A Tale of Two Moods: Energy Deficiency in Bipolar Disorder

Hamza Mahmood, Rosemary Thomas, Danielle Sychowski
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

Abstract

Bipolar disorder (BD) is a chronic psychiatric disorder characterized by mood and energy fluctuations and is associated with a combination of changes in genetics, environment, and brain chemistry. Patients spend most of their time in a depressive phase and fail to realize they are in a manic phase. These phases can be devastating to patients, as 15% commit suicide. BD treatment currently includes anti-manic agents such as lithium, tamoxifen, and valproate. This review will focus on three molecular mechanisms of BD. The first includes sleep abnormalities due to circadian dysregulation from polymorphisms and changes in gene expression. This sleep disturbance is associated with metabolic changes that lead to higher body fat composition, leptin levels, and increased weight gain. Second, there is also an accumulation of glutamate in the synaptic cleft that causes neuronal death due to excessive stimulation of the postsynaptic glutamate receptors. Third, smaller mitochondria and impaired oxidative phosphorylation leads to less ATP synthesis and lower energy levels in the neurons. Understanding of these mechanisms is limited due to insufficient animal and cellular models of BD. Insights into these molecular mechanisms are important because they will help in the formation of novel drug treatments.

Introduction

Bipolar disorder, a manic depressive disorder, is one of the leading causes of disability in young people (Merikangas et al., 2011). In the world, Bipolar disorder (BD) affects 2% regardless of ethnicity, nationality, or socioeconomic standing. It is a devastating disorder, as 9-15% of BD patients eventually commit suicide, and it has been linked to increased rates of obesity and diabetes (Kim et al., 2017).

BD is classified along a spectrum with varying severity of mood changes. Patients with unipolar disorder only experience depressive episodes. Patients with Bipolar II or I disorder have pronounced mood elevations throughout their lifetime. These patients often experience the depressive state of BD for the majority of their illness and infrequently experience the manic state. Often, patients fail to recognize the manic state of BD, and this adds to the complexity of diagnosing BD, as patients are often diagnosed only 5-10 years after the initial onset of the illness (Hirschfeld et al., 2003). In addition, the lack of any biological markers further complicates the diagnosis process of BD patients (Vieta, 2007). Today, the widely used diagnostic tools include the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Grande et al., 2016). In these classifications, at least one manic episode must be presented in order to be diagnosed with Bipolar I. In order to be diagnosed with Bipolar II, at least one hypomanic episode and major depressive episode must be presented.

After diagnosis, it is important to confirm the patient's current mood state (Angst et al., 2005). After, mood stabilizers and antipsychotic medications are used for acute management of mania and depression. In comparison, long-term management includes the use of lithium for both manic and depressive episodes. Mood stabilizers could be given in combination with antipsychotic or antidepressant medication. Other possible treatments, such as psychoeducation, cognitive behavioral therapy, and family-focused therapy have also been shown to improve the lives of patients with Bipolar I and II.

Circadian Rhythm

Characterization of Circadian Rhythm Disruption

Bipolar disorder patients show sleep and circadian abnormalities. Disturbance of sleep and circadian activity usually precede the initial onset of BP (Jackson et al., 2003). Twin studies have indicated changes in sleep time, time in bed, sleep onset latency, and more (Linkowski et al., 1999). When patients are experiencing a manic episode, there is a reduction of sleep. Patients experiencing a depressive episode report insomnia and hypersomnia (Melo et al, 2016). Severe sleep disturbance in patients with BD has been correlated with functional impairment, decreased well-being, and treatment resistance. Previous research has shown that light therapy can be used effectively with medication to treat manic-depressive patients with a seasonal mood cycle, showing that insight into sleep disturbance could advance knowledge on the molecular mechanisms of bipolar patients. (Lewy et al, 1982).

Dysfunction in Circadian Rhythms

There are multiple hypotheses for the dysregulation of circadian rhythm in BD patients. One possible link is to the genetic changes that occur on the CLOCK gene, a gene that controls circadian rhythm (Rybakowski et al, 2014). Polymorphisms of the CLOCK gene are thought to be possible predispositions to BD. Two polymorphisms of the CLOCK gene, aryl hydrocarbon receptor nuclear translocator-like (ARNTL) and timeless circadian clock (TIMELESS), are indicated to change lithium responsiveness in BD patients. Increased expression of genes important for the circadian clock, Per2, Cry1, and Rev-Erbα, increased the therapeutic effects of lithium (Schnell et al., 2015). Another hypothesis involves the pineal hormone melatonin which regulates circadian rhythms. In BD patients, there are more melatonin receptors in the hypothalamic suprachiasmatic nucleus and changes in melatonin levels (Wu et al., 2013). Circadian rhythm and clocks are also regulated by metabolic cues that can lead to cardiovascular problems. Cardiovascular illness is one of the main causes of the shorter life expectancy of BD patients (Kessing et al., 2015). Dysfunction of the circadian rhythm has been linked to increased percent of body fat composition. Leptin, a hormone produced by fat cells and important for regulation of food intake and sleep duration, is increased in BD patients (Barbosa et al., 2016).

