Mitochondrial Dysfunctions in Bipolar Disorder: Effect of the Disease and Pharmacotherapy

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Abstract: Exact pathophysiological mechanisms of bipolar disorder have not been sufficiently clarified. We review the evidence of mitochondrial dysfunctions on the relation between both disease and pharmacotherapy. Mitochondria produce the most of energy-rich molecules of adenosine triphosphate (ATP), apart from energy production they are involved in other functions: regulation of free radicals, antioxidant defenses, lipid peroxidation, calcium metabolism and participate in the intrinsic pathway of apoptosis. According to increasing evidence dysfunctions of mitochondria are associated with affective disorders, a hypothesis of impaired mitochondrial functions has been proposed in bipolar disorder pathogenesis. Mitochondrial DNA mutations and/or polymorphisms, impaired phospholipid metabolism and glycolytic shift, decrease in ATP production, increased oxidative stress and changes of intracellular calcium are concerned in mood disorders and effects of mood stabilizers. Recent studies have also provided data about the positive effects of chronic treatment by mood stabilizers on mitochondrial functions.

Keywords: Bioenergetics, bipolar disorder, electron transport chain complexes, mitochondria, mitochondrial DNA, mood stabilizers, oxidative phosphorylation.

1. INTRODUCTION

Bipolar disorder (BD) is one of the psychiatric disorders leading to substantial impairment in psychosocial function, the sixth leading cause of disability worldwide. Patients with BD very often experience periods of depression, hypomania or mania, even if the best available treatment is used. Residual symptoms of this illness impaired functions persist many times between episodes [1]. BD still has low recovery rates and high rates of treatment-resistant cases, about one-third of BD patients admit to at least one suicide attempt. Against the general population the rates of disability and premature mortality are two to three times higher [2].

The pathophysiology of BD is complex, multifactorial, and not fully understood. Insights into the pathophysiological processes underlying BD has been provided by studies examining structural and functional changes in the brain, damage in neuronal circuits, impairment in neuronal plasticity and resilience, and disturbances of synaptic transmission and signal transduction caused by or associated with oxidative and nitrosative stress, neurotrophins, mitochondrial dysfunctions, neuroinflammation, autoimmune processes, tryptophan and tryptophan metabolites, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation [3]. BD is characterized by multiple associations between disturbed brain development, neuroplasticity, and chronobiology, caused by genetic and environmental factors, and defects in apoptosis, immune-inflammatory, neurotransmitters, neurotrophins, and calcium signaling pathways, oxidative and nitrosative stress, cellular bioenergetics, and membrane or vesicular transport. There is a growing number of evidence for the association of mitochondrial dysfunction and psychiatric illnesses both in vitro and in vivo.

2. COMMON ASPECTS OF BIPOLAR DISORDER AND MITOCHONDRIAL DISEASES

Morphological changes, altered cellular location, decreased number and function of mitochondria has been found in diverse psychiatric conditions [4]. Mutations of mitochondrial DNA (mtDNA) are known to modify energy metabolism of brain, neurotransmission, and are causative in the pathophysiology of neurodegenerative disorders [5].

Mitochondria are subcellular organelles enriched in energetic tissues, such as brain, liver and muscle and located in...
the cytoplasm [6]. Mitochondria regulate production of adenosine-5'-triphosphate (ATP) through electron transport chain (ETC), with associated generation of reactive oxygen species (ROS), which can result in oxidative stress and cellular impairment, especially in the case of insufficient antioxidant defenses [7]. System of oxidative phosphorylation (OXPHOS) is the main source of ATP, supplying more than 95% of total energy requirements in the cells. Tissues with high demands of energy contain a great number of mitochondria; therefore, these tissues (e.g. brain) are more vulnerable to reduction of the aerobic metabolism. As neurons spend 40 to 60% ATP energy on maintaining the ion gradient on the membrane and transmitting the impulse, the OXPHOS impairment in mitochondrial diseases takes the key place in the clinical picture of ‘mitochondrial encephalomyopathy’ [8]. Main psychoneurological symptoms are mental retardation, seizures and stroke-like episodes. These data support the hypothesis that mitochondrial dysfunction may play a central role in the pathophysiology of BD [9].

Mitochondrial dysfunctions and defects in oxidative metabolism are characteristic for many chronic illnesses, without categorization as mitochondrial diseases. To the group of such illnesses belong for example autism, BD, chronic fatigue syndrome, depression, multiple sclerosis, Parkinson’s disease, and schizophrenia [10]. Clinical syndromes caused by a primary impairment of mitochondrial functioning are much more than previously appreciated. Primary mitochondrial disease by definition has a genetic etiology either in mitochondrial DNA (mtDNA) or nuclear DNA genetic abnormalities, with an estimated prevalence of 9.2 per 100,000 adults for mutations in mtDNA alone. Diseases of the mitochondria appear to cause the most damage to cells of the brain, liver, heart, kidney, skeletal muscles, and the endocrine and respiratory systems [8].

