New Pharmacological Interventions in Bipolar Disorder

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Contents

Abstract The biological bases of bipolar disorder include aspects related, among others, to neurohormonal pathways, neurotransmission, signal transduction, regulation of gene expression, oxidative stress, neuroplasticity, and changes in the immune system. There is still a gap in understanding its complex neurobiology and, consequently, developing new treatments. Multiple factors probably interact in this complex equation of pathophysiology of bipolar disorder, such as genetic, biochemical, psychosocial, and environmental stress events, correlating with the development and

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severity of the bipolar disorder. These mechanisms can interact to exacerbate inflammation, impair neurogenesis, and increase oxidative stress damage, cellular mitochondrial dysfunction, changes in neurotrophins and in epigenetic mechanisms, neuroendocrine dysfunction, activation of neuronal death pathways, and dysfunction in neurotransmission systems. In this review, we explore the up-to-date knowledge of the neurobiological underpinnings of bipolar disorders. The difficulty in developing new drugs for bipolar disorder is very much associated with the lack of knowledge about the precise pathophysiology of this disorder. Pharmacological treatment for bipolar patients is vital; to progress to effective medications, it is essential to understand the neurobiology in bipolar patients better and identify novel therapeutic targets.

Keywords Bipolar disorder · Depression · Mania · Targets · Treatment

1 Introduction

Although current therapeutic agents for bipolar disorder are valuable, long-term response for most of the bipolar patients remains low (Gitlin et al. 1995). In general, treatment for bipolar disorder, can be challenging to manage, as treatments that act on manic/hypomanic episodes can lead to a depressive episode and the use of antidepressants can cause manic or hypomanic mood episodes (Geddes and Miklowitz 2013). Lithium is considered the gold standard drug for all phases of bipolar disorder (López-Muñoz et al. 2018).

Lithium, so far, is the only one with benefit in both poles and efficacy also for suicidal behavior (Geddes and Miklowitz 2013). Therefore, the investigation of potential new therapeutic goals is a priority. In this review, we explore the up-to-date knowledge of the neurobiology bases of bipolar disorders and the neurobiological mechanisms of dysfunction in a wide range of pathways, including: glutamatergic dysfunction, oxidative stress, mitochondrial dysfunction, impaired neurogenesis, increased inflammation, and apoptosis. The difficulty in the development of new drugs for bipolar patients is associated with a lack of knowledge about the precise pathophysiology of this disorder (Lund et al. 2012). Investigating these new pathophysiology systems purportedly related to the complexity of the neuronal systems in bipolar patients could improve our knowledge of the complex mechanisms related to the action of psychotropic drugs, as well as the neurobiology in bipolar patients (Fig. 1).

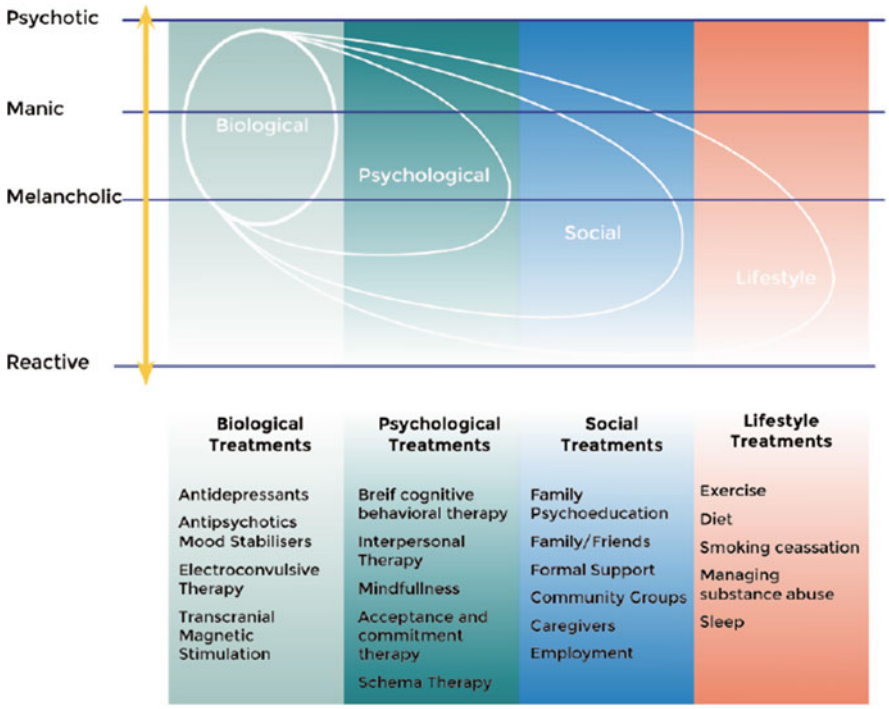

Fig. 1 The diagram provides a useful model for understanding the factors that contribute to planning clinical management. Therefore, a broad range of treatments is usually needed to treat bipolar disorders satisfactorily, adapted from Malhi et al. (2015). Illustrations are courtesy of Romayne Gadelrab