Glutamate Hyperexcitability

Glutamate: Mechanisms of Action

Glutamate, the major excitatory neurotransmitter, is distributed widely throughout the neurons of the cortex (Kim et al., 2017). Normally, glutamate levels are maintained through the glutamate-glutamine cycle. In this cycle, glutamate goes into the synaptic cleft, generating postsynaptic currents. Astrocytes take up the glutamate and convert it into glutamine, which is non-toxic. This is then transported back by the neurons and later converted back to glutamate thus creating a cycle (Kim et al., 2017). Problems with astrocyte transport of glutamate and ability to synthesize glutamine will lead to problems in the brain. Research has shown that astrocyte dysfunction might be the cause for glutamate concentration changes in the brain of BD patients (Stork and Renshaw, 2005). Particularly, the SLC1A2 gene that encodes for astrocytic excitatory amino acid transporter 2 (EAAT2) (Kim et al., 2017).

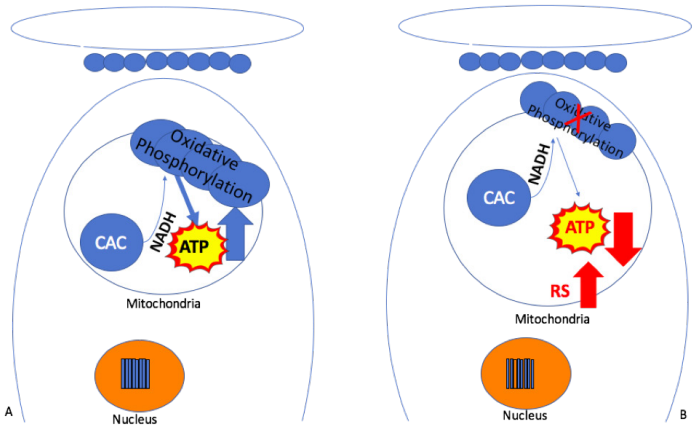

Figure 1: Mitochondrial Dysfunction in Bipolar Disorder Cells of the Frontal Cortex
A) In healthy cells, there is proper release of glutamate into the synaptic cleft, high ATP levels in mitochondria, and normal gene expression. B) In BD cells, there is an excess of glutamate levels in the synaptic cleft due to excessive stimulation of glutamate receptors. In the mitochondria, oxidative phosphorylation is impaired, so there is less ATP production. There is also an accumulation of reactive species (RS). In the nucleus, polymorphisms of the CLOCK gene have been associated with circadian rhythm dysregulation.

Excess Glutamate Levels

Adult BD patients show a consistent increase in glutamate levels in the frontal brain areas, specifically the frontal cortices. There is also a change in glutamatergic neurotransmission in BD patients (Hashimoto et al., 2007). This increase in glutamatergic neurotransmission results in higher energy demand from neurons. In addition, accumulation of glutamate in the synaptic cleft causes excess excitation and neuronal death due to overstimulation of postsynaptic glutamate receptors (Kim et al., 2017). There is further excitation due to defects in inhibition in the frontal cortex of BD patients (Levinson et al., 2007). Mood stabilizers, such as lithium and valproate, have been shown to return high glutamate levels back to normal, healthy levels.

Mitochondrial Dysfunction

Characterization of Mitochondria in Neurons

In any cell, mitochondria are important organelles heavily involved with the production of ATP which provides energy to carry out cellular functions. Mitochondria also have a role in calcium signaling and the regulation of apoptosis (Li et al., 2004). In the context of BD, neurons of the prefrontal cortex are affected, and it has been shown that the energy metabolism in this region of the brain is significantly altered (Frey et al., 2007). Specifically, evidence has suggested that lower levels of subunits in the electron transport chain impact complex I activity in the mitochondria, which in turn causes oxidative damage to the mitochondria and proteins in the prefrontal cortex (Andreazza et al., 2010).

Mitochondria are also important in neurons because they have been shown to play a role in synaptic activity and plasticity (Li et al., 2004; Quiroz et al., 2008). Synaptic activity has already shown to play a role in BD, as seen with the glutamate levels. However, mitochondria may be playing a role directly in the formation of dendritic spines and synapses, and when the mitochondria are dysfunctional as in BD, this accounts for the lower levels of synaptic activity seen in regions of the brain such as the prefrontal cortex and the hippocampus (Li et al., 2004; Morris and Hollenbeck, 1993).

