Current Understanding of Pharmacology of Lithium in Treating Bipolar Disorder

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Abstract: Bipolar disorder is a mental health condition that is present in 4.8% of the global population at least once in their lifetime and has significant impact on patients' physical and mental health. Physiology of bipolar disorder, as well as the mechanism of action of the primary medicine for treating bipolar disorder- lithium that has been found to exhibit neuroprotectiveness and regulatory effect on neurotransmitters- is not clearly understood. This article briefly summarizes contributing mechanisms of bipolar disorder and proposed mechanism of action of lithium in treating the disease. However, no single mechanism is responsible for the multifaceted effect of lithium on bipolar disorder, and the underlying mechanisms still require extensive investigation. Deepening the understanding of pharmacology of lithium is likely to help in finding more and better treatments for bipolar disorder and also in implicating on mechanism of bipolar disorder.

1. Introduction

Bipolar disorder (BD) is a mental health condition characterized by alternation between episodes of manic and depressive symptoms. It has a lifetime prevalence of about 4.8% worldwide, which breaks down to 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, and 3.8% for cyclothymic disorder and other unspecified bipolar disorders [1]. In the United States, the lifetime prevalence of bipolar disorder is about 3% [2]; In Canada, 0.87% of the population suffer from bipolar I disorder, while 0.57% of the population suffer from bipolar II disorder [3]. However, the true proportion of the population with bipolar disorder is projected to be substantially greater than the proportion estimated, because it is common for bipolar symptoms to be diagnosed as a unipolar condition (diagnosing bipolar disorder as either mania or depression only) using the unrevised DSM-IV criteria, which was the prevalent criteria for bipolar disorder diagnosis in the majority of the past studies prior to 2013 [4].

Based on the pattern of alternation between manic and depressive episodes and symptoms in each episode, bipolar disorder is divided into generally 4 types: bipolar I disorder, which is characterized by one episode of mania or hypermania or mixed episode accompanied by at least one episode of depression, bipolar II disorder, which is characterized by hypomanic episodes accompanied by several protracted depressive episodes, cyclothymic disorder (also known as cyclothymia), which is characterized by episodes of manic and depressive symptoms in which depressive symptoms do not meet the criteria to be diagnosed as depressive periods, and unspecified bipolar disorders, which is characterized by alternation between manic and depressive symptoms while not falling into any of the criteria of the three divisions above [5]. Among the four types of bipolar disorder, bipolar I disorder has the worst prognosis and the greatest degree of impairment.

Manic episodes of bipolar disorder are characterized by elevated, expansive, and irritable mood, increased activity and energy, and psychosis and hallucinations in severe cases. Hypermania and hypomania are the more and less severe forms of mania respectively. Depressive episodes are characterized by the loss of interest and feeling of pleasure, which are featured by sadness, difficulty in reasoning and concentrating, and a significant increase or decrease in appetite and sleep. Mixed episodes are episodes in which manic and depressive symptoms coexist, to which it meets the diagnostic criteria for both mania and depression except duration (which is about one week, typically

shorter than that of major depression); Patients with mixed episodes commonly have more severe impairment on thinking, higher rate of comorbidities, and worse prognosis [6]. Bipolar disorder has comorbidities including social phobia, eating disorders, attention-deficit/hyperactivity disorder (ADHD), obstructive sleep apnea, migraine, multiple sclerosis, brain tumor, type II diabetes, etc. 6% of the individuals with bipolar disorder committed suicide over 20 years, while about 30%-40% of the population committed self-harm [7]. Since bipolar disorder leads to unstable mood and reduced ability in judgment and concentration, patients with bipolar disorder suffer from unemployment which worsens their economic burden often already in jeopardy because of the expenses in treating the disease and its comorbidities.

Lithium was introduced for treating mania and bipolar disorder more than a half century ago back into the near 1950s. It has striking effectiveness in treating bipolar disorder and its comorbidities along and has been improved and modified from then on. However, its mechanism is still yet clearly understood after 70 years. The following content is going to first introduce some proposed mechanisms that contribute to bipolar disorder, and then introduce the pharmacology of lithium as well as some other therapies effective in treating bipolar disorder, in hoping to provide insight into the integrated mechanism of action of lithium, and thus implicating on the optimal system of solution in treating bipolar disorder.

2. Mechanisms contributing to bipolar disorder

Researchers' current understanding of bipolar disorder is still limited. However, based on massive statistical data and association studies, numerous pathological pathways have been suggested. These suggested mechanisms, including neurobiological dysfunctions, circadian disruption, metabolic mood syndrome, mitochondrial dysfunction, and behavioral approach system dysregulation theory, would help to understand the pharmacology of lithium discussed in the next section and provide insight into the integrated system of mechanisms of bipolar disorder and potential treatments. Note that the role of dopamine, glutamate, and gamma-aminobutyric acid (GABA) in bipolar disorder are not discussed in this section, while the pharmacology section is going to introduce partial mechanisms of these neurotransmitters for the sake of consistency and easy understanding.