2 Hypothalamic-Pituitary-Adrenal Axis (HPA)

It is believed that disturbance of the hormonal stress system (the hypothalamic-pituitary-adrenal axis) can cause cognitive problems and worsen depressive symptoms in bipolar disorder (Watson et al. 2004) and can predict an inadequate clinical response to pharmacological treatments (Juruena et al. 2009a). One example of this is suggested in animal models, where a dysregulation in the HPA axis has an impact on serotonergic medications (Gartside et al. 2003).

The end product of the HPA axis is cortisol, which mediates its effects via two main receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) (Juruena 2014). MR receptors modulate hormone release and complex behavior, such as emotion, memory, and sleep. In humans, the role of MR and GR receptors in the neurobiology of severe mental disorders has not been sufficiently characterized. However, recent research findings raise possibilities for new pharmacotherapies via modulation of the function of these receptors to normalize effects of cortisol and restore HPA axis balance (Geddes and Miklowitz 2013).

2.1 Treatments Targeting the HPA Axis

The effects of exogenous steroids on mood, including the potential to both elevate and lower mood, and to exacerbate mood disorders, are widely known. From a therapeutic standpoint, previous studies have shown that spironolactone, a mineralocorticoid receptor antagonist, can have antidepressant effects and can also maintain or improve cognition and memory (Murck et al. 2012). Hendler (1978) first described the therapeutic effects of spironolactone for prophylaxis in a case series of bipolar patients: after replacing lithium with spironolactone, five of the six patients were well maintained for at least 1 year (Hendler 1978). Some studies have demonstrated the therapeutic impact of spironolactone on affective symptoms in women with premenstrual syndrome (O'Brien et al. 1979; Wang et al. 1995) and eating disorders (Wernze 2000) and bipolar patients without remission, decreasing the sensitivity to stressful life events (Juruena et al. 2009).

Mifepristone is an antagonist of the glucocorticoid receptor and preliminary evidence suggested potential cognitive enhancing properties (Young et al. 2004). A larger RCT of adjunctive mifepristone failed to demonstrate a significant improvement in depressive symptoms in bipolar depression, although mifepristone was associated with improvement in cognitive function – and specifically spatial working memory (Young et al. 2004; Watson et al. 2012).

Ketoconazole and metyrapone, inhibitors of glucocorticoid synthesis, have also been investigated in bipolar disorder. In a trial with a very small sample in bipolar depression, with a treatment-resistant history, ketoconazole led to significant improvement in the severity of depression, but not mania (Brown et al. 2001). However, no RCTs have been performed.

A Cochrane review summarized the findings from antiglucocorticoid treatments for mood disorders (Gallagher et al. 2008). This comprised nine studies (three in psychotic major depression, five in non-psychotic major depression, and one in patients with bipolar depression); the authors described a significant reduction in the severity of depressive symptoms with antiglucocorticoid treatments.

3 Mitochondrial Dysfunction and Oxidative Stress in the Neurobiology of Bipolar

There is increasing data in the literature describing oxidative stress in the neurobiology of bipolar disorder. Corroborating the involvement of mitochondrial dysfunction in the pathophysiology of bipolar disorders, a study demonstrated that bipolar patients have an imbalance between the processes of mitochondrial fusion and fission (Scaini et al. 2017) observed by increased protein levels of fission protein (Fis-1) and decreased levels of fusion proteins (Mfn-2 and Opa-1), suggesting that the process of mitochondrial dynamics in patients with bipolar disorder is dysfunctional, which may increase mitochondrial fragmentation (Scaini et al. 2017). In

addition, the same study indicated that the changes observed peripherally were directly correlated with functional decline in bipolar patients (Scaini et al. 2017). Effects of lithium in redox systems may have this effect in psychopathological disorders (Khairova et al. 2012).