While mitochondrial disorders can present in any system, the central nervous system is particularly vulnerable to impairments of mitochondrial function because of its high energy demands. Common clinical features of mitochondrial disorders include ataxia, fatigue, migraine, seizures, stroke-like episodes, diabetes mellitus, cardiomyopathy, hearing loss, ophthalmoplegia, optic atrophy, ptosis, and proximal myopathy [8]. Mitochondrial disorders are usually progressive and multisystemic [11]; common psychiatric symptoms of mitochondrial diseases include cognitive impairment, anxiety and affective symptoms, psychotic symptoms, and personality disorders. Sometimes they manifest before the other classical symptoms of the mitochondrial disease appear and patients start getting treatment for psychosomatic condition [12]. The main difficulty of the differential diagnosis in those cases is the origin of the psychiatric symptoms: whether they act as the reaction to the disease or they can be assigned to general mitochondrial condition. Diagnostic difficulty results from both wide symptomatology and signs of each individual patient and from the absence of a reliable screening or diagnostic biomarker, which would be specific and sensitive in all cases of mitochondrial disease [11].

Pathophysiology of BD involves dysfunctions at multiple levels and systems with a convergent impact at cellular downstream signaling cascades; some of these molecular targets include central and peripheral stress pathways, intracellular signaling cascades, inflammation, and organelles (endoplasmic reticulum and mitochondria) dysfunction [13]. BD is associated with reduced ATP production, indicated by decreased brain energy metabolism and a shift from OXPHOS to glycolysis [14-17], upregulation of genes influencing the apoptotic processes compared to controls [18], downregulation of mitochondrial genes controlling the OXPHOS system and degradation of proteasome, decreased antioxidant capacities, including decreased glutathione peroxidase 1 and 4 as well as superoxide dismutase [19], increased lipid peroxidation, and abnormal calcium metabolism [20, 21]. Moreover, abnormalities in the mitochondrial distribution and structure have been identified in brain and peripheral cells obtained from patients with BD [22]. Mitochondria play an important role in calcium signaling and thus in various processes such as excytosis, synaptic plasticity, and apoptosis, in which calcium ions are involved. Mitochondrial calcium dysregulation might be also involved in the pathophysiology of BD, specifically changing the neuronal plasticity and vulnerability to cell death [20].

3. MITOCHONDRIAL HYPOTHESIS OF BIPOLAR DISORDER

Current knowledge provides the background for formulation of several biological hypotheses of BD based on the identification of biomarkers for vulnerability, disease expression and course, and treatment response. Biomarkers in BD are still in stage of research; structural brain changes are searched using neuroimaging methods, polymorphisms in a number of susceptibility genes have been discovered in genetic studies, and neurochemical biomarkers are studied in periphery above all. Potential peripheral biomarkers for BD include oxidative stress and mitochondrial dysfunction, trophic factors, inflammatory cytokines, and urinary metabolites [23]. Several hypotheses of BD have been formulated, according to allocation of the decisive role to a specific process or alteration of a biomarker, including genetic factors, protein expression, oxidative stress, calcium signaling, impaired functions of mitochondria and neuropathological alteration [24].

A hypothesis of mitochondrial dysfunction in BD arises from findings of magnetic resonance spectroscopy (MRS); decreased high-energy phosphates, elevated lactate, and decreased pH together suggest that impaired OXPHOS, decreased substrate availability, decrease in total energy production, and a conversion to glycolytic energy production can be presumed in the brains of BD patients [16, 25]. Further, increase of oxidative stress, dysregulated calcium signaling, and downregulation of mitochondrial complexes, especially complex I are present. Therapeutic effects of remedies/mitochondrial modulators, which are putative neuroprotective agents for use in treatment of BD, have been shown to affect many of these processes [9, 26-29].

Intracellular calcium regulates multiple functions of neurons, implying neuronal plasticity and survival, synaptic transmission, and neurotoxicity [30, 31]. Uptake and release of cytosolic calcium ions are included in basic mitochondrial functions and participate on the control of cellular Ca^{2+} signals. Calcium-phosphate complex in the mitochondrial matrix buffers the free Ca^{2+} and regulate calcium-dependent
processes in cytosol. Excess of matrix Ca\(^{2+}\) causes the mitochondrial permeability transition [32], which leads to inhibition of OXPHOS, inhibition of citric acid cycle enzymes, decrease of ATP synthesis, increase of ROS production, and release of calcium and apoptogenic factors into cytosol [33].

4. MITOCHONDRIAL DNA AND BIPOLAR DISORDER

Genetic cause of mood disorders is intensively studied; mitochondrial genetic variations and mtDNA mutations were included in pathophysiology of BD [8]. All subunits of mitochondrial respiratory complexes (except for complex II) are encoded by both nuclear DNA and mtDNA [34, 35]. The mitochondrial genes encode 13 mitochondrial proteins: 7 ND subunits of complex I (NADH dehydrogenase), 3 subunits of complex IV (cytochrome c oxidase, COX), 2 subunits of complex V (ATP synthase), and apocytochrome b as a part of complex III (coenzyme Q10-cytochrome c reductase).