2.1 Neurobiological dysfunctions

Abnormal functioning or degeneration in areas of the brain responsible for emotion generation and regulation and for higher-level thinking among patients of bipolar disorder has been observed. These abnormal functions would be explained and interpreted from the superficial physiological level in this division, while the cause of these abnormal functionings could be other factors that may or may not be introduced in this article.

2.1.1. The ventral prefrontal cortex-amygdala interplay

Amygdala, which plays a role in emotion perception and regulation, has been observed to have regional hyperactivity in response to different stimuli among patients with bipolar disorder in both manic and depressive episodes [8, 9]. Consistently, the ventral prefrontal cortex, which is involved in modulating amygdala activity, has been observed to function abnormally widely among patients with bipolar disorder. Decreased activation of lateral and medial ventral prefrontal regions has been observed across a variety of cognitive tasks, and ventral cortical underactivation is observed irrespective of mood episodes [9]. Specifically, reduced activity in the right ventral prefrontal cortex is observed in bipolar patients in manic episodes, while reduced activity in the left ventral prefrontal cortex is observed in bipolar patients in depressive episodes [9]. Furthermore, it has been found that there is a decreased functional connectivity, which suggests the level of interrelationship and level of correspondence between brain parts, between the amygdala and ventral prefrontal regions in patients of bipolar disorder during manic episodes, strengthening the idea that ventral prefrontal underactivity is the cause of amygdala hyperactivity [10]. In this sense, a rather complete pathway is elicited:

reduced activity in the ventral prefrontal cortex leads to hyperactivity of the amygdala, which leads to liable and intense moods characterized in bipolar disorder.

2.1.2. Change in activity of cortical-cognitive brain network and ventral limbic brain regions

Patients with bipolar disorder exhibit reduced activity and volume of gray matter in the cortical-cognitive brain network, which is associated with regulation of emotions, paired with increased activity in ventral limbic brain regions, which is responsible for experiencing and generating emotions [11]. This combination of changes in activity results in liable mood and possible mood swings.

2.2 Circadian disruption due to melatonin dysregulation

Melatonin in humans is a hormone rhythmically secreted by the pineal gland in the brain and some other structures in response to the absence of light. It regulates circadian as well as seasonal rhythms, and circadian disruption is both a cause and consequence of mood disorders. Manic episodes of bipolar disorder are characterized by reduced need for sleep, while depressive episodes are characterized by insomnia or hypersomnia, which could both have resulted from circadian disruption. And the fact that sleep deprivation and light therapies used for treating circadian disruption also help treat bipolar disorder may imply some more associations between bipolar disorder and circadian disruption [12]. Moreover, melatonin has been found to regulate circulation including blood pressure and dysregulation of melatonin has been found to be associated with cardiovascular diseases, while it has been found that cardiovascular diseases are more common among individuals with bipolar disorder [13, 14]. Following this view, however, the mechanism contributing to manic and depressive episodes in bipolar disorder may be wholly different from that contributing to a unipolar disorder: it could be a set of mechanisms leading to a series of symptoms that is similar to the symptom in a unipolar disorder. However, it should be noted that there are other models suggesting each episode of bipolar disorder to occur via similar mechanisms in that of unipolar disorder. Thus, sleep disruption caused by circadian disruption is more likely to serve a less significant role in causing bipolar disorder. To sum up, it is possible that circadian disruption is a potential contributing factor to bipolar disorder. Nevertheless, researchers should be cautious in considering the role circadian disruption plays in bipolar disorder, since many other pathways may have contributed to symptoms of bipolar disorder in a way similar or dissimilar to the way circadian disruption does.

2.3 The “metabolic mood syndrome” hypothesis

The metabolic mood syndrome hypothesis arises from the close associations between psychiatric disorders and many metabolic disorders, including ones resulting from circadian disruptions discussed in 2.2. This hypothesis suggests that the mechanisms leading to metabolic disorders and psychiatric disorders are shared, or even uniform, which provides insight for a unique explanation for the comorbidities of bipolar disorder as well as fundamental physiology of bipolar disorder similar to that discussed in the division above [15]. During early stages of bipolar disorder, patients often exhibit reduced appetite and sleep and increased energy, and metabolic disorders in bipolar disorder such as obesity and increased food and fluid intake (mostly during manic episodes) could be viewed as compensatory pathways to offset the metabolic imbalance in the brain during initial stages of bipolar disorder [12, 16]. This is also consistent with the “selfish brain” hypothesis in that the brain with exceptionally high energy requirements would disturb other bodily functions to fulfill its own energy need. The metabolic mood syndrome hypothesis is further supported by the fact that the initial side effects of many drugs used in treating bipolar disorder, including both antipsychotics and mood stabilizers (especially for lithium, which is generally considered as the most effective mood stabilizer in treating bipolar disorder), points bodily function towards increasing anabolism, which is manifested as further weight gain and increased appetite [12, 16].