3.1 Oxidative Stress and Pharmacological Approaches

Several clinical and preclinical studies have suggested the involvement of oxidative stress in bipolar disorders (Frey et al. 2006). Mitochondrial dysfunction has been described as the main triggering agent of this system with a consequent impairment in cellular energy metabolism (Berk et al. 2011b). An abnormal cellular energy state can lead to loss of neuronal function and plasticity and cognitive and behavioral changes characteristic of bipolar disorders (Kato 2007).

Several studies have found elevated levels of malondialdehyde (MDA) and carbonyl groups in the blood of patients with bipolar disorders (Descamps-Latscha et al. 2001). Postmortem studies have shown high levels of carbonyl, 4-HNE, and 8-ISSO groups in bipolar patients (Imai and Nakagawa 2003; Wang et al. 2009). In addition, the antioxidant defense system also appears to be altered in bipolar patients, even in the early stages of the disorder. A study detected an increase in glutathione (GST) in bipolar patients in the early stages of the disorder (Andreazza et al. 2009). The superoxide dismutase (SOD) enzyme has also been found to be increased in the blood of bipolar patients during episodes of mania and depression (Andreazza et al. 2010).

3.2 Alternative and Experimental Treatments Targeting Oxidative Stress

N-acetylcysteine (NAC) has been investigated in the treatment of acute and maintenance treatment of bipolar disorder. NAC is an immediate precursor to glutathione, an antioxidant protein with a significant role in the removal of numerous reactive oxygen species, levels of which are reduced in bipolar disorder (Rosa et al. 2014). In the first placebo-controlled RCT, adjunctive NAC treatment resulted in a significant improvement in depressive symptoms over placebo in bipolar patients at the maintenance treatment stage (Berk et al. 2008). Studying a subgroup analysis of bipolar patients in a depressive phase at baseline, the NAC treatment group showed significant improvements in depressive symptoms (eight of ten patients on NAC had treatment response at endpoint), alongside measures of executive function and QoL (Magalhaes et al. 2011). A further open-label study of 149 individuals with bipolar depression again showed adjunctive NAC treatment led to significant and robust reductions in depression scores and improvements in functioning and quality of life

(Berk et al. 2011a). However, more recently, a large RCT found no difference between adjunctive NAC and placebo in bipolar depression in terms of reduction of depressive symptoms at the 16-week endpoint (Berk et al. 2019).

Creatine is the precursor of phosphocreatine (PCr), which has an important role in brain energy homeostasis through the phosphocreatine circuit and has been shown to have antioxidant properties (Pereira et al. 2018). In a small sample of patients with unipolar and bipolar treatment-resistant depression, open label adjunctive treatment with creatine monohydrate led to significantly improved depressive symptoms; however, in both bipolar disorder patients, there was a momentary switch to elevated mood (Roitman et al. 2007).

In a placebo-controlled RCT evaluating creatine monohydrate as an added treatment in bipolar disorder in a depressive episode, the patients did not show improvement in depressive symptom scores. However, the study did find significant superiority of creatine augmentation over placebo using remission criteria (Toniolo et al. 2018).

Cytidine is a pyrimidine with the main function on phospholipid homeostasis and membrane balance, which potentially alleviates mitochondrial dysfunction and regulates dysfunctional glia-neuronal glutamatergic cycling in bipolar disorder. In a 12-week RCT of 35 individuals with bipolar depression, adjunctive cytidine resulted in an earlier decrease in depressive severity alongside a decrease in glutamate/glutamine levels as measured by proton magnetic resonance spectroscopy (^{1}H-MRS) (Yoon et al. 2009).

4 Immune System in Bipolar Disorder

It is known that multiple factors related to the immune system may be involved in the pathophysiology of bipolar disorder, including tumor necrosis factor-alpha (TNF-α) and interleukins (IL). These mechanisms, in turn, promote deleterious effects that contribute to exaggerated inflammation (Carvalho et al. 2013). Studies have suggested that the pathophysiology of bipolar disorder may be related to changes in the immune system, with mood episodes being characterized as pro-inflammatory states. A pro-inflammatory increase in cytokines has been described in patients with bipolar disorders, mainly TNF-α. In addition, IL-2, IL-1β, IL-4, IL-6, and IL-10 concentrations are elevated in bipolar patients (Modabbernia et al. 2013). Investigations about inflammation in bipolar disorder have significantly increased in the last years, showing the importance of the immune system in the neurobiology of bipolar disorder, but with variable results regarding the type of episode, the effect of treatments, and the progression of the disorder (Leboyer et al. 2012).

