activity inhibition (King et al., 2001; King and Jope, 2005; Lai et al., 2006). Although lithium might exert its anti-apoptotic effect through other mechanisms, the present studies suggest that lithium might protect against cell degeneration by enhancing complex I activity in mitochondria.

Apart from the promising therapeutic potentials, lithium also has adverse effects. Animal studies revealed that lithium treatment resulted in reproductive toxicity in male mice (Ommati et al., 2021) and nephrotoxicity in rats (Ommati et al., 2022). Interestingly, oxidative stress and mitochondrial impairment were implicated in the pathogenesis of these lithium-induced toxicities. On the one hand, it was found that lithium has elevated the kidney ROS level and lipid peroxidation (LPO), which further alters the kidney mitochondrial function. The ATP level in renal tissues was also depleted (Ommati et al., 2021). On the other hand, lithium-treated male mice were presented with infertility due to mitochondrial impairment resulting in an energy crisis, affecting sperm motility (Ommati et al., 2022). Taken together, findings from these studies emphasised the unfavourable outcome of lithium treatment towards mitochondria function. Nevertheless, it is suggested that antioxidants or mitochondria-protecting agents could be used to counteract the adverse effects.

Valproic acid

Valproic acid (VPA) is the primary drug treatment for BD patients. VPA is a short-chain fatty acid used to alleviate manic and depressive phases in BD. VPA can increase the γ-aminobutyric acid (GABA) neurotransmitter by enhancing its receptor (Laeng et al., 2004). VPA inhibits lipid peroxidation and protein oxidation in the neuronal tissue culture model. Besides, VPA modulates endoplasmic reticulum (ER) stress response by regulating *WFS1* gene expression (Kakiuchi et al., 2009). *WFS1* encodes a protein on the ER membrane regulated by the XBP1 transcription factor pivotal for ER stress (Kakiuchi et al., 2006). A study using *WSF1*-knockout mice shows behavioural changes like depression such as anhedonia, passive coping response and reduced social interaction (Park and Yang, 2015). The finding suggests the mechanism of VPA in regulating WFS1 might involve ER stress response in BD.

B-Cell Lymphoma 2 (BCL-2) family proteins are embedded in the inner mitochondrial membrane and reside in the endoplasmic reticulum and nuclear membranes (Hockenbery et al., 1990; Krajewski et al., 1993). BCL-2 proteins modulate mitochondrial function by exerting pro- and anti-apoptotic functions (Marie Hardwick and Soane, 2013). Over-expression of BCL-2 protein in immortalised murine hypothalamic neurons demonstrated enhanced mitochondrial Ca^{2+} uptake capacity. This indicates that BCL-2 can inhibit neuronal cell death associated with ischemia and excitotoxicity by increasing Ca^{2+} uptake in mitochondria (Murphy et al., 1996). Chronic treatment of VPA resulted in a doubling of mRNA expression in rat frontal cortex; this data suggest that the VPA might serve as a long-term neuroprotective effect in the central nervous system (Chen et al., 1999).

On the other hand, VPA can be harmful as well. Administration of VPA in rats has caused negative impacts on renal mitochondria functions, such as increased kidney ROS level and lipid peroxidation, reduced tissue antioxidant properties, and depleted glutathione levels. These ultimately resulted in oxidative stress and mitochondria dysfunction in the VPA-treated rats (Heidari et al., 2022). Moreover, in vitro studies revealed that prolonged exposure to VPA can cause toxicity in the hepatocytes through mitochondria dysfunction (Wang et al., 2022; Caiment et al., 2020). Interestingly, it was found that a transcription factor C/EBPα, is causally linked to the molecular mechanism of VPA-induced hepatotoxicity in the hepatocytes. This finding has provided valuable information about the signalling pathway involved in VPA-induced mitochondrial dysfunction. Hence, future studies are warranted to discover other therapeutic options to combat the adverse effects of VPA.

Antidepressant

Selective serotonin reuptake inhibitors (SSRI) affect mitochondria structure and function (Adzic et al., 2016; Anglin et al., 2012; Chan et al., 2020; Klinedinst and Regenold, 2014; Wang, 2007). Fluoxetine, a class of SSRI, exhibits direct and indirect effects on mitochondrial bioenergetics both in vitro and in vivo (de Oliveira, 2016). Fluoxetine reduced brain mitochondria function isolated from rats and pigs by inhibiting or decreasing state 3 or ADP-stimulated respiration rates. Fluoxetine has also been reported to inhibit isolated mitochondria-membrane-bound ATPase activity and reduce the production of ATP as well as disruption of the phosphorylation process. The finding suggests that fluoxetine interferes with the physical state of the lipid bilayer of the inner mitochondrial membrane (Curti et al., 1999; Hroudová and Fišar, 2012). A similar finding was also reported in the mitochondria isolated from rat liver (Souza et al., 1994). The current finding of oncogenic and respiratory inhibitory properties of fluoxetine in vitro suggested that fluoxetine antidepressant is less suitable for treating BD when compared to mood stabilisers. However, acute treatment of fluoxetine enhanced mitochondrial function in the rat brain model. Acute treatment of fluoxetine at 25 mg/kg for 24 h increased citrate synthase activity in the rat striatum and complex I activity in the rat hippocampus (Agostinho et al., 2011a, 2011b). On the other hand, chronic administration of fluoxetine at 5 mg/kg per day in a chronic unpredictable stress rat model restored mitochondrial respiration control and ATP synthesis (Wen et al., 2014).

N-acetylcysteine (NAC)

N-acetyl cysteine (NAC) is a modified form of the essential amino acid cysteine and serves as a glutathione precursor. Glutathione is the primary brain antioxidant. Glutathione maintains oxidative stress below the threshold by scavenging oxygen and nitrogen species. Besides, NAC can suppress chronic stress that induces mitochondrial dysfunction. NAC also play a vital role in enhancing neurogenesis, neuromodulating glutamates and dopamine, and altering mitochondria function in the brain (Samuni et al., 2013). A study reported that N-acetyl-cysteine amide (NACA), a derivative of NAC, provides neuroprotection in acute contusion spinal cord injury rats. The result showed significant improvement in mitochondrial respiration in a dose-dependent manner with an effective dosage of 300 mg/kg 24 h post-treatment. NACA treatment significantly maintained acute synaptic and non-synaptic mitochondrial bioenergetics associated with decreased oxidative stress and damage. NACA treatment also normalised GSH levels following contusion spinal cord injury. On the other hand, prolonged treatment of NACA for 7 days post-injury enhanced neuroprotection and improved functional recovery (tissue sparing and hindlimb function) (Patel et al., 2014) The finding suggests that NAC can be a potential agent for neuroprotection and be used for preventive therapy for high-risk patients (for example, first-degree relatives such as parents and siblings). Other than this, NAC can potentially be explored as adjunctive therapy for BD with mood stabilisers such as lithium, given that NAC can reduce chronic stress related to mitochondria function in the brain. This is relatable to adult BD patients, whose onset was triggered by early life stress leading to dysregulation of mitochondrial function in the brain.

Conclusions

Emerging evidence revealed mitochondria's potential as a therapeutic target in the current and future clinical prospects. However, the delivery of any drug that directly targets mitochondria in the brain needs to overcome a few barriers to be effective: the blood-brain barrier (BBB) and the mitochondrial membranes. The BBB comprises several types of cells in which the interactions between these cells create a tight junction that impedes the penetration of water-soluble substances (Dong, 2022), whereas the mitochondria membrane consists of two layers, and the high membrane potential makes it difficult for molecules to pass through them (Buchke et al., 2022). Several studies have reported a few mechanisms of mitochondrial-targeted drug delivery in the brain. These mechanisms are membrane potential-driven localisation through the lipophilic cation triphenylphosphonium (TPP), affinity-based localisation that partitions drugs through the distinct mitochondrial compositions, intrinsic mitochondrial protein trafficking system that uses its own transport machinery to transport the drugs linearly, and polymeric nanoparticles that are biocompatible, biodegradable, at the same time allow BBB penetration and also mitochondrial localisation (reviewed in 179). Despite the advancement in discovering possible mitochondrial-targeted drug delivery mechanisms in the brain, however, a generalised drug delivery system that gives rise to therapy has yet to be established. Thus, this issue is worth investigating in future studies as it would be beneficial for clinical applications in all the mitochondrial dysfunction-related brain diseases, including BD.

Despite regular treatment, many BD patients experienced relapses. Some patients do not respond to current treatments and are considered therapeutically resistant. The treatment resistance could be caused by limited options and the lack of effective targeted drugs. Conventional

treatment options for drug resistance include increasing doses or combining multiple drugs. In addition, a clinician may add other psychotropic drugs to the individual's treatment plan, such as atypical antipsychotics or antidepressants, to improve the treatment effect. Although this may be effective for some people, some individuals fail to improve symptoms or may not be able to tolerate the increased doses or combination of drugs or relapse after a temporary improvement.

Furthermore, some patients suffer significant emotional instability in the long run and a decline in quality of life after the intense treatment. Therefore, novel therapeutics for BD are urgently needed. Understanding the mechanism of mitochondrial dysfunction may provide clues for developing new therapies and offer opportunities for these treatment-resistant patients with improved outcomes. In recent years, significant progress has been made in identifying biological differences associated with BD, which creates the possibility of developing new therapies that may directly address the underlying biological defects of the disease. Research of peripheral biomarkers indicates some biological differences in the altered mitochondrial functions and oxidative stress, which provide potential targets for following researchers. More information was obtained from genome-wide association studies (GWAS), which involved the susceptibility of several genes related to mitochondrial abnormalities. All these biological factors have attracted attention as potential drug targets.

While finding a therapeutic target is essential, understanding the biology of the disease onset and progression of BD would allow the formulation of potential preventive measurements. The literature on BD has lingered around neuroimaging, peripheral marker screening and analysis of the postmortem brain. Most researches focus on the rather crude manifestation of BD and missing out on the golden period before the disease onset. The advent of human-induced pluripotent stem cells (hiPSCs) has enabled us to understand the risk conferred by candidate genes via gene editing within an isogenic environment. Besides, the differentiation of hiPSC into different 2D cell types and 3D cerebral organoids allows us to dissect the molecular defects in a better-controlled environment. Most importantly, it provides the opportunity to look into the affected molecular signatures or functional mechanisms during neuronal cell development, which has been almost impossible to carry out among high-risk individuals before disease onset. Assessments on the neuronal cell network, chemistry and electrophysiology on both 2D and 3D models are now possible. Cerebral organoids may serve as an excellent tool for drug screening in a high-throughput laboratory setting.

Conflicts of Interest

None.

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