2.4 Mitochondrial dysfunction

Accumulating evidence has been suggesting mitochondrial dysfunction as a key feature in bipolar disorder. Patients with bipolar disorder have been found to have less phosphocreatine, which serves as

a reservoir for ATP synthesis during periods of intense energy demand, in the prefrontal cortex regardless of mood stage, and this reduced phosphocreatine level signals mitochondrial dysfunction [12, 17]. Furthermore, there is an increase in the level of lactate and glucose in the cerebrospinal fluid of patients with bipolar disorder, which indicates cellular respiration shifting from the cooperation of glycolysis and oxidative phosphorylation to solely glycolysis, eliciting mitochondrial dysfunction among patients with bipolar disorder [18]. In support of this observation, there is a decrease in expression of genes encoding for complexes I, III, IV, and V of the electron transport chain in mitochondria in cells of the hippocampus and prefrontal cortex among patients with bipolar disorder, which corresponds to the finding of reduced oxidative phosphorylation [12]. The prefrontal cortex and hippocampus cell-specific mitochondrial dysfunction results from mosaicism, the term for the condition in which the embryo carrying dysfunctional mitochondrial DNA passes on an uneven number of dysfunctional mitochondria, thus leading to a tissue-specific level of dysfunctional mitochondria, as illustrated in figure 1.

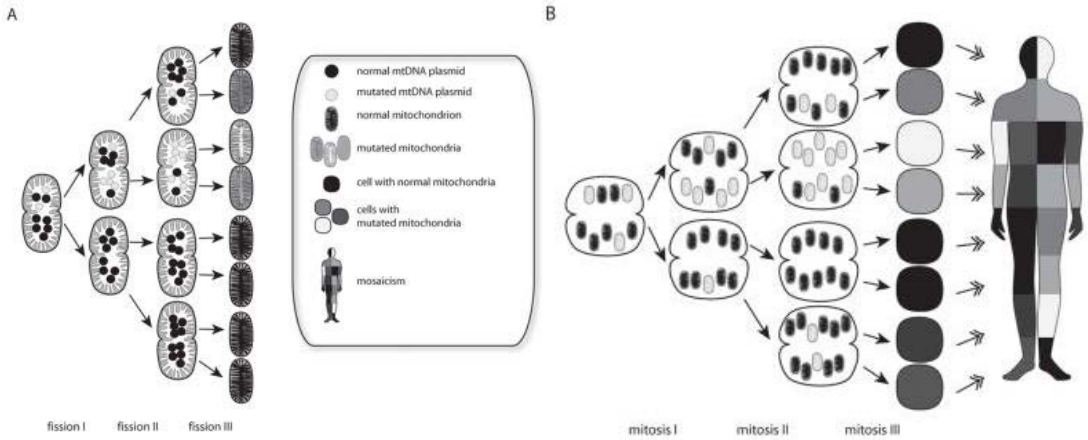

Figure 1. Illustration of mechanism of mosaicism [19]. (A) Mutant mitochondrial DNA is unevenly partitioned across the daughter mitochondria during fission. (B) Mitochondria exhibiting different levels of dysfunction are unevenly partitioned across the daughter cells during mitosis.

There are several mechanisms by which mitochondrial dysfunction impact people's mood. The mitochondria serve as a buffer for Ca2+ ions, and Ca2+ overload leads to endoplasmic reticulum stress, which would release Ca2+ in response and lead to a series of events eventually resulting in apoptosis [19]. Dysfunctional mitochondria have less buffering effect, and combined with the fact that increased cellular calcium is associated with increased energy demand which is exhibited in bipolar disorder, it is likely in bipolar disorder that calcium homeostasis is disturbed and cells with dysfunctional mitochondria degenerate. Mitochondrial energy production at the presynaptic region is also crucial for the normal functioning of neurotransmission, regulation of cytosolic Ca2+, and synaptic vesicles release that is associated with cytosolic Ca2+ concentration [20]. In addition, dysfunctional mitochondria also lead to oxidative stress, in which electrons escaping from the (ineffective) electron transport chain form reactive species while levels of antioxidants such as glutathione which prevents damage of reactive species have reduced, resulting in damage of basic cellular building blocks including proteins, lipids, and nucleic acids, which leads to cell dysfunction or cell death [12].