Horrobin and Lieb (1981) were the first to link immunological disorders with bipolar disorder; the authors hypothesize that relapses of mood episodes in bipolar patients would be driven by the immune system as well as in other inflammatory diseases such as multiple sclerosis (Maes 2011; Drexhage et al. 2010).

Specifically, alterations in the arachidonic acid (AA) signalling pathway and regulation of cyclooxygenase (COX)-generated metabolites including prostaglandins and thromboxanes have been implicated in the neurobiology of bipolar patients, and targeting AA pathway may be a potential therapeutic approach (Rao and Rapoport 2009). A postmortem brain study of bipolar patients showed changes in the AA metabolism cascade (Rao et al. 2010). As well as a significant increase in pro-inflammatory and anti-inflammatory cytokines, they have been consistently reported in patients with bipolar disorder (Modabbernia et al. 2013). The study suggests that pro-inflammatory cytokines are increased regardless of the mood episode of patients with bipolar disorder, as well as the occurrence of a reduction in anti-inflammatory cytokines (Barbosa et al. 2014).

Studies have highlighted TNF-α as an important marker of bipolar progression, with a significant increase in patients with a chronic history when compared to first-episode bipolar patients (Tatay-Manteiga et al. 2017). These studies reinforce the presence of changes in inflammatory biomarkers in bipolar patients (Modabbernia et al. 2013).

4.1 Inflammation and Treatment in Bipolar Disorders

The AA cascade has been the subject of some studies, and it may be the common route of action of several medications used to treat bipolar patients, for example, anticonvulsants (sodium valproate and carbamazepine) and lithium (Rao et al. 2008). Possible effectiveness of adjuvant celecoxib treatment in both poles of bipolar patients has also been reported, suggesting an essential impact of the inflammation pathway (Arabzadeh et al. 2015; Mousavi et al. 2017).

Reports of lithium's anti-inflammatory properties may contribute to its therapeutic efficacy. However, data demonstrated in the literature are contradictory about the effects of lithium on pro- or anti-inflammatory markers (Rapaport and Manji 2001). In pre-clinical studies, chronic lithium treatment reduced levels of motor impulsivity, plasma levels of IL-1β, IL-10 and RANTES (CCL-5) were reduced selectively within the orbitofrontal cortex of lithium-treated rats (Adams et al. 2020). These findings demonstrate that lithium may improve impulse control deficits in clinical populations decreasing the pro-inflammatory signalling on neuronal activity, particularly within the orbitofrontal cortex (Adams et al. 2020). Studies evaluated the action of the medications utilized in bipolar patients and suggest that the AA cascade, as well as the decreased activity of cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE2), can be a common target in the mood-stabilizing action of these drugs (Bosetti et al. 2002). A further study demonstrated that bipolar patients who showed a poor response to lithium had increased levels of TNF-α compared to those with a good response (Guloksuz et al. 2012) (Fig. 2).