According to Kato et al. [36, 37], mtDNA polymorphisms/mutations could cause mitochondrial dysregulation of calcium, leading to the symptoms of BD. Evidence of mtDNA polymorphisms in BD:

- A10398G polymorphism modifies amino-acid in the complex I ND3 subunit, A10398G polymorphism alters amino-acid in the complex I ND3 subunit, effect of this polymorphism on complex I activity has never been examined;
- 5178 C/A polymorphism was associated with BD;
- Polymorphisms of MT-ND1, MT-ND2, MT-ND3 and MT-ND5 have been associated with BD [38];
- G10398A polymorphism may be related to lithium treatment response [39];
- Increased expression of LARS2 gene (gene for mitochondrial leucyl-tRNA synthetase) and mtDNA A3234G mutation were found in postmortem frontal cortices of BD patients [40].

Mitochondria-related genes were reported to be differentially expressed in BD patients compared to controls. Altered expression of 23 genes related to mitochondria, including 8 ETC components, was found postmortem in frontal cortices from BD patients (study using technology of DNA microarrays) [41]. In this study, subunits of complex I (encoded by NDUF57, NDUF58), complex III (encoded by UQCC), complex IV (encoded by COX5A, COX5C), and complex V (encoded by ATP5C1, ATP5G, ATP5G3) in patients with BD were down-regulated in patients with BD [41]. Medication-free BD patients showed a tendency to up-regulate genes, encoding respiratory chain components (gene for a complex I subunit, NADH dehydrogenase [ubiquinone] flavoprotein 2; NDUFV2) [42]. The expression of complex I subunit was increased in patients treated with lithium compared to patients without lithium treatment [41]. Decreased expression of NDUFV2 was reported in lymphoblastoid cell lines of BD patients; a significant increase of NDUFV2 messenger RNA expression was observed in lymphoblastoid cell lines cultured with mood stabilizer, which presented the evidence of a biological significance in BD [43]. ETC genes expression differed in patients suffering from BD and controls in response to glucose deprivation stress, these results suggested deficient adaptation to energy stress in lymphocytes from BD patients [17]. The data from microarray studies showed downregulation in complex I related genes in patients with BD [44]. Limitations of performed studies should be noted. Only 20% of mtDNA genome was examined and the sensitivity of mutation detection had been presumed about 80%. Therefore, some mtDNA mutations could be missed [37].

McMahon et al. did not reveal any point mutations of mtDNA in the major mtDNA European haplogroups, which could explain excess maternal transmission of the disorder. 15 variants with possible pathologic significance were compared and no significant difference was found between BD patients and healthy controls. The results from comparisons did not find any change, when probands with apparent paternal transmission were excluded [45].

Low-penetrance of mtDNA variants involved in BD transmitted through the maternal line can be presumed [38]. No polymorphism was identified in study, where mitochondrial genomes in 25 BD patients with psychiatric disorder histories were analyzed. Closely related haplotypes in group of BD patients were observed compared to healthy control group, suggesting selection against maternal lineages in BD [46]. Linkage between the MT-ND1 gene polymorphism 3644T>C (associated with BD), a decreased complex I activity as well as mitochondrial membrane potential were also observed [21]; an accumulation of mtDNA 3243 mutation in the brains of BD patients was found [40]. 10398A>G polymorphism has been associated with altered mitochondrial Ca\(^{2+}\) levels as well as BD [47]. There are studies, which did not find any evidence for mtDNA deletions or mutations taking part in the development of BD [42, 48]. Increased expression of messenger RNA and proteins of complex I subunits NDUFV1, NDUFV2 and NADUF1 in the parieto-occipital cortex and decreased expression in cerebellum were observed in patients with BD [49]. This study examining complex I abnormalities showed similarities and diversities of mental disorders, such as BD, depression and schizophrenia. Although psychotropic medication received by the treated patients could contribute to complex I abnormalities, the effects of lithium, valproate and antipsychotic drugs were not detected. The study was also limited by small size of sample.

Additionally, nuclear encoded proteins can participate on mitochondrial dysfunctions observed in various diseases [50]. Expression of 12558 nuclear genes was determined in the human hippocampus in healthy control subjects and those with BD. Messenger RNA encoding mitochondrial proteins was significantly decreased compared to controls. This finding supports the hypothesis that dysfunction of energy metabolism in BD is related to ATP-dependent processes [19].

5. IMPAIRED ENERGY METABOLISM IN BIPOLAR DISORDER

Altered brain energy metabolism - decreased phosphocreatine was found in lithium resistant BD patients. This finding was detected by a photic stimulated \(^{31}\)P-nuclear MRS and is compatible with mitochondrial dysfunction [51].
5.1. Impaired Phospholipid Metabolism and Glycolytic Shift in Bipolar Disorder

Abnormalities in phospholipid metabolism and cellular energy was found using proton or phosphorus nuclear MRS. MRS studies demonstrated also increased lactate, decreased pH, phosphocreatine, and ATP levels. Decreased phosphonoester values of euthymic BD patients and increased values in depressed patients with BD were reported [52]. A phosphonoester peak area and intracellular pH were found higher in the manic period than in the euthymic period in BD patients [53]. The decreased pH is related probably to BD pathophysiology more than to effect of medication, further research reported decreased pH in drug-free patients [54].