2.5 Kindling hypothesis and the behavioral approach system dysregulation theory

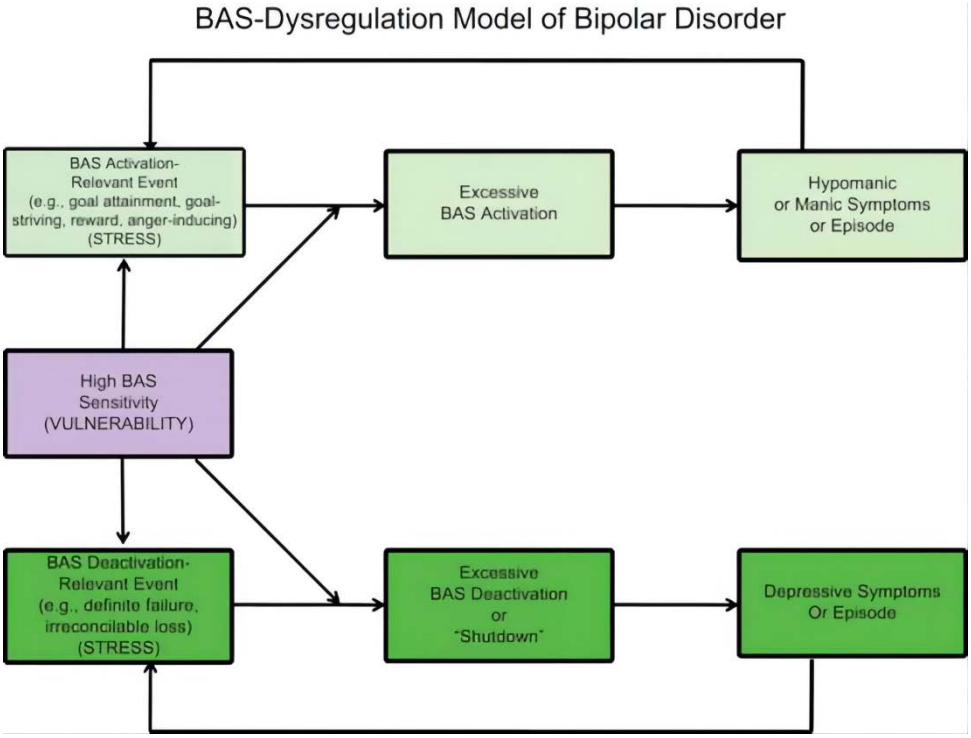

Figure 2. Illustration of behavioral approach system dysregulation model of bipolar disorder [23].

The concept of kindling refers to the progressively reduced need for strength of electrical current required to elicit a seizure in mice; the electrical current by the end of this process is no longer needed to elicit a seizure and, in other words, spontaneous seizures occur [21]. In the context of bipolar disorder, the kindling hypothesis refers to the phenomenon in which repetitive stressors among some predisposed individuals gradually reduce the stress threshold required for initiation of an episode of mania or depression, and eventually spontaneous initiation and alternation of manic and depressive episodes occur [22]. Using this model as its basis, the behavioral approach system dysregulation theory has emerged (as illustrated in figure 2). According to this theory, behavior is regulated by the behavioral approach system, which drives approach behavior and is driven by motivation for rewards, and the behavioral inhibition system, which drives withdrawal behaviors and is driven by fear of punishment [22]. Kindling in this context refers to rewards and provocations which activate the behavioral approach system as well as punishments and threats which deactivate this system [23]. This system may end up over-activating and deactivating itself spontaneously in some individuals. It has been found that patients with bipolar disorder have overactivated behavioral approach system, which is believed to contribute to optimism, irritability, increased energy, etc., during manic episodes, while patients in depressive episodes have underactivated behavioral approach system, which is believed to contribute to hopelessness, reduced confidence, decreased energy, etc. [22].

3. Pharmacology of lithium

Therapeutic schedules of bipolar disorder are patient-specific and based on their state of mood and degree of bipolar disorder development [24]. In general, for patients in manic episodes, antipsychotics which rapidly alleviates the manic symptoms and lithium or other drugs which has better effect in long term treatments are administrated together; For patients in the depressive episodes, antidepressant drugs may or may not be administrated due to increasing evidence proving numerous antidepressants to be ineffective in treating bipolar disorder and other evidence suggesting several antidepressant drugs to be effective, and antipsychotics are often paired with the administration of antidepressants, which is believed to reduce the risk of treatment-emergent mania and to have synergistic interactions with antidepressant drugs [24].

For long-term treatment of bipolar disorder, lithium has been proven to be the most reliable solution. Apart from terminating the emergence of psychiatric episodes with the best effect, lithium is also effective in treating the comorbidities of bipolar disorder, including reducing suicide risk by 60-70% even when mood stabilization is not attained and significantly reducing the degree of dementia, through identical or distinct mechanisms to that in treating bipolar disorder [24, 25]. However, lithium is also associated with adverse effects including end-stage renal failure, congenital malformation of babies for lithium administration during pregnancy, hyperparathyroidism, etc., so alternatives to lithium are required [24].

3.1 Neurotransmission-regulatory pathways

Bipolar disorder is a disease characterized by mood swings between mania and depression from the superficial (neurotransmission) level, and due to the extensive influence of the monoamine hypothesis of depression early on in the past century, bipolar disorder was once extensively investigated with regard to the effect of serotonin and dopamine [25]. The results of these early studies combined with the modern focus on other and more complex neurotransmitter and their interplay elicit increasingly complete and multifaceted mechanisms from the perspective of neurotransmission.

3.1.1 Regulation of dopamine and G-proteins

Dysregulation of the neurotransmitter dopamine, which is responsible for reward and movement regulation, has been found to be associated with both the manic and depressive episodes of bipolar disorder [26]. As an excitatory neurotransmitter, higher levels of synaptic dopamine have been associated with mania, while in some predisposed individuals increased dopamine is associated with secondary homeostatic downregulation of dopamine transmission pathways, which leads to depressive episodes [26]. Postsynaptic G-protein coupled receptors that mediate the transmission of dopamine, which is coupled with adenyl cyclase (AC), inhibits (Gi protein) or stimulates (Gs protein) cyclic adenosine monophosphate (cAMP), which in turn influence neurotransmission [27]. Administration of lithium inhibits Gi protein and thus increases AC and cAMP levels; lithium also inhibits Gs proteins when the cell is stimulated, and this reduces fluctuations of AC and cAMP. These two pathways in the long term improve modulation of neurotransmission and further modify AC and cAMP levels by altering gene transcription [25].