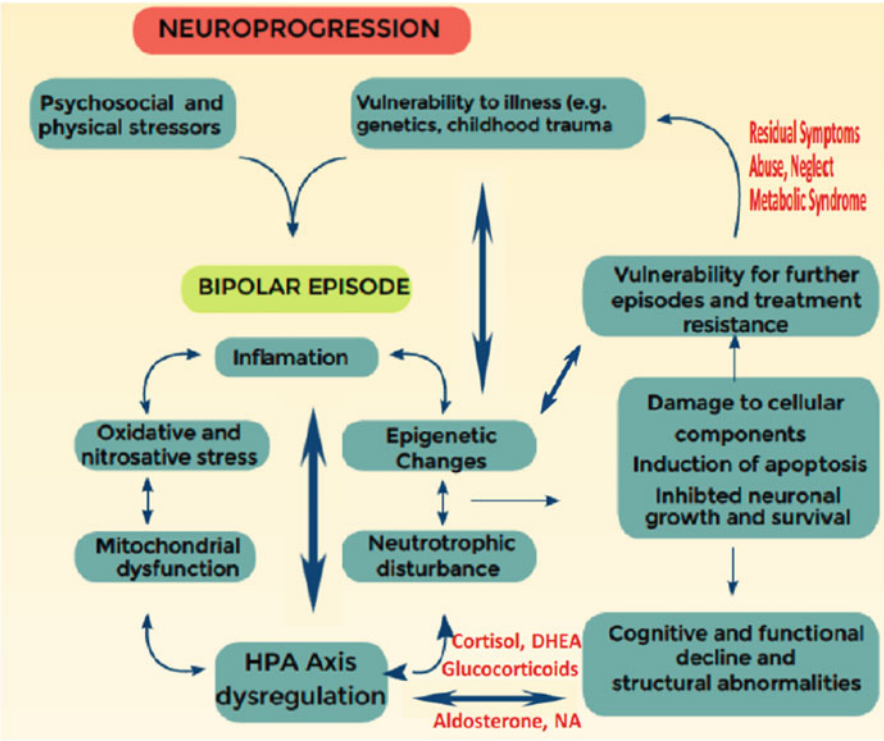

Fig. 2 Importance of early treatment: the impact on neuroprogression, Psycho-Neuro-Immune-Endocrine cascade. Adapted from Moylan et al. (2013). Illustrations courtesy of Romayne Gadelrab

4.2 Alternative and Experimental Treatments and Inflammation

Among non-steroidal anti-inflammatories (NSAIDs), there is the class of those specific inhibitors of COX-2; among these drugs is celecoxib. COX isoenzymes have a role as precursors of prostaglandin, thromboxanes, and prostacyclins. Prostaglandins are autacoid mediators with influence in most of the neurophysiological or pathophysiological progressions through the membrane receptors connected to the G-protein (Fitzpatrick 2004).

A meta-analysis examining the antidepressant effects of adjunctive anti-inflammatory agents in mood disorders, including MDD and bipolar disorder, found a moderate to large effect size (Husain et al. 2017). Interestingly, this meta-analysis also showed a significant reduction in manic symptoms when pooling the results of adjunctive anti-inflammatories (NSAIDs and NAC) in bipolar disorder.

The use of omega-3 fatty acids (naturally occurring anti-inflammatory molecules) in bipolar depression is restricted with one meta-analysis of five RCTs indicating a

significant outcome in favor of omega-3 over placebo with moderate effect size (Sarris et al. 2012).

In a RCT with bipolar patients using celecoxib controlled with placebo, the authors found a significant decrease in TNF-α levels. However, in this study, there was no significant difference in the levels of IL-1β, IL-6, and high-sensitivity C-reactive protein (Kargar et al. 2014). This study evaluated inflammatory markers in the use of celecoxib. Although several studies are correlating bipolar disorder progression with inflammatory markers, the data are still controversial, highlighting the importance of new research in this area (Giridharan et al. 2019). Overall, these studies demonstrate strong evidence of inflammation in bipolar disorder leading to new therapeutic targets, such as the use of anti-inflammatory drugs, highlighting celecoxib and the AA pathway involved in the action of this drug (Husain et al. 2016).

A meta-analysis including three RCTs ($n = 121$) showed a significant effect on Young Mania Rating Scale scores from patients with bipolar disorder receiving adjunctive celecoxib treatment compared with placebo (Bavaresco et al. 2019). An RCT of adjunctive celecoxib in treatment-resistant bipolar depression found higher response and remission rates in the celecoxib than in the placebo arm (Halaris et al. 2020).

Minocycline is a second-generation tetracycline with anti-inflammatory properties. The effects of minocycline in combination with aspirin have also been examined in an RCT in bipolar depression that showed a significantly higher sustained clinical response rate in the minocycline and aspirin-treated group compared with placebo (Savitz et al. 2018).

A study investigating minocycline for bipolar depression patients demonstrated a significant effect size in reducing depressive symptoms (Soczynska et al. 2017). Remarkably, the clinical trials indicate that this second-generation tetracycline has more significant effects in bipolar disorder subjects with higher inflammatory indicators which highlights the need for inflammatory analysis +/− stratification in forthcoming RCTs of minocycline in bipolar patients. However, the largest and most recent RCT (*n*-266) in bipolar I and II and unipolar depression did not find a significant effect comparing placebo with celecoxib or minocycline (Husain et al. 2020). Husain et al. (2020) conclude that a possible therapeutic effect should not be considered in bipolar depression. Notwithstanding this negative finding, anti-inflammatory treatments are becoming a promising alternative for use in psychiatry.

5 Neurotrophins and Bipolar

In the middle of the twentieth century, the first neurotrophin, the nerve growth factor (NGF), was identified. This discovery broadened the horizon of neurobiology for the identification and elucidation of cellular functions. Almost 30 years after the identification of NGF, the prototype of neurotrophins for neurons of the autonomic

nervous system was isolated, a homologue of NGF, which was called brain-derived neurotrophic factor (BDNF) (Lessmann et al. 2003).

Recent studies indicate that impairment of neuroplasticity and neuronal survival are the main events involved in the pathogenesis of bipolar disorders. These events are influenced by several factors, such as the harmonic action of neurotransmitters, hormones, neurotrophins, and inflammatory mediators, such as cytokines (Brietzke and Kapczinski 2008).

It has been shown that high levels of cortisol, released due to stress, can cause damage to the membranes of neuronal mitochondria, especially in patients with bipolar disorder, leading to the release of toxic compounds and culminating in changes in the structure of the DNA molecule in nucleus of these cells. All of this transformation triggers apoptosis mechanisms (Berk et al. 2011b).

5.1 Neurotrophins and Bipolar Treatment

The family of tyrosine kinase (Trk) receptors is composed of three receptors that can be activated by one or more neurotrophins: NGF, BDNF, NT-3, and NT-4/5. In studies on depression models, antidepressants increase TrkB signaling, which is dependent on the concentration of BDNF (Saarelainen et al. 2003). Antidepressants and mood stabilizers can increase serum BDNF levels (Frey et al. 2006). Chronic administration of antidepressants increases the expression of BDNF in the hippocampus, as well as in the CPF (Duman et al. 2000). Chronic treatment with lithium or sodium valproate demonstrated higher BDNF expression in preclinical studies (Fukumoto et al. 2001).

Several studies have suggested that BDNF/TrkB induction is one of the mechanisms responsible for the therapeutic effects of antipsychotics, mood stabilizers, and antidepressants (Coyle and Duman 2003; Nibuya et al. 1995). For example, it has been shown that the use of lithium modulates the phosphorylation of the TrkB and CREB receptors (Rantamaki et al. 2006). Studies show that the neuroprotective characteristics of lithium or sodium valproate may be responsible for its therapeutic effects, and one of the mechanisms involved would be the release of neurotrophins (Rosa et al. 2006; Laeng et al. 2004).

It has been proposed that the augmented expression of BDNF can trigger the neuroprotective properties of lithium and valproate (de Sousa et al. 2011; Hu et al. 2010).

Chronic treatment with lithium or sodium valproate produces protective effects against excitotoxicity and cell death induced by glutamate (Shao et al. 2005). Regarding BDNF, there is much evidence regarding its long-term role in synaptic plasticity in the hippocampus and neocortex. The application of exogenous BDNF enhances presynaptic efficacy by increasing the release of glutamate in excitatory synapses (Lessmann et al. 2003).

6 Bipolar Disorder and the Glutamatergic System

For a long time, the monoaminergic hypothesis explained both the neurobiology of bipolar disorders and the mechanisms of action of psychotropic drugs. Glutamate is related to a diversity of crucial functions including synaptic plasticity, learning, and memory (Riedel et al. 2003). This neurotransmitter acts on two classes of receptors: ionotropic and metabotropic. There are three types of ionotropic glutamate receptors: α-amino acid-3-hydroxy-5-methylisoxazol-4-proprionic (AMPA), N-methyl-D-aspartate (NMDA), and kainate. These three proteins are ion channels that, when activated, generate postsynaptic excitatory potential (Kew and Kemp 2005). Metabotropic receptors are not ion channels and are not exclusively located in the synapse region. When they bind to glutamate, they activate the G-protein, which is responsible for sending the message into the cell (Baudry et al. 2012).

Although all glutamate receptors respond to the same neurotransmitter, they perform very different functions (Jun et al. 2014). In physiological situations, ionotropic and metabotropic receptors regulate neurotransmission through excitatory synapses and modulate various neurophysiological functions in the brain, which include synaptic plasticity, mood, learning, and memory (Kew and Kemp 2005).

Several researchers have shown changes in glutamate receptors in the brain of patients with bipolar disorders, with decreased expression of NMDA receptor in the hippocampus and the prefrontal cortex of bipolar patients (McCullumsmith et al. 2007; Beneyto and Meador-Woodruff 2008). These functionally different receptors can be co-expressed in individual synapses, allowing precise temporal modulation of postsynaptic excitability and plasticity (Scheefhals and MacGillavry 2018). Recently, the NMDA receptor has been associated with the sociability and pathogenesis of autism spectrum disorder, which encourages further studies for the therapeutic exploration of the modulation of this receptor (Burket and Deutsch 2019).

6.1 Glutamate Neurotransmission and Bipolar Treatment

Several pharmacological approaches used in the treatment of psychiatric disorders act on the glutamatergic system. Significant evidence for the role of glutamate in bipolar disorder emerged from pharmacological interventions; for example, lamotrigine, an anticonvulsant also used in bipolar depression pharmacotherapy, indirectly inhibits the release of glutamate (Leach et al. 1991). Lithium is the gold standard mood stabilizer; it leads to an acute increase in the concentration of glutamate in the synapse and the chronic upregulation of transporter activity; its chronic use seems to promote the stabilization of excitatory neurotransmission (Li et al. 2002). Lithium attenuates the release of Ca^{2+} after acting on mGluR1 and mGluR5 receptors (Machado-Vieira et al. 2012; Sourial-Bassillious et al. 2009). As previously described, mitochondrial dynamics involve not only the processes of fission and fusion but also the movement of mitochondria through neurons, a process

influenced by the concentration of ATP and Ca^{2+}, with lithium's influence (Curtis et al. 2011). In addition to changes in ATP levels, as already mentioned, studies have pointed out that bipolar patients show changes in intracellular Ca^{2+} signaling, causing an increase in cytosolic Ca^{2+} concentrations, related to excitotoxicity, decreased mitochondrial viability, and, ultimately, cell death (Mehta et al. 2013). The neuroprotective effects of lithium against the excitotoxicity of glutamate influences BDNF. Antipsychotics and anticonvulsants reduce glutamate in the central nervous system (Sitges et al. 2007; Juruena et al. 2009b; McLoughlin et al. 2009; Paraskevas et al. 2006; de la Fuente-Sandoval et al. 2013).

6.2 Alternative and Experimental Treatments Targeting the Glutamatergic System

6.2.1 Ketamine

Several studies have shown that glutamate-mediated synaptic plasticity is involved in bipolar pharmacotherapy. In addition, ketamine (an NMDA antagonist) has attracted attention for its rapid antidepressant activity, including in patients with bipolar depression (Zarate et al. 2012)

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with significant evidence to treat both unipolar and bipolar depression, including in treatment-resistant cases (Coyle and Laws 2015). In an RCT crossover add-on study of 18 individuals with treatment-resistant bipolar depression (continued on lithium or valproate), following a single ketamine infusion (0.5 mg/kg over 40 min), depressive symptoms significantly decreased within 40 min compared with placebo, the effect lasting up to day 3 (Diazgranados et al. 2010). There was a notable response rate, with approximately 70% of subjects responding to ketamine. Acute dissociative symptoms were the most common side effect; otherwise ketamine at this dose was generally well tolerated. These findings were replicated in a similar clinical trial with treatment-resistant bipolar depression, which again showed a single ketamine infusion led to rapid, robust antidepressant effects, alongside significant improvements in suicidal ideation (Zarate et al. 2012). Although the antidepressant effects of ketamine are transient, the response may be maintained with repeated infusions (Diamond et al. 2014). Other forms of administration (oral, sublingual, intranasal, intramuscular, subcutaneous) may demonstrate more viable alternatives for repeated dosing. Nevertheless, additional research is required to fully assess and compare the safety and effectiveness of repeated dosing across different routes.

6.2.2 Memantine

Memantine is a non-competitive NMDA antagonist which, unlike ketamine, does not produce dissociative side effects at therapeutic doses. In a small RCT of

memantine augmentation of lamotrigine in bipolar depression, although a primary benefit of memantine over placebo was demonstrated at 4 weeks, this effect was not maintained at the 8-week primary endpoint (Anand et al. 2012). A subsequent larger RCT exploring memantine augmentation to valproate in bipolar II depression again found no significant benefit over placebo in terms of response in the severity of depression (Lee et al. 2014). Of interest, this study found that TNF-α levels were decreased in the memantine arm, suggesting a potential anti-inflammatory mechanism. An open-label pilot trial in individuals with acute mania associated with bipolar I disorder found memantine monotherapy to have anti-manic effects at 3 weeks (Keck et al. 2009); however, larger RCTs are required to explore this further.