Phosphocreatine levels were decreased in euthymic and manic patients with BD in right frontal lobe [55]. Phosphocreatine acts as a reservoir of high-energy phosphates and in case of high neuronal activity its level decreases to maintain the ATP concentration [56]. The creatine and phosphocreatine levels correlated inversely 17-item Hamilton Depression Rating Scale [57]. Alterations of brain metabolism were observed in medication-free BD patients, increased γ-aminobutyric acid and grey-matter lactate support the shift from OXPHOS to toward to glycolysis [56]. Elevated lactate is often used as diagnostic tool for mitochondrial disease [58]. Increased lactate levels were localized in caudate and anterior cingulate cortices of BD patients in the study using MRS [59]; increased lactate concentrations were found also in cerebrospinal fluid [57, 60].

At brain activation, elevated lactate may be produced by astrocytes through aerobic glycolysis to cover acutely increased energy demands of neurons. When mitochondrial metabolism is intact, lactate is not present in cerebrospinal fluid; however it can cumulate in mitochondrial disorders [60]. Glutamate-glutamine cycle alteration takes part in the pathophysiology of the glycolytic shift in BD through increasing the brain cells [57, 61].

N-acetylaspartate (NAA) is known as a general marker of neuronal viability, integrity and metabolic function [62, 63]. NAA is related to mitochondrial OXPHOS [64, 65]. According to MRS studies, BD patients have significantly lower NAA in specific cortical brain region than controls [66]. Decreased NAA levels indicate a neuronal/axonal loss or compromised neuronal metabolism. No significant differences were reported in ratios NAA/choline and NAA/creatine in the basal ganglia of BD patients and controls using proton MRS [67]. Other studies using proton MRS found reductions of NAA in hippocampal formation of BD patients [68-70]. Association between the disease duration and decreased NAA concentrations in right hippocampus can support the hypothesis that neuronal pathology may increase with disease progression [69]. Lower NAA levels of BD patients were reported in both Heschl's gyri and planum temporale of superior temporal gyrus [71]. Decreased concentration of NAA in the left hippocampal area observed in BD patients suggested that neuronal integrity is decreased in this region [72]. Decreased NAA levels were found in euthymic and medication-free BD patients in dorsolateral prefrontal cortex compared to controls [73], as well as in orbital frontal grey matter of BD patients [74] and bilaterally in hippocampus [65].

5.2. Impairment of the Mitochondrial Functions

Structural abnormalities of mitochondria have been reported in patients with BD and depression. They include abnormal size, increased/decreased quantity in the cell or distribution within cell regions, abnormal shape, location/movement, and different changes in the morphology of mitochondria both in postmortem brain cells and blood cells of BD patients [22]. The observed changes have been linked to energy deficits and have consequences for cellular plasticity and survival of neurons [22]. Impairment of mitochondrial functions in BD was not observed consistently. No differences in activity of citrate synthase, succinate dehydrogenase, and malate dehydrogenase have been found in drug-naive BD patients in depressive episode compared to healthy controls [75]. Impaired activity of ETC complexes of in blood elements of patients with BD was not reported [76]. Complex I activity was found decreased and oxidative damage was found increased in the pre-frontal cortex of BD patients [76]. Complex I activity was found decreased and oxidative damage was found increased in the pre-frontal cortex of BD patients [77]. Activities of ETC complexes were examined in BD patients in mononuclear cells; no significant changes in complex I, complex II and complex II + III activities were found. However, this study was limited by small number of patients; samples were obtained in euthymic mood [76].

Mitochondria have a large tubular network with dynamic fission and fusion processes. Altered balance of these processes can interact with bioenergetics properties of mitochondria [78] and participate in pathophysiology of different diseases; firstly mentioned mitochondrial dynamics abnormalities were found in neurons from Alzheimer’s disease patients [79]. Dynamin-1-like protein (Drp1), mitofusin-1 (MFN1) and mitochondrial dynamin like GTPase (OPA1) as fission proteins were analyzed in BD patients; no significant changes were observed [80]. Altered mitochondrial network can be caused by impairment of complex I activity [78]; consequently, impairment of complex I activity was likely associated with increased oxidation and nitration of proteins [77]. Increased impairment of RNA and DNA caused by oxidative stress is associated to BD pathophysiology [31]. Increased levels of protein oxidation was found postmortem in dopaminergic areas of prefrontal cortex of BD patients [81]; increased lipid peroxidation was observed in BD patients compared to controls [82]. Increased oxidation of RNA and DNA was found in manic and hypomanic episodes of BD compared to euthymic episodes [83]. Increased oxidative stress was observed in post-mortem brain tissues obtained from BD patients [84].

6. EFFECTS OF MOOD STABILIZERS ON ENERGY METABOLISM

6.1. Effects of Mood Stabilizers on Phospholipid Metabolism and on Glycolytic Shift

Decreased intracellular pH was detected in the frontal lobes of BD patients in euthymic phase compared to controls. Interestingly, pH was found normal in the manic and depressive states [85]. Decrease of intracellular pH was not related to age, age at onset, duration of illness, subtype (BDI or BDII), but significantly correlated with duration of lithium treatment.
Phospholipid metabolism was examined in the temporal lobes of euthymic bipolar patients using magnetic resonance spectroscopic imaging. The results showed that BD patients demonstrated significantly lower phosphomonoester levels in both temporal lobes [86]. Global down-regulation of mitochondrial genes, such as those encoding respiratory chain components, was observed at postmortem brains of patients with BD and schizophrenia. These changes at mitochondrial genes were associated with the low intracellular pH. However, this was likely due to the medications effect, because medication-free patients showed tendency of up-regulation of mitochondrial genes [42].

The effect of mood stabilizers on NAA levels is also shown in different studies: treatment with VPA, lithium and lamotrigine is likely to increase NAA levels in patients with BD [87, 88]. A four-week lithium treatment had a positive association with significant increases in NAA levels in the frontal, temporal, parietal, and occipital lobes in both BD patients and controls [89]. Other study did not confirm increase of NAA level after lithium exposure in the dorsolateral prefrontal cortex of healthy individuals [90]. Lithium increased NAA level in BD patients chronically treated with lithium, in contrast to VPA. VPA did not increase NAA levels in BD patients compared to controls [91]. After 12 weeks of lamotrigine treatment at patients with bipolar depression, significant increase was observed in NAA level compared with patients at baseline [62]. It is suggested that long term treatment by drugs, which increase NAA levels may mediate some neuroprotective events. In to the future, NAA level could serve as a biomarker for identifying drug and clinical responses.

Lithium-treated patients had comparable level of NAA as healthy control and significantly higher NAA level than BD patients with no current long-term lithium exposure [92]. The interaction between lithium and components of protein kinase C signaling pathway was examined in rats after 3 weeks of lithium and myo-inositol treatment, inhibition of inositol-1-phosphatase as the initial component of lithium effect on protein kinase C pathway was observed [93].

Elevated NAA/phosphocreatine-creatine levels, choline/phosphocholine-creatine and myo-inositol/phosphocholine-creatine ratios were revealed in the basal ganglia region of patients with BD treated with lithium [94]. No difference between the levels of myo-inositol and phosphomonoesters in treated patients with BD and healthy controls were found and can be hypothesized that medication may normalize phosphoinositol cycle activity [95]. There was found no significant difference between the choline/creatine, N-acetyl-aspartate (NAA)/creatine, or NAA/choline levels in BD patients and controls [67].

There is multiple research data confirming an impaired activity of different respiratory chain complexes and OXPHOS components. In animal models of mania (after administration of fenproporex) activities of malate dehydrogenase, succinate dehydrogenase, and mitochondrial respiratory chain complexes (complex II and IV) were found decreased, lithium and VPA prevented fenproporex-induced inhibition, except of complex IV activity [96].

It also could be a drug-induced effect as most drugs used to treat psychiatric disorders have mitochondrial toxicity [42]. Carbamazepine and VPA contribute to antidepressant response probably by enhancing neurotransmission on 5-HT_1A receptors [97]. Elevated intracellular Ca" levels in platelets and lymphocytes are associated with the BD. VPA and carbamazepine, are capable to regulate intracellular Ca" levels by extension the expression of endoplasmic reticulum (ER) stress proteins. Owing to overexpressed GRP78, GRP97 and calreticulin (the members of ER stress protein family) the Ca"-binding capability of the ER Ca" stores are increased and the resistance of neurons is enhanced to the lethal fluctuations in intracellular Ca" and cytotoxic insult. Regulatory mechanisms in mitochondria attempt to buffer excess Ca" by mitochondrial Ca"-ATPase channels direct to the ER Ca" stores [98]. VPA increases the expression of the antiapoptotic gene BCL2 probably by the same mechanism as lithium. Upregulation of Bcl-2 by VPA and lithium leads to inhibition of the pro-apoptotic enzyme, e.g. GSK-3β and caspase-3. These neuroprotective and anti-apoptotic processes may also be caused by increased ER stress proteins after VPA treatment [99].

6.2. Effects of Mood Stabilizers on Mitochondrial Function

The mood stabilizing effect of drugs has not been clearly understood. Some of the drugs are metabolized in mitochondria and step in various mitochondrial processes: participate in prevention of excitotoxicity by oxidative stress decrease, inhibit enzymes with pathological impact on mitochondrial metabolism, down/up-regulate gene expression and calcium handling by mitochondria [100-102]. Both lithium and valproate (VPA) primarily using to treatment of BD have neuroprotective properties at the level of reduction of apoptosis (Fig. 1). Lithium and VPA inhibit the activity of glycogen synthase kinase-3 (GSK-3), as enzyme responsible for modulating gene expression of proteins involved in apoptosis, synaptic plasticity and cellular resilience [103]. VPA and lithium exhibited protection against glutamate-induced, N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity in rat cortical neurons and cerebellar cells. Lithium inhibited tyrosine phosphorylation of NMDAReceptor subtype 2B, which resulted in inactivation of synaptic activity mediated by NMDA receptor and contributed to neuroprotective effects against excitotoxicity [104].

7. LITHIUM

Lithium potentiates effect of antidepressants; augmentation of antidepressant therapy by co-administration of lithium is mediated by increased 5-HT_1A neurotransmission [105], other data mention also 5-HT_1B receptors [97]. Subchronic lithium pre-treatment increased extracellular serotonin levels in combination with MAO-A inhibitor, lithium may enhance the anxiolytic action of MAO-A inhibitor [106].

Lithium increased complex I activity in leukocytes from BD patients during the depressive episode of BD, it was positively associated with plasma lithium levels [107]; mitochondrial complexes I-IV were unchanged during the depressive episodes. Effect of lithium was investigated in
Fig. (1). Effects of mood stabilizers on energy metabolism. Both lithium (Li) and valproate (VPA) have neuroprotective properties at level of apoptosis reduction. Mood stabilizers attenuate formation of mitochondrial permeability transition pores (MPTP), release of proapoptotic factors and cytochrome c (cyt c) and other proapoptotic factors from mitochondria. Lithium and VPA inhibit glycogen synthase kinase 3 (GSK-3). Activation of Wnt receptor (WntR) leads to inhibition of β-catenin phosphorylation; unphosphorylated β-catenin enters nucleus and promotes T cell factor (TCF)-mediated gene transcription. Phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway is signaling pathway promoting the survival in response to extracellular signals. ERK pathway regulates cytosolic targets and many cellular transcription factors, including cAMP response element-binding protein (CREB). Phospholipase C (PLC), which may be activated via neurotransmitter G protein–coupled receptors (GPCR), neurotrophin receptors (TrkB) or netrin receptors, catalyses hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) and give arise to inositol triphosphate (IP3) and diacylglycerol (DAG) as the second messengers. Inhibition of recovery of PIP2 due to inhibition of inositol monophosphatase (IP) may be key step in the action of Li in treating BD. DAG activates protein kinase C (PKC); Li and VPA indirectly inhibit PKC. IP3 is binding to intracellular receptors (IP3R), and is causing the trigger of Ca2+ from endoplasmic reticulum (ER). Excessive entry of Ca2+, e.g. through activated N-methyl-D-aspartate receptor (NMDAR), may affect neuroplasticity and induce excitotoxicity. Intracellular Ca2+ increase activates nuclear factor of activated T cells (NFAT) proteins, involved in axon growth. Release of cyt c, second mitochondria-derived activator of caspases (SMACs) and apoptosis inducing factor (AIF) from mitochondria induce the apoptosis.

study, where post-mortem brain cortex of humans were exposed to lithium (maximum concentration 10 mM). Complex I + III activities and complex II + III activities were dose-dependently on the increase dose-dependently with the maximum at 1 mM. Complex II activity was unchanged to 2 mM and increased above 2 mM. Complex IV was not significantly affected [108]. Recent data suggests that chronic treatment by VPA and lithium enhanced respiration of respiration rate and mitochondrial function. Thus, long-term pharmacotherapy with VPA and lithium prevent from methamphetamine-induced mitochondrial toxicity by decrease of the mitochondrial antiapoptotic Bcl-2/Bax ratio, mitochondrial cytochrome c, and complex IV activity [109]. Lithium also interferes in BDNF mediated signaling pathways in human neuroblastoma cells SH-SY5Y. Elevated GSK-3β moderates CREB phosphorylation provoked by BDNF. Lithium blocked the BDNF-induced phosphorylation inhibition of CREB in SH-SY5Y cells overexpressing GSK-3β, and further facilitated the activation of CREB phosphorylation. Contrary to lithium, lamotrigine and VPA did not influence BDNF signaling pathway. Carbamazepine had a positive effect on the induction of CREB phosphorylation, however without affecting BDNF-mediated signal transduction pathways [110]. Most likely lithium suppresses the pro-apoptotic genes expression, such as Bax and p53, whilst promotes the anti-apoptogenic gene Bcl-2 expression. The ratio of Bcl-2/Bax protein levels was increased almost 5-fold after lithium treatment in cerebellar granule cells [111]. Upregulating of Bcl-2 by chronic lithium inhibits the pro-apoptotic enzyme GSK-3β. Anti-apoptogenic gene Bcl-2 could protect
the neurons by varied mechanism including caspase activation, mitochondrial Ca\(^{2+}\) homeostasis and prevention of cytochrome c release from mitochondria [111-113].