3.1.2 Regulation of glutamate and N-methyl-D-aspartate (NMDA) Receptor

Glutamate is an excitatory neurotransmitter that is elevated during manic episodes. The postsynaptic receptor of glutamate, NMDA receptor, is deactivated by magnesium, while the simultaneous presence of glutamate and glycine, a regulator of glutamate, displaces magnesium and activates the NMDA receptor [25]. Although in the short-term lithium competes with magnesium and stimulates the NMDA receptor, thus increasing post-synaptic glutamate, long-term stable neurotransmission of glutamate (that is, chronic administration of lithium) stabilizes NMDA receptors, thus enabling normal glutamate transmission [25]. However, there are several other mechanisms through which lithium regulates NMDA activity, and the comprehensive effect of lithium on glutamatergic neurotransmission is still yet to be clarified: lithium administration facilitates serotonin 5-HT1A receptor, which consequently deactivates the NMDA receptor; Lithium administration reduces dopamine level (as discussed in 3.1.1), and this leads to decreased NMDA receptor activity; Lithium administration also increase GABA level, which reduce glutamate level and downregulate NMDA receptors [25, 28].

3.1.3 Regulation of GABA

Low GABA levels have been found to be associated with dysregulated glutamate and dopamine transmission, which are a part of the pathology of bipolar disorder, and the administration of lithium is able to inhibit glycogen synthase kinase-3β (GSK-3β), which decreases neuronal excitability in the GABAergic system and increase GABA levels and the sensitivity of GABA receptors [29]. Such direct

action on GABA results in both improved regulation of glutamate and dopamine transmission and reduced excitotoxicity of glutamate (partially explaining the neuroprotective nature of lithium).

3.1.4 Action on the phosphoinositide (PI) cycle, protein kinase C (PKC), and myristoylated alanine-rich C-kinase substrate (MARCKS)

The PI cycle refers to the process in which activation of PI cycle related membrane receptors results in the formation of inositol triphosphate (IP3) and diacylglycerol (DAG), which activates PKC and release intracellular calcium respectively, and enzymes inositol phosphate 1-phosphatase (IPPase) and inositol phosphate-phosphatase (IMPase) successively phosphorylate IP3 to replenish myo-inositol (mI, which could also be replenished by mI in the extracellular spaces via high-affinity sodium mI transport (SMIT)) that is used to synthesize PIs, which is the precursor of many signaling molecules that play crucial roles in signal transduction pathways [25]. In the context of bipolar disorder, disruption of homeostasis of intracellular calcium leads to cell signaling abnormalities, and PKC dysregulation leads to abnormalities in neurotransmission and extracellular receptor localization, while dysregulation of phosphoinositide may also lead to problems with neurotransmission. The “mI depletion hypothesis” is currently the most prevalent hypothesis in explaining the action of lithium on the phosphoinositide cycle. This hypothesis postulates that lithium inhibits the activity of IPPase and IMPase and the activity of the SMIT system, leading to cellular depletion of inositol and thus a reduced production of PIs. Interestingly, the inhibitory effect of lithium has been found only among patients of bipolar disorder, whose IPPase and IMPase are in excess, but not among healthy people even for those exhibiting euthymic moods [30].

PKC also phosphorylates MARCKS, which has been found to influence actin-related cell bioactivities, including migration, secretion, phagocytosis, etc., which are responsible for normal neurotransmission, neuroplasticity, and partly gene expression [31]. Although administration of lithium in the short-term increase PKC activity, chronic administration leads to downregulation of PKC and its downstream target MARCKS in the hippocampus, which is associated with anti-manic pathways [32].

3.1.5 Regulation of intracellular calcium

Calcium plays a key role in neurotransmission. When the cell is stimulated, calcium enters the cell (and is released by intracellular endoplasmic reticulum as well), creating an intracellular gradient of calcium that propagates the signals. The increase in basal and stimulated cellular calcium levels has been extensively associated with bipolar disorder [33]. Lithium reduces calcium influx upon activation of NMDA receptor and activation of metabotropic glutamate receptors (mGluR) 1/5. Lithium also reduces intracellular calcium storage levels. Lithium improves neurotransmission and blocks excitotoxic pathways by inhibiting kainate and consequently inhibiting calpain, which plays a part in apoptotic pathways.