Oxidative Stress

When there is a decline in oxidative phosphorylation, there is an increase in superoxide generation due to unused electrons that were originally destined for the electron transport chain. This leads to oxidative stress in which there is an increased production of reactive species (RS) (Data-Franco et al., 2017). Previous studies associate the progression of BD with increased oxidative stress (Scaini et al, 2016; Data-Franco et al., 2017). One study observed increased nitric oxide and lipid peroxidation in the blood of BD patients (Andreazza et al., 2008).

As the number of manic episodes and time with BD increases, the dysfunction caused by oxidative stress will accumulate and worsen (Hatch et al., 2015). One study showed that there was higher lipid hydroperoxide and carbonyl protein in BD adults compared to BD adolescents (Hatch et al., 2015). Mood stabilizers have also been shown to have antioxidant effects (Cui et al., 2007). More research must be done on oxidative stress, as it is a secondary effect of mitochondrial dysfunction.

Overview of Bipolar Disorder Treatments

Proper treatment of BD requires a combination of drugs specifically targeted at the depressive and manic sides of BD. BD treatment focuses on acute stabilization or bringing a patient's mood from either manic or depressive to a stable mood. Treatment, therefore, is commonly divided into two sections: treatment of mania and treatment of bipolar depression (Geddes, 2013).

Treatment of Mania

Lithium and chlorpromazine, two drugs developed in the 1970s, are the most common forms of treatment for the manic episodes of BD. In the 1980's, antiepileptics were also found to help treat
BD. However, the most effective treatment for mania in BD is lithium (Geddes, 2013).

Treatment of Bipolar Depression

Treatment of bipolar depression is also complex with only a few effective drugs. Antipsychotics, such as Quetiapine olanzapine and fluoxetine, are commonly used to treat the depressive episodes of bipolar disorder (Geddes, 2013). Although these drugs are the common form of treatment, they still show variable results.

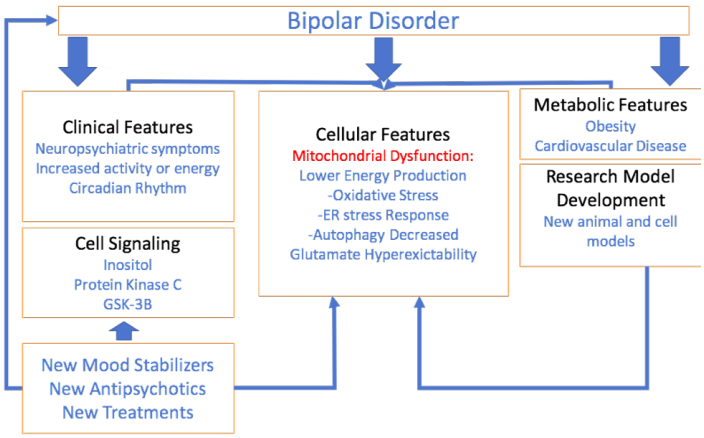

Figure 2: Clinical and fundamental research interventions in bipolar disorder (BD). Low energy caused by mitochondrial dysfunction in BD patients causes metabolic and neuropsychiatric symptoms. Oxidative stress, ER stress, decrease in autophagy, and changes in glutamate levels contribute to the vulnerability of BD cells. Mouse and IPSC models can be used to elucidate the pathway of BD pathology and develop novel therapies.

Alternative treatment

The use of natural treatments such as light therapy in addition to drugs such as lithium have shown positive results in patients (Benedetti 2005). Light therapy involves the use of a light box that mimics natural light and the patient is exposed to this light. Light therapy is often used to treat depression caused by Seasonal Affective Disorder.

Cognitive behavior therapy has also shown positive results in treatment of depression in BD patients (Patelis-Siotis, 2001). Cognitive therapy focuses on finding specific solutions to specific issues that arise. The goal of cognitive therapy is to change negative perceptions of certain situations to positive perceptions thus improving the patient's mood and helping with depression.

Conclusion

Sleep dysfunction commonly seen in BD patients might be due to polymorphisms of the CLOCK gene, changes in gene expression, and increased melatonin receptors. Models of bipolar disorder exist but are not effective at providing an effective testing source and more importantly do not offer insight into the mechanisms of bipolar disorder.

The use of IPSCs models can allow for the testing of new treatments, give an insight into the mechanisms of bipolar disorder, and provide an efficient treatment for individuals suffering from bipolar disorder (O'shea et al., 2015).

Targeting the electron transport chain subunits that show lower levels of activity in the mitochondria of the prefrontal cortex may prove to be an effective way to consistently boost the energy levels in the neurons. While postmortem tissue samples are useful in examining the mitochondria of BD patients, better models are needed in order to see them in action and how their dysfunction affects synaptic activity.

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