Increased intracellular level of Ca\(^{2+}\) is associated with neurotoxicity and could lead to cellular apoptosis [114]. Excessive accumulation of Ca\(^{2+}\) in the matrix can cause an induction of mitochondrial permeability transition that can lead to depolarization and swelling of the organelles. The depolarization causes multiple effects: OXPHOS inhibition, a release of mitochondrial apoptogenic proteins, and can lead to an excitotoxic neuronal death. Lithium by augmenting Ca\(^{2+}\) capacity protects mitochondria against high calcium levels, desensitizes mitochondria to the impact of Ca\(^{2+}\) by suppressing depolarization and prevents swelling of the organelles and releasing of cytochrome c from brain mitochondria. The long-term treatment by low concentrations of lithium inhibits Ca\(^{2+}\) influx through NMDA glutamate receptors and thus mitochondria are protected against excitotoxicity. Lithium antagonizes the Ca\(^{2+}\)-induced mitochondrial permeability transition by the competition with Ca\(^{2+}\) for the binding sites placed inside of mitochondria [115]. High level intracellular Ca\(^{2+}\) concentration in the blood platelets is associated with BD. Phosphatidylinositol membrane turnover and Ca\(^{2+}\) influx cause platelet and lymphocyte intracellular calcium homeostasis abnormalities at the patients with BD [116]. Efficacy of lithium in the treatment BD consists also in inhibition of inositol monophosphatase, which attenuates whole phosphatidylinositol signal transduction pathway and prevents release Ca\(^{2+}\) from ER [116, 117].

8. VALPROATE AND ANTIEPILEPTICS

VPA interferes with mitochondrial β-oxidation by fatty acid and influences the availability of cofactors as carnitine and CoA of lipid mitochondrial metabolism [118]. Valproyl-CoA directly inhibits medium-chain acyl-CoA dehydrogenase and short-chain acyl-CoA dehydrogenase, whilst VPA itself does not significantly influence acyl-CoA dehydrogenases activities. VPA can cause carnitine deficiency of carnitine primarily during high-dose and/or long-term treatment. The valproyl-CoA and other its metabolites can sequester the restricted CoA pool and thus slowing down CoA-dependent processes of metabolism [119]. Carnitine depletion prevents long-chain fatty acid from entry to mitochondria and afterwards causes impairment of β-oxidation and the inhibition of acetyl-CoA and ATP production [120]. Thus, acyl-CoA esters formed from VPA as branched-chain fatty acid seem to be more resistant to hydrolysis than straight-chain acyl-CoAs. Depletion of intramitochondrial CoA causes subsequent impairment of ATP production.

Based on the investigation of the mitochondrial effect mechanisms of VPA on isolated rat mitochondria is known that VPA induces oxidative stress by different ways, caused significant reduction of mitochondrial enzymatic complex II activity (succinate dehydrogenase); significantly induced mitochondrial permeability transition pore opening with consecutive mitochondrial membrane collapse depending on the VPA concentration. Addition of VPA brings about the opening of mitochondrial ion channels and membrane pores which leads to mitochondrial swelling and releasing of cytochrome c. By impairing mitochondrial functions VPA exerts the intrinsic cell death signaling pathway, which could be mediated mainly by permeability transition pore opening owing to large amplitude swelling and releasing cytochrome c as a key of apoptosis [121].

Administration of VPA is strongly associated with liver toxicity in mtDNA polymerase γ (POLG) mutated patients. VPA caused a significant increase of several genes expression and some regulators of mitochondrial biogenesis in both - POLG-deficient cells and control cell lines. The capacity of POLG-deficient cells to forward (address) the increase metabolic rate caused by VPA is significantly impaired. VPA triggered higher metabolic rate and increased mitochondrial respiratory chain activity, but genetic defect prevents it by altering mtDNA replication and repair mechanism. Exhaustive metabolic reserve capacity in POLG mutated cells can explain VPA-induced liver failure [122].

The oxidative stress was immediately developed after administration of VPA (500 mg/kg) at rats. The oxidative stress was demonstrated by elevated levels of 15-F2t-isoprostane in the plasma and liver after single dose and reached a plateau after 2 days of VPA treatment. Increased serum level of α-glutathione S-transferase already by day 4 indicated hepatotoxicity, which was confirmed by liver histology (inflammation of the liver capsule, necrosis and steatosis were proved). β-oxidation level of metabolites of VPA was also significantly slowed down by day 14 [123]. Further increased levels of 15-F2t-isoprostane and 2,7′-dichlorofluorescin (also as a marker of oxidative stress) were detected at glutathione-reduced hepatocytes compared to freshly isolated rat hepatocytes without glutathione reducing pretreatment after the exposure to VPA (1000 µg/ml). Significant cytotoxicity related with reduced mitochondrial membrane potential was observed in the glutathione-depleted hepatocytes. It supposes that glutathione plays an important role in protection to hepatocytes against mitochondrial damage by VPA [124]. After the assay of the VPA oxidative metabolites in relation to contribute generation the toxicity in situ in sandwich-cultured rat hepatocytes was revealed that only the unsaturated metabolites of VPA generates comparable response to VPA. 2,4-diene-VPA is 10-fold more potent to increase levels of markers of oxidative stress, necrosis, and cell viability than VPA [125].

8.1. Effects of Other Antiepileptic Drugs on Mitochondrial Energy Metabolism

Interestingly, epilepsy can be often manifestation of mitochondrial disorders [126]. Other antiepileptic drugs may also interfere with mitochondrial metabolism; it was described in carbamazepine, ethosuximide, gabapentin, oxcarbazepine, phenytoin, phenobarbital, topiramate, vigabatrin, and zonisamide [126]. These drugs can trigger or worsen mitochondrial disorders. Mitochondrial toxicity and oxidative stress were implemented in pathogenesis of antiepileptics-induced hepatotoxicity [127, 128].