3.2 Neuroprotective pathways

Bipolar disorder is being increasingly recognized as a neurodegenerative process. Neurodegeneration occurs as a result of excitotoxicity from unregulated neurotransmission and cellular abnormalities, and the latter two are potential causes of bipolar disorder. Conversely, neurodegeneration also leads to bipolar disorder. There are several theories in explaining the relationship between neurodegeneration in bipolar disorder. The “neurosensitization model” suggests that frequent alternation between manic and depressed episodes leads to alterations in genetic expression, which renders the neuron and neuronal networks dysfunctional, thus contributing to further mood disorders and ineffectiveness of some treatment solutions [34]. The “allostatic load hypothesis” suggests that the frequent alternation between manic and depressed episodes leads to dysfunction of key brain circuits, thus resulting in reduced cognitive ability [35]. Other related hypotheses include “neuroprogression model” and “neurodevelopmental model”, which has more emphasis on the relatedness between the cause of bipolar disorder and that of neurodegeneration [25].

Bipolar disorder leads to alterations of brain structures in the cortical and subcortical areas and reduction of volume of gray matters in brain regions including the subgenual and anterior cingulate cortex and the prefrontal cortex [25]. Such neurodegeneration results mostly from similar mechanisms as those of bipolar disorder, and its symptoms, primarily unstable mood and reduced judgment, are a part of bipolar disorder. Lithium has been found to prevent and even reverse neurodegeneration (promoting neuroproliferation) among patients with bipolar disorder, especially for the gray matters of the frontal limbic network, including anterior cingulate, ventral prefrontal cortex, left amygdala, hippocampus, etc., which are responsible for mood generation and regulation and cognition [25]. Interestingly, the neuroprotective effect of lithium on the gray matter seems to take effect only among patients with bipolar disorders, but not among healthy experimental controls, implicating potential complex actions of lithium on bipolar disorder that is still yet clarified [36].

3.2.1 Improving mitochondrial functions and relieving oxidative stress

As mentioned in 2.4., mitochondrial dysfunction and oxidative stress which comes along play a significant role in bipolar disorder and accompanying neurodegeneration. Increased D-amphetamine has been associated with inhibition of protein complex I, II, III, and IV in the electron transport chain, while lithium is able to prevent the inhibition of protein complexes in the striatum, prefrontal cortex, and hippocampus. In addition, inhibitors of the complex proteins lead to increased DNA methylation levels, which lead to apoptosis, while lithium administration counteracts these effects, thus reducing neurodegeneration [37]. In alleviating oxidative stress, lithium increases glutathione reductase and glutathione S-transferase, which are antioxidant enzymes that reduce the damage of oxidative species, and stimulate mitochondria respiratory complexes, which reduces the production of oxidative species.

3.2.2 Increasing brain-derived neurotrophic factor (BDNF)

BDNF is a neuroprotective protein that protects the brain from the excitotoxicity of excess glutamate and was found to have reduced in concentration among patients with bipolar disorder [36]. Lithium administration has been found to increase BDNF expression, which is believed to contribute to the neuroprotectiveness of lithium [38]. Interestingly, lithium has been found to take 5 days before increasing BDNF expression, while clinically lithium takes 6-10 days to achieve its anti-manic effect (the discrepancy in the time of effect results from the time required for BDNF to rise to neuroprotective levels), partially substantiating the effect of lithium on BDNF in treating bipolar disorder [25].

3.2.3 Action on B-cell lymphoma 2 (Bcl-2)

Bcl-2 is a neuroprotective protein that plays a key regulatory role in cell apoptosis, and decreased Bcl-2 level has been associated with mania [39]. Lithium administration is able to increase levels of Bcl-2 and its messenger RNA in the prefrontal cortex, thus reducing neurodegeneration.

3.2.4 Regulation of glycogen synthase kinase 3 (GSK-3) and autophagy

GSK-3 is a regulator of glycogen synthesis, which is involved in gene transcription and neuronal structure and resilience, and a downstream target of several monoaminergic systems, which is associated with mood [40]. GSK-3 is activated in response to long-term stressors, which leads to hyperactivity. Lithium administration regulates GSK-3 levels by inhibiting serine 9-phosphorylation 3, while a reduced level of GSK also triggers the PI3K-Akt neuroprotective signaling pathway. GSK-3 inhibition also activates rapamycin (mTOR, a negative regulatory of autophagy), which reduces the autophagy process. One thing to notice, however, is that IP3 reduction due to the administration of lithium (discussed in 3.1.4) increases autophagy. In this sense, lithium both prevents and induces autophagy, implying the complex nature of the mechanisms of lithium in treating bipolar disorder.

Table.1. Summary of pharmacology of lithium

	Target(s)	Consequences of dysregulation	Effect of lithium
Neurotrans-mission	Dopamine	Mania or depression	Regulate G protein and thus stabilize neurotransmission
	Glutamate and NMDA receptor	Mania and neurodegeneration	Long-term stabilization of NMDA receptors
	GABA	Dysregulated dopamine and glutamate transmission	Increase GABAergic actions
	PI cycle, PKC, and MARCKS	PKC, MARCKS, and PI, and thus neurotransmission dysregulation	Regulate PI cycle and thus other activities along
	Calcium	Abnormal neurotransmission	Reduce calcium influx and intracellular store
Neuroprotect-iveness	Dysfunctional mitochondria and oxidative stress	Abnormal neuro-transmission and cell death	Increase protein complexes in electron transport chain and increase antioxidants level
	BDNF	Neurodegeneration	Increase BDNF expression
	Bcl-2	Increased apoptosis	Increase Bcl-2, alleviating neurodegeneration
	GSK-3 and autophagy	Hyperactivity, contributing to mania	Reduce GSK-3 and trigger Akt pathway and mTOR

4. Conclusions

Bipolar disorder has been a concern for over half a century due to its devastating effect on the mentality and physiology of the patients. Bipolar disorder is complex in nature, leaving significant challenges to researchers trying to investigate its mechanisms. Lithium has been luckily identified among a series of solutions. It participates in the majority of the mechanisms of bipolar disorder currently elicited, including regulation of many aspects of dysregulated neurotransmission and reducing neurodegeneration and even reversing this process; It also alleviates the comorbidities of bipolar disorder, including suicide and dementia, suggesting the extensive inter-relatedness of its mechanisms with that of bipolar disorder. But lithium is not the optimal solution. Numerous side effects and clinical restrictions have been elicited. New treatment solutions therefore must be devised. This paper, including the though limited current understanding of mechanisms of bipolar disorder and the mechanisms of lithium in treating it, was articulated in hope of eliciting insights to the key to the optimal solution for treating bipolar disorder and stopping the detriment of this disease upon hundreds of millions of the world population.

References

[1] Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. The Lancet, 387(10027), 1561-1572.

[2] Schmitt, A., Malchow, B., Hasan, A., & Fallkai, P. (2014). The impact of environmental factors in severe psychiatric disorders. Frontiers in neuroscience, 8, 19.

[3] McDonald, K. C., Bulloch, A. G., Duffy, A., Bresee, L., Williams, J. V., Lavorato, D. H., & Patten, S. B. (2015). Prevalence of bipolar I and II disorder in Canada. The Canadian Journal of Psychiatry, 60(3), 151-156.

[4] Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M. C., ... & Rossi, A. (2013). Prevalence, chronicity, burden and borders of bipolar disorder. Journal of affective disorders, 148(2-3), 161-169.

[5] Phillips, M. L., & Kupfer, D. J. (2013). Bipolar disorder diagnosis: challenges and future directions. The Lancet, 381(9878), 1663-1671.

[6] Solé, E., Garriga, M., Valentí, M., & Vieta, E. (2017). Mixed features in bipolar disorder. CNS spectrums, 22(2), 134-140.

[7] Anderson, I. M., Haddad, P. M., & Scott, J. (2012). Bipolar disorder. Bmj, 345.

[8] Strakowski, S. M. (2012). Integration and consolidation. Bipolar Brain Integrating Neuroimaging Genet, 253.

[9] Strakowski, S. M., Adler, C. M., Almeida, J., Altshuler, L. L., Blumberg, H. P., Chang, K. D., ... & Townsend, J. D. (2012). The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar disorders, 14(4), 313-325.

[10] Chepenik, L. G., Raffo, M., Hampson, M., Lacadie, C., Wang, F., Jones, M. M., ... & Blumberg, H. P. (2010). Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. Psychiatry Research: Neuroimaging, 182(3), 207-210.

[11] Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., & Wessa, M. (2011). Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. Journal of affective disorders, 132(3), 344-355.

[12] Kim, Y., Santos, R., Gage, F. H., & Marchetto, M. C. (2017). Molecular mechanisms of bipolar disorder: progress made and future challenges. Frontiers in cellular neuroscience, 11, 30.

[13] Tseng, P. T., Chen, Y. W., Tu, K. Y., Chung, W., Wang, H. Y., Wu, C. K., & Lin, P. Y. (2016). Light therapy in the treatment of patients with bipolar depression: A meta-analytic study. European Neuropsychopharmacology, 26(6), 1037-1047.

[14] Dominguez‐Rodriguez, A., Abreu‐Gonzalez, P., Sanchez‐Sanchez, J. J., Kaski, J. C., & Reiter, R. J. (2010). Melatonin and circadian biology in human cardiovascular disease. Journal of pineal research, 49(1), 14-22.

[15] Goldstein, B. I., Carnethon, M. R., Matthews, K. A., McIntyre, R. S., Miller, G. E., Raghuveer, G., ... & McCrindle, B. W. (2015). Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation, 132(10), 965-986.

[16] Leboyer, M., Soreca, I., Scott, J., Frye, M., Henry, C., Tamouza, R., & Kupfer, D. J. (2012). Can bipolar disorder be viewed as a multi-system inflammatory disease?. Journal of affective disorders, 141(1), 1-10.

[17] Fagiolini, A., Chengappa, K. N., Soreca, I., & Chang, J. (2008). Bipolar disorder and the metabolic syndrome. CNS drugs, 22(8), 655-669.

[18] Frey, B. N., Stanley, J. A., Nery, F. G., Serap Monkul, E., Nicoletti, M. A., Chen, H. H., ... & Soares, J. C. (2007). Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication‐free individuals with bipolar disorder: an in vivo1H MRS study. Bipolar Disorders, 9, 119-127.

[19] Clay, H. B., Sillivan, S., & Konradi, C. (2011). Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. International Journal of Developmental Neuroscience, 29(3), 311-324.