6.2.3 Riluzole

Riluzole is an NDMA modulator that is licensed for amyotrophic lateral sclerosis (ALS) treatment, acting to increase glutamatergic reuptake and enhance the production of neural growth factors, including BDNF (Bellingham 2011). Preliminary results in acute bipolar depression, in an open trial with riluzole added to lithium, found a significant treatment effect at 4 weeks with no switch observed and good tolerability (Zarate et al. 2005). However, in a subsequent RCT of 19 subjects with acute bipolar depression, there were no significant differences in depressive symptoms between riluzole monotherapy and placebo groups (Park et al. 2017).

7 Bipolar Disorder and the Cholinergic System

The cholinergic-adrenergic hypothesis of bipolar disorder was first proposed many decades ago (Janowsky et al. 1972) and suggested that mania was associated with an adrenergic predominance, while depression was associated with a central cholinergic predominance. Since this initial hypothesis, converging evidence has supported cholinergic dysfunction in bipolar disorder. A positron emission tomography (PET) study demonstrated decreased muscarinic type 2 (M2) binding in bipolar patients (Cannon et al. 2006); another study has reported reduced muscarinic receptor binding (M2 and M3) in the prefrontal cortex in bipolar patients (Gibbons et al. 2009).

7.1 Treatments Targeting the Cholinergic System

The short-acting acetylcholinesterase inhibitor physostigmine has been shown to lead to rapid but temporary reductions in manic symptoms in a few small case series (Davis et al. 1978). Augmentation with donepezil, a long-acting acetylcholinesterase

inhibitor, was also shown to lead to marked reductions in mania in a small case series (Burt et al. 1999). However, a subsequent small RCT failed to show any significant benefit of adjunctive donepezil over placebo in treatment for refractory manic symptoms (Eden Evins et al. 2006).

Scopolamine, a muscarinic receptor antagonist and NMDA modulator, has also been examined for potential treatment of bipolar patients. In a double-blind RCT, including subjects with both major depressive disorder and bipolar depression, scopolamine administration led to a significant rapid and robust antidepressant response (Furey and Drevets 2006). An RCT (SCOPE-BD) is studying scopolamine in bipolar patients in a depressive episode (Hallahan n.d., ClinicalTrials.gov ID: NCT04211961).

8 Bipolar Disorder and the Melatonergic System

Melatonin is a vital hormone in the brain that is responsible for the regulation of circadian rhythms but also has essential roles in metabolic, immune, antioxidative, and mitochondrial functioning (Claustrat et al. 2005). Melatonin exerts its effects primarily through the MT_1 and MT_2 G-protein-coupled receptors.

There is accumulating evidence on the role of the melatonin system in bipolar disorder, with studies reporting changes in patters on melatonin secretion and supersensitivity of light-induced melatonin suppression (Lanfumey et al. 2013).

8.1 Treatments Targeting the Melatonergic System

Agomelatine is a potent MT_1 and MT_2 agonist and 5HT-2C antagonist and also acts to increase dopamine and noradrenaline levels (Guardiola-Lemaitre et al. 2014). A clinical trial in bipolar depression with agomelatine found that 81% of patients showed greater than 50% response in HAM-D score after 6 weeks (Calabrese et al. 2007); however, a larger RCT subsequently did not find a difference in depressive severity between agomelatine or placebo adjunctive therapy (Yatham et al. 2016).

Ramelteon is an MT_1 and MT_2 agonist, which has been shown to improve depressive symptoms in bipolar disorder with sleep problems (McElroy et al. 2011). Further work has shown ramelteon to be effective in maintaining mood stability in euthymic bipolar disorder individuals with sleep disturbances (Norris et al. 2013). Most recently a phase 3 RCT examining the efficacy and safety of adjunctive ramelteon as a maintenance treatment in bipolar disorder failed to show the efficacy of ramelteon in preventing relapse in bipolar subjects (Mahableshwarkar et al. 2017).

9 Conclusion

In the face of the complex symptomatology of bipolar disorder, there is still a hiatus in the understanding of its more complex neurobiology and, accordingly, in the treatment of bipolar disorder. Understanding new biological pathways will provide data with potential for clinical translation. This update of the neurobiological bases shows multiple factors probably interact in this complex equation of pathophysiology of bipolar disorder, such as genetic, biochemical, psychosocial, and environmental stress events, correlating with the development and severity of the bipolar disorder. Developing new pharmacological treatment for bipolar patients is crucial; however, new effective medications can only be developed when we understand better the neurobiology of bipolar disorder and find novel targets such as those described in this chapter.

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