Active metabolites of carbamazepine, phenytoin and phenobarbital caused decreased mitochondrial respiration, ATP production, effected membrane potential and calcium-induced swelling [127]. Interestingly, phenobarbital was able to affect mitochondrial respiratory rate, membrane potential
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and ATP production; but had no effect on calcium signaling [127]. Phenytoin is a commonly used antiepileptic drug with hepatotoxic adverse effects [129]. Phenytoin induced mitochondrial impairment, increased ROS production, increased lipid peroxidation, decreased intracellular levels of reduced glutathione in rat hepatocytes [129]. Topiramate is an antiepileptic evaluated for other neurological indications including BD. Significant effects of topiramate on the acute bipolar mania were reported [130, 131]. Topiramate is considered to be an inhibitor of calcium channels, which could make clear mechan for mood stabilization [132]. Some preclinical data suggest that pathophysiology of BD and epilepsy is common, i.e. in the balance between excitatory and inhibitory neurotransmitters or a dysfunction of some cellular cation channels.

The novel antiepileptic drug levetiracetam has neuroprotective effects on mitochondrial metabolism. Treatment with levetiracetam had a significantly positive effect, increased activities of mitochondrial enzymes: citrate synthase, aconitase, complex I of ETC and α-ketoglutarate dehydrogenase were observed in levetiracetam-treated rats compared to control group treated with saline [133]. Complex II/III activities remained unchanged. Gabapentin inhibits glutamatergic neurotransmission by various ways, i.e. by decreased mitochondrial pool of tricarboxylic acid for synthesis of glutamate [134]. However, gabapentin did not demonstrate significantly positive effect in adjunctive treatment BD [135, 136].

CONCLUSION

Mitochondrial dysfunctions are one of the characteristic features, which can be manifested in BD symptoms. Disturbances, such as mitochondrial genetic variations and mtDNA mutations, impaired energy metabolism, OXPHOS and respiratory chain activities, diminished mitochondrial biogenesis and dynamics, impaired calcium homeostasis, oxidative stress, neuronal survival and apoptotic processes, could be reflected in mitochondrial pathology. In spite of the increasing evidence, that these dysfunctions play a central role in the pathophysiology of BD, it remains unclear, whether they are primary or secondary cause of this mental disease.

Mood stabilizers cause changes in signaling intracellular pathways and should improve energy metabolism [137]. Lithium and VPA attenuate formation of mitochondrial permeability transition pores, and consequently release of cytochrome c and other proapoptotic factors from the intermembrane space of mitochondria; they participate in prevention of excitotoxicity and inhibit enzymes with pathological impact on mitochondrial metabolism. Other antiepileptic drugs very often interfere with mitochondrial bioenergetics. Therefore, effects of mood stabilizers on mitochondria should be investigated in the context to clinical symptoms of BD. In conclusion, a complex view of the cellular pathology in BD is crucially important for therapeutic strategies for BD, and the development of new diagnostic tools.

LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AMP</td>
<td>Response Element Binding Protein</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine-5'-Triphosphate</td>
</tr>
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<td>Bax</td>
<td>Bcl-2 Associated X Protein, Pro-apoptotic Protein of the Bcl-2 Protein Family</td>
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<tr>
<td>Bcl-2</td>
<td>B-Cell Lymphoma 2, Anti-apoptotic Protein of the Bcl-2 Protein Family</td>
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<tr>
<td>BD</td>
<td>Bipolar Disorder</td>
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<tr>
<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
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<tr>
<td>CoA</td>
<td>Coenzyme A</td>
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<tr>
<td>CREB</td>
<td>Cyclic Adenosine Monophosphate</td>
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<tr>
<td>ER</td>
<td>Endoplasmic Reticulum</td>
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<tr>
<td>ETC</td>
<td>Electron Transport Chain</td>
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<tr>
<td>GSK-3</td>
<td>Glycogen Synthase Kinase 3</td>
</tr>
<tr>
<td>MAO</td>
<td>Monoamine Oxidase</td>
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<tr>
<td>MAOI</td>
<td>Monoamine Oxidase Inhibitor</td>
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<tr>
<td>MPT</td>
<td>Mitochondrial Permeability Transition</td>
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<tr>
<td>MRS</td>
<td>Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>mtDNA</td>
<td>Mitochondrial DNA</td>
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<tr>
<td>NAA</td>
<td>N-acetylaspartate</td>
</tr>
<tr>
<td>NDUFV2</td>
<td>NADH Dehydrogenase [ubiquinone] flavoprotein 2</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-Aspartate</td>
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<tr>
<td>OXPHOS</td>
<td>Oxidative Phosphorylation</td>
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<tr>
<td>POLG</td>
<td>mtDNA Polymerase γ</td>
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<tr>
<td>ROS</td>
<td>Reactive Oxygen Species</td>
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<tr>
<td>VPA</td>
<td>Valproate</td>
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</table>

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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