[20] Raffaello, A., Mammucari, C., Gherardi, G., & Rizzuto, R. (2016). Calcium at the center of cell signaling: interplay between endoplasmic reticulum, mitochondria, and lysosomes. Trends in biochemical sciences, 41(12), 1035-1049.

[21] Cyrino, L. A. R., Delwing-de Lima, D., Ullmann, O. M., & Maia, T. P. (2021). Concepts of neuroinflammation and their relationship with impaired mitochondrial functions in bipolar disorder. Frontiers in Behavioral Neuroscience, 15.

[22] Bender, R. E., & Alloy, L. B. (2011). Life stress and kindling in bipolar disorder: review of the evidence and integration with emerging biopsychosocial theories. Clinical psychology review, 31(3), 383-398.

[23] Alloy, L. B., & Abramson, L. Y. (2010). The role of the behavioral approach system (BAS) in bipolar spectrum disorders. Current Directions in Psychological Science, 19(3), 189-194.

[24] Geddes, J. R., & Miklowitz, D. J. (2013). Treatment of bipolar disorder. The lancet, 381(9878), 1672-1682.

[25] Malhi, G. S., Tanious, M., Das, P., Coulston, C. M., & Berk, M. (2013). Potential mechanisms of action of lithium in bipolar disorder. CNS drugs, 27(2), 135-153.

[26] Berk, M., Dodd, S., Kauer‐Sant'anna, M., Malhi, G. S., Bourin, M., Kapczinski, F., & Norman, T. (2007). Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. Acta Psychiatrica Scandinavica, 116, 41-49.

[27] Quiroz, J. A., Machado-Vieira, R., Zarate Jr, C. A., & Manji, H. K. (2010). Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. Neuropsychobiology, 62(1), 50-60.

[28] Ghasemi, M., & Dehpour, A. R. (2011). The NMDA receptor/nitric oxide pathway: a target for the therapeutic and toxic effects of lithium. Trends in pharmacological sciences, 32(7), 420-434.

[29] Sato, K. (2021). Why is lithium effective in alleviating bipolar disorder?. Medical Hypotheses, 147, 110484.

[30] Silverstone, P. H., & McGrath, B. M. (2009). Lithium and valproate and their possible effects on the myo-inositol second messenger system in healthy volunteers and bipolar patients. International Review of Psychiatry, 21(4), 414-423.

[31] Chen, Z., Zhang, W., Selmi, C., Ridgway, W. M., Leung, P. S., Zhang, F., & Gershwin, M. E. (2021). The myristoylated alanine-rich C-kinase substrates (MARCKS): A membrane-anchored mediator of the cell function. Autoimmunity reviews, 20(11), 102942.

[32] Khayachi, A., Ase, A., Liao, C., Kamesh, A., Kuhlmann, N., Schorova, L., ... & Milnerwood, A. (2021). Chronic lithium treatment alters the excitatory/inhibitory balance of synaptic networks and reduces mGluR5–PKC signalling in mouse cortical neurons. Journal of Psychiatry and Neuroscience, 46(3), E402-E414.

[33] Harrison, P. J., Hall, N., Mould, A., Al-Juffali, N., & Tunbridge, E. M. (2021). Cellular calcium in bipolar disorder: systematic review and meta-analysis. Molecular psychiatry, 26(8), 4106-4116.

[34] Arango-Dávila, C. A., & Rincón-Hoyos, H. G. (2018). Depressive disorder, anxiety disorder and chronic pain: multiple manifestations of a common clinical and pathophysiological core. Revista Colombiana de Psiquiatría (English ed.), 47(1), 46-55.

[35] Dargél, A. A., Volant, S., Brietzke, E., Etain, B., Olié, E., Azorin, J. M., ... & FACE‐BD collaborators. (2020). Allostatic load, emotional hyper‐reactivity, and functioning in individuals with bipolar disorder. Bipolar Disorders, 22(7), 711-721.

[36] Sassi, R. B., Nicoletti, M., Brambilla, P., Mallinger, A. G., Frank, E., Kupfer, D. J., ... & Soares, J. C. (2002). Increased gray matter volume in lithium-treated bipolar disorder patients. Neuroscience letters, 329(2), 243-245.

[37] Scola, G., Kim, H. K., Young, L. T., Salvador, M., & Andreazza, A. C. (2014). Lithium reduces the effects of rotenone-induced complex I dysfunction on DNA methylation and hydroxymethylation in rat cortical primary neurons. Psychopharmacology, 231(21), 4189-4198.

[38] Fukumoto, T., Morinobu, S., Okamoto, Y., Kagaya, A., & Yamawaki, S. (2001). Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. Psychopharmacology, 158(1), 100-106.

[39] Lien, R., Flaisher-Grinberg, S., Cleary, C., Hejny, M., & Einat, H. (2008). Behavioral effects of Bcl-2 deficiency: implications for affective disorders. Pharmacological Reports, 60(4), 490.

[40] Snitow, M. E., Bhansali, R. S., & Klein, P. S. (2021). Lithium and therapeutic targeting of GSK-3. Cells, 10(2), 255.