Intracellular Signaling Cascades in Bipolar Disorder

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Contents

Abstract Bipolar spectrum disorders carry a significant public health burden. Disproportionately high rates of suicide, incarceration, and comorbid medical conditions necessitate an extraordinary focus on understanding the intricacies of this disease. Elucidating granular, intracellular details seems to be a necessary preamble to advancing promising therapeutic opportunities. In this chapter, we review a wide range of intracellular mechanisms including mitochondrial energetics, calcium

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signaling, neuroinflammation, the microbiome, neurotransmitter metabolism, glycogen synthase kinase 3-beta (GSK3β), protein kinase C (PKC) and diacylglycerol (DAG), and neurotrophins (especially BDNF), as well as the glutamatergic, dopaminergic, purinergic, and neurohormonal systems. Owing to the relative lack of understanding and effective therapeutic options compared to the rest of the spectrum, special attention is paid in the chapter to the latest developments in bipolar depression. Likewise, from a therapeutic standpoint, special attention should be paid to the pervasive mechanistic actions of lithium as a means of amalgamating numerous, disparate cascades into a digestible cognitive topology.

Keywords Brain-derived neurotrophic factor (BDNF) · Glycogen synthase kinase 3-beta (GSK3β) · Lithium · Protein kinase C (PKC) and diacylglycerol (DAG)

1 Introduction

BD has a lifetime prevalence of approximately 4% in the general population and imposes substantial medical and psychosocial morbidity on patients and families (Kessler et al. 2005). Bipolar disorder (BD) has been associated with a wide range of neurobiological models whose pathophysiological mechanisms have not yet been fully characterized. As our attempts to understand and treat this disease evolve, the clearer it becomes that BD is a multifactorial disease comprised of many dynamic, interdependent systems. Findings in recent decades have encouraged a transition from research predominantly centered around monoamine neurotransmission to intracellular signaling, synaptic/neural plasticity, and other cellular mechanisms. Cumulative data also demonstrates that conventional mood stabilizers and other efficacious compounds work by modulating many of these pathways. In this present chapter, we provide updated descriptions of the prominent pathophysiologic models as well as the latest therapeutic developments in the treatment of BD.

2 Mitochondrial Dysfunction

Dysfunction in brain-energy metabolism has been considered a key mechanism in the pathophysiology of BD (Zuccoli et al. 2017). Mitochondria primarily regulate intracellular energy metabolism, and abnormalities in both mitochondrial structure and function have been associated with the development of BD. In that regard, cells from individuals with BD demonstrate distinct abnormalities in mitochondrial structure (Cataldo et al. 2010). Moreover, some reports have indicated that patients with various mitochondrial diseases demonstrate up to a 20-fold higher incidence of BD than the general population (Goodwin and Jamison 2007). Accumulated deletions in

mitochondrial DNA (ΔmtDNA) of transgenic mice have been shown to result in recurrent, spontaneous depression-like episodes which are both prevented SSRI therapy and worsened by lithium withdrawal (Kato 2017). Postmortem analysis of brain tissue from BD patients also demonstrates increased rates of ΔmtDNA (Kato et al. 1997; Sequeira et al. 2012).

Mitochondria regulate energy production in the cell, and their dysfunction can result in neuronal damage via multiple pathways: oxidative damage, decreased ATP production, abnormal calcium sequestration, and apoptosis via activation of caspase proteases. During times of cellular stress and increased energy demand, ATP production through the anaerobic pathway is upregulated. This results in an increased buffering burden for neuronal lactate, forming more lactic acid and decreasing intracellular pH. This process also enhances the production of various reactive oxygen species, which can lead to further free-radical damage. Due to its relatively higher energy demand and limited buffering capacity, the brain is far more susceptible to this paradigm than other body systems. In line with this theory, there have been several magnetic resonance spectroscopy (MRS) studies in BD patients showing increased neuronal lactate and decreased pH levels.

Furthermore, patients with BD in a current major depressive episode have shown a significant decrease in cingulate cortex lactate after being treated with a 6-week course of lithium monotherapy (Machado-Vieira et al. 2017b; Clay et al. 2011; Dager et al. 2004). Another indication of mitochondrial dysfunction is the decreased levels of N-acetyl-aspartate (NAA) seen in BD patients compared to normal controls (Kubo et al. 2017). NAA is produced in the mitochondria and is one of the most abundant brain metabolites, also serving as an important marker of neuronal viability (Rosso et al. 2017). In a clinical trial assessing NAA levels using MRS, BD patients were shown to have significantly lower NAA levels than controls. Furthermore, they had significant NAA increases after treatment with a 12-week course of lamotrigine (Croarkin et al. 2015). In addition to mitochondrial dysfunction, elevations of peripheral markers of oxidative stress have been described in BD patients, which correlate with a longer duration and earlier onset of illness (Machado-Vieira et al. 2007; Brown et al. 2014). De Sousa et al. have further demonstrated that a reactive increase in antioxidant enzymes occurs early in the developmental course of BD, especially during depressive phases. Additionally, BD patients have been shown to exhibit a decrease in lipid peroxidation following lithium treatment (de Sousa et al. 2014). Thus, oxidative damage appears to play a significant inciting role in the development of BD, subsequently interfering with endogenous repair mechanisms if left untreated.

Within the mitochondria itself, the electron transport chain (ETC) serves as a major mediator of oxidation/reduction and overall mitochondrial function. Postmortem analysis of cerebral tissue in patients with bipolar disorder demonstrates a decrease in ETC complex I concentration (Andreazza et al. 2010). Furthermore, lithium has been shown to increase mitochondrial complex I activity in BD patients significantly, and post-treatment complex I activity positively correlates with plasma lithium levels (de Sousa et al. 2015a, b). This strongly suggests that beyond its acute

therapeutic mechanisms (discussed elsewhere), lithium provides a long-term, neuroprotective benefit to patients by reducing overall oxidative damage to neurons.

Converging lines of this hypothesis have proffered several substances as mitochondrial activity modulators: omega-3 fatty acids, coenzyme Q10, acetyl-L-carnitine, N-acetylcysteine (NAC), S-adenosylmethionine (SAM), alpha-lipoic acid, creatine monohydrate, melatonin, L-tryptophan, magnesium, folic acid, and branched-chain amino acids (BCAAs) (Nierenberg et al. 2013; Sarris et al. 2011). Overall, NAC has demonstrated the largest effect size in treating bipolar depression. Mixed, but mostly positive, evidence also supports the use of omega-3 fatty acids. Significant reductions in mania have also been demonstrated with the use of L-tryptophan, magnesium, folic acid, and BCAAs (Sarris et al. 2011). While some of these compounds may demonstrate efficacy as monotherapies, ultimately, this class may prove most effective as augmentation therapy for conventional BD treatments (Sarris et al. 2009; Mischoulon 2009). Larger, more-robust clinical trials are needed before their use becomes commonplace.

3 Calcium Channel Modulators

Ca2+ signaling is a tightly regulated process that plays an important role in a variety of cellular processes, including neuronal excitability, neurotransmitter synthesis/release, synaptogenesis, and plasticity. Even small perturbations in the balance between intracellular and extracellular calcium can trigger cell-death programs which are unresponsive to molecular rescue. Two cellular organelles, mitochondria and endoplasmic reticula (ER), are critical in maintaining a delicate balance of intracellular Ca2+ concentrations through sequestration, buffering, and mobilization. As previously discussed, increasing evidence suggests that mitochondrial function plays a key role in governing the synaptic properties of neuronal circuits that govern complex human behaviors. Mitochondrial dysfunction has also been implicated in a wide array of neurological and psychiatric disorders (Kato 2017).

In 1922, Weston and Howard observed that individuals with mania had lower spinal fluid concentrations of Ca2+ compared to depressed individuals (Weston 1922). This realization was subsequently obscured by decades of controversial findings regarding Ca2+ homeostasis in BD. However, more recent studies have revived this hypothesis by demonstrating that, compared to healthy controls, BD patients have elevated Ca2+ levels in platelets and lymphocytes, in addition to increased Ca2+ ATPase activity in red blood cells (Dubovsky et al. 1992; Warsh et al. 2004). As mitochondrial structure plays a significant role in Ca2+ homeostasis, these findings are in accordance with an ion-imbalance hypothesis in BD (Clay et al. 2011).

Various lines of pharmacologic evidence also support the relationship between calcium signaling and mood disorders. In animal and human models, lithium has been shown to significantly reduce NMDA receptor-stimulated Ca2+ responses (Nonaka et al. 1998). Moreover, both lithium and valproate are potent enhancers

of Bcl-2 expression (Chen and Chuang 1999). The Bcl-2 family of proteins promote neuronal survival in part by inhibiting Ca2+ release from the ER (Rong and Distelhorst 2008). SNPs of the Bcl-2 gene, which are associated with developing BD, are also associated with elevated basal calcium levels and increased cytosolic Ca2+ release (Machado-Vieira et al. 2011). This alteration in membrane excitability may disrupt several neural components responsible for controlling mood and behavior.

Additionally, through separate pathways, lithium and valproate both cause depletion of inositol, a key calcium signaling intermediary. Lithium inhibits inositol monophosphatase (IMPase) involved in phosphatidylinositol 4,5-biphosphate (PIP2) turnover, which in turn reduces calcium entry into the cell and thus overall neuronal excitability. This may partially explain the efficacy of lithium in correcting neurotransmission, which has been shown to be altered in BD (Berridge 2014). Furthermore, inositol depletion has been shown to increase synapse formation between hippocampal neurons in vitro (Kim and Thayer 2009). Thus, modulation of calcium signaling appears to have multiple benefits, acutely stabilizing neurotransmission as well as the long-term potentiation of synaptogenesis.

As follows, researchers have investigated various calcium channel antagonists (CCAs) as possible therapeutic targets for BD. Studies indicate that only slow-gated L-type channels (LTCCs) are sensitive to CCAs in neurons. In that regard, three antihypertensive medications with LTCC activity, verapamil, nimodipine, and diltiazem were initially tested, with mixed results. Verapamil was first to be compared to lithium and placebo to treat mania. Both compounds had similar anti-manic effects, which were superior to placebo (Giannini et al. 1984). Despite this initial promise, recent reviews have shown inconsistent findings. Janicak et al. (1998) found no benefit over placebo in treating mania (Janicak et al. 1998). Keck et al. (2000) found both positive and negative results, suggesting the need for further investigation (Keck et al. 2000). Giannini et al. (2000) found that verapamil combined with magnesium oxide was superior to verapamil monotherapy (Giannini et al. 2000). More recently, verapamil was compared to lithium in a double-blind continuation study for acute mania. Individuals unresponsive to lithium (phase 1) were randomized to either continue lithium or switch to verapamil (phase 2). Non-responders in phase 2 were further allocated to verapamil-lithium combination treatment (phase 3). Authors found some efficacy for verapamil as monotherapy, but no significant difference compared to lithium and no superiority in combination (Mallinger et al. 2008).

In 1998, Pazzaglia et al. conducted a double-blind placebo-controlled study investigating the efficacy of nimodipine in 30 patients with refractory affective disorders (23 with bipolar and 7 with unipolar depression). One-third of the patients showed a significant response to nimodipine monotherapy. Non-responders ($n = 14$) added carbamazepine, with roughly another third achieving remission. Authors further noted that individuals with rapid-cycling BD were more apt to respond to the carbamazepine-nimodipine combination therapy (Pazzaglia et al. 1998). Subsequent studies were conducted around this time, most with modest results, and some evidence suggesting that low baseline CSF somatostatin may predict response to nimodipine (Frye et al. 2003).

Lastly, investigators have attempted to demonstrate the efficacy of diltiazem as add-on therapy in BD. In 2000, researchers conducted an open-label study with eight women in either a manic or depressive episode, generating promising findings. In comparing the 6 months before and after starting the add-on therapy, they observed a significant improvement in manic/depressive symptoms (Silverstone and Birkett 2000). However, several studies have reported that verapamil and diltiazem may enhance lithium excretion, increase carbamazepine levels, and create a synergistic, neurotoxic effect with either mood stabilizer (Brodie and MacPhee 1986; Bahls et al. 1991; Price and James Giannini 1986).

Despite a lack of definitive clinical outcomes and potential adverse side effects, recent preclinical research has reinforced the importance of aberrant calcium signaling in BD (Harrison 2016; Heyes et al. 2015). Specifically, genomic data shows that several LTCC-subunit-encoding genes, especially the CACNA1C locus, are associated with BD, schizophrenia, and MDD (Craddock and Sklar 2013). Additionally, neuron-like cells derived from BD patients show increased CACNA1C gene expression and enhanced calcium signaling (Yoshimizu et al. 2015). Mertens et al. further found that induced stem-cell-derived (iPSC) hippocampal neurons from patients with BD display a characteristic, hyperexcitable phenotype in relation to calcium signaling. Importantly, this phenotype was selectively reversed by lithium in vitro, only in neurons derived from patients that responded to lithium clinically (Mertens et al. 2015).

In summary, despite contradictory findings in the early twentieth century, more recent preclinical evidence has strongly implicated alterations in mitochondrial function and calcium signaling in the pathogenesis of BD. Elevated endogenous calcium concentrations in bipolar patients and reductions calcium hyperexcitability caused by lithium clearly demonstrate promise for this line of investigation. Building on this hypothesis, conventional CCAs (verapamil, diltiazem, nimodipine) demonstrated some initial promise. However, subsequent, more-rigorously designed studies failed to replicate these findings, in addition to revealing several adverse side effects. Despite this obstacle, the large quantity of in vitro evidence underscores a need for further proof-of-concept trials, potentially involving other CCAs. Given the wide distribution of LTCCs throughout the body, future clinical interventions should focus on developing more-targeted and genome-directed compounds with greater blood-brain barrier penetration and higher specificity for CNS-LTCC ligands. Most importantly, genomic evidence strongly suggests that future patients should be selectively enrolled in trails based on genetic and phenotypic amenability to such therapies.

4 Intracellular Signaling and Inflammation

Numerous studies support the role of the immune dysfunction in the development of BD (Rosenblat and McIntyre 2015; Munkholm et al. 2013; Goldstein et al. 2009; Leboyer et al. 2012). Bipolar disorder has been implicated in increased rates (1.5–3

times) of premature death due to medical comorbidities, higher prevalence of metabolic syndrome, and greater cardiovascular mortality than that in the adult general population (Leboyer et al. 2012). Furthermore, there is evidence that patients with BD have a reduced life expectancy (9–14 years) and exhibit shortened telomeres compared to the general population (Rizzo et al. 2013; Chang et al. 2015). BD has also been associated with numerous other immunological conditions: systemic lupus erythematosus, autoimmune thyroiditis, psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and others (Rosenblat and McIntyre 2015). Though causality in this regard has yet to be established, recent research indicates that the relationship is likely bidirectional (Perugi et al. 2014).

These associations are reinforced by several cross-sectional studies which have demonstrated that, compared to healthy controls, patients with BD have significant elevations in proinflammatory cytokines such as TNF-α, IL-1β, IL-4, IL-6, and others. These studies have even suggested a state-dependent association with various inflammatory markers. For example, during manic episodes, BD patients demonstrate increased expression of TNF-α, IL-4, IL-6, CXCL10, and other inflammatory molecules (Barbosa et al. 2014; Modabbernia et al. 2013). Many of these markers have not yet been robustly investigated in bipolar depression; however evidence from MDD patients suggests that similar cytokine alterations also occur during depressive episodes (Rosenblat et al. 2014; Felger and Lotrich 2013). A recent meta-analysis of 32 inflammation studies found TNF-α to be the only biomarker elevated in both mania and bipolar depression (Rowland et al. 2018). Though further longitudinal research is necessary to fully validate a causal link in this regard, mounting evidence suggests that BD patients experience a chronic, low-grade inflammatory state which may be enhanced during acute mood episodes (Rosenblat et al. 2014; Fillman et al. 2014).

It is important to note that the majority of the aforementioned studies measure peripheral cytokine levels. While the direct observation of CNS inflammation may be more desirable, doing so is typically a highly invasive and cost-prohibitive endeavor. As with most neuroinflammatory conditions, altered blood-brain barrier (BBB) permeability allows for the bidirectional passage of peripheral and central immune mediators. Additionally, recent paradigm-shifting animal research has demonstrated a contiguous link between systemic lymphatic drainage and dural sinus vasculature, further allowing for the amalgamation of CNS and systemic immune constituents (Louveau et al. 2015). As follows, numerous BD studies have demonstrated a correlation between peripheral and central cytokine expression (Munkholm et al. 2013; Barbosa et al. 2014).

Several mechanisms have been proposed as to the specific, deleterious effects of inflammation in mood disorders. Under normal conditions, CNS macrophages (microglia) play several vital roles: immune surveillance, scavenging unwanted cellular products, and pruning of underutilized synaptic pathways. However, in states of elevated inflammation, microglia disproportionately adopt a proinflammatory phenotype leading to unwanted pruning, increased BBB permeability, and resultant influx of peripheral immune cells (Stertz et al. 2013). Evidence for this mechanism is supported by both PET imaging and postmortem tissue

analysis, demonstrating increased microglial activity in the hippocampus and prefrontal cortex of BD patients (Haarman et al. 2014a, b; Rao et al. 2010). Proinflammatory cytokines have also been shown to alter the concentration of monoamines, for example, by decreasing the conversion of tryptophan to serotonin, accelerating serotonin breakdown, and increasing levels of depressogenic tryptophan metabolites (Capuron et al. 2003; Zhang et al. 2001). This process has been shown to be mediated in part by HPA axis over-activation and resultant hypercortisolemia (Maes et al. 2011). A detailed explanation of the HPA axis and cortisol overproduction in BD is discussed elsewhere in this chapter. In short, cortisol upregulates hepatic tryptophan 2,3-dioxygenase activity, causing unwanted monoamine catabolism. Additionally, proinflammatory cytokines interfere with hypothalamic glucocorticoid receptor function, disrupting normal feedback inhibition on cortisol production (Pace and Miller 2009).

With regard to systemic inflammation, significant attention has recently been directed towards elucidating a connection between the enteric nervous system (ENS) and the CNS, otherwise known as the "gut-brain axis." Numerous in vitro and animal studies have suggested that the mucosal microbiome may exert substantial influence on behavior and cognition via alterations in immune function and neurotransmitter metabolism. Though microbiome research in psychiatry is in its relative infancy, there has been a long-standing association between various gastrointestinal pathologies and psychiatric disorders (Severance et al. 2015; Lee et al. 2015). Recent research suggests that an imbalance in gut microflora (dysbiosis) may cause luminal inflammation which facilitates microbial translocation into systemic circulation (Dickerson et al. 2017).

Recently, researchers have developed antibodies to diagnose Crohn's disease, which detect the presence of normal gut microbes in systemic circulation (Desplat-Jego et al. 2007). Elevated antibody production against one such yeast (*Saccharomyces cerevisiae)* has been detected in patients with both schizophrenia and BD. Importantly, titers were significantly higher in individuals experiencing recent-onset of their disorder and those who were antipsychotic-naïve, suggesting an inciting mechanism that cannot be solely attributed to medication usage (Severance et al. 2012, 2014). Dickerson et al. have conducted several longitudinal observation studies which demonstrated that, compared to healthy controls, BD patients in acute manic episodes have increased production of antibodies directed against gliadin (a marker of gluten sensitivity), NR2 (an NMDA receptor peptide), Mason-Pfizer monkey virus 24, and *Toxoplasma gondii*. These findings appeared to be state-dependent, as titers did not differ from controls at 6-month follow-up.

Furthermore, elevated inflammation scores during initial manic episodes were predictive of psychiatric re-hospitalization during the follow-up period (Dickerson et al. 2012a, b, 2013). Though initial findings are intriguing, more research is needed to delineate specific microbial-inflammatory mechanisms. We must also assess the influence of confounding variables such as environment, medication usage, and smoking. Furthermore, there is a relative paucity of evidence regarding the interplay between gut dysbiosis and neurotransmitter-mediated, retrograde communication between the ENS and CNS. In that regard, more information is needed to bolster

therapeutic efforts, as initial studies with general probiotics have yet to yield impactful results (Dickerson et al. 2017).

Current knowledge gaps notwithstanding, specifically targeting immune dysfunction in BD, is highly desirable, especially given that doing so can potentially ameliorate numerous associated comorbidities. Emerging evidence suggests that some antipsychotics and lithium downregulate the expression of inflammatory genes in the cells of BD patients (Haarman et al. 2014a, b). However, the exact mechanism by which these agents exert their anti-inflammatory effects is unknown. As previously mentioned, the anti-inflammatory/antioxidant compound N-acetylcysteine (NAC) has shown significant promise as an adjunct treatment in BD. Multiple DBRPCTs have demonstrated significant reductions in depressive symptoms compared to placebo in bipolar patients (Berk et al. 2008, 2012). A small number of trials have also investigated the efficacy of the anti-inflammatory agents like celecoxib (Arabzadeh et al. 2015) and aspirin (Berk et al. 2013) as adjunctive treatment in BD, with mixed results. Specifically, Arabzadeh et al. found celecoxib 400 mg to be superior to placebo as adjunctive therapy to sodium valproate in treating bipolar mania without psychotic features.

Pioglitazone is a peroxisome proliferator-activated receptor-gamma agonist with well-established, potent anti-inflammatory and anti-hyperglycemic properties. In a 2015 double-blind RCT of BD patients in a current major depressive episode (MDE), Zeinoddini et al. found that pioglitazone caused significant reductions in depressive symptoms after 6 weeks (Zeinoddini et al. 2015). Further research has shown it to be particularly effective in reducing depressive symptoms when used as an adjunct therapy in BD patients with comorbid metabolic dysfunction (Kemp et al. 2014). Importantly, in this study, elevated baseline levels of the proinflammatory cytokine IL-6 correlated with greater reductions in depression severity. Likewise, a recent 12-week, randomized, double-blind, placebo-controlled, parallel-group trial of 60 participants investigated the use of adjunctive infliximab in the treatment of adults with bipolar I/II depression. Despite being a negative trial overall infliximab significantly reduced depressive symptoms compared to placebo in patients with baseline elevations in serum CRP and TNF-α.

Preclinical evidence supports an intricate association between immune function, the microbiome, BD, and many of its comorbid conditions. Immune cells and inflammatory signaling molecules have been shown to produce local damage, prevent repair, and affect downstream neurotransmitter metabolism through a myriad of interconnected pathways. Beyond demonstrating therapeutic potential, several trials of anti-inflammatory compounds have importantly shown enhanced efficacy in patients with elevated levels of pre-treatment inflammation. This underscores the significant need for further investigation in this area, both in developing targeted therapies and screening/selecting patients based on their inflammatory profile. Numerous immune modulators have been approved for various systemic conditions over the last two decades, only a handful of which have been evaluated in the treatment of psychiatric disorders. Thus, given the ability to bypass significant startup costs and regulatory obstacles inherent to developing novel agents, it

would seem prudent going forward to dedicate more resources towards clinical trials which investigate the efficacy of approved but untested medications in this class.

5 Glycogen Synthase Kinase 3-Beta (GSK3β)

Several lines of investigation have implicated the enzyme GSK3β in the parthenogenesis of BD. In 1996, GSK3β was discovered to be a target of lithium, specifically mediated by a magnesium-competitive inhibition mechanism (Klein and Melton 1996). Since that time, researchers have uncovered nearly 50 substrates of GSK3β that are key modulators in several processes related to neuronal function. The most prominent group of these compounds are known as Wnt molecules. Throughout early development and adult life, Wnt ligands mediate cell patterning, differentiation, proliferation, neuronal morphology, and cellular-integration into established neuronal circuits. The Wnt pathway facilitates these processes by first inhibiting the constituently active GSK3β enzyme, leading to the nuclear translocation of β-catenin and subsequent activation of several enhancers/transcription factors involved in neurotrophic generation (BDNF), circadian regulation, and inflammatory modulation (Valvezan and Klein 2012). Indeed, GSK3β overactivity has been linked to dysfunction in all of these domains, causing decreased BDNF production (Machado-Vieira et al. 2009), prevention of medication-mediated mood-stabilization and neurogenesis (Hussaini et al. 2014), increased expression of pro-inflammatory cytokines such as IL-6 and TNF-α (Ajmone-Cat et al. 2016), and lengthening of the circadian rhythm (McCarthy et al. 2013).

Various lines of animal and human evidence further support the role of aberrant Wnt/GSK3β activity in BD. Transgenic mice that over-express GSK3β develop hyperactive symptoms akin to human mania, whereas haplo-insufficient mice ($GSK3^{+/-}$) with decreased GSK3β activity exhibit features that replicate chronic lithium treatment. Moreover, induced GSK3β overexpression in mice nullifies the effect of chronic lithium treatment. Importantly, lithium is a well-validated GSK3β inhibitor (Cole 2013).

Patients with BD exhibit decreased levels of β-catenin mRNA and protein in the dorsolateral-prefrontal and temporal regions compared to those with schizophrenia and healthy controls (Pandey et al. 2015). Moreover, several SNPs within the promoter region for GSK3β are associated with an earlier age of onset and sensitivity to lithium therapy (Cole 2013).

Researchers have also demonstrated decreased GSK3β inhibition in the peripheral blood mononuclear cells (PBMCs) of bipolar individuals. Notably, in this small cohort study, a lower magnitude of GSK3β inhibition significantly correlated with the severity of manic/depressive episodes (Polter et al. 2010). More recent evidence has bolstered these findings by demonstrating that treatment with lithium causes an increase in PBMC-GSK3β inhibition, which also correlates with symptomatic improvement (de Sousa et al. 2015a, b).

Apart from lithium, other psychoactive compounds with efficacy in BD also demonstrate GSK3β pathway activity. Conflicting evidence exists regarding the GSK3 activity of anticonvulsant mood stabilizers such as valproic acid and carbamazepine (Muneer 2017). However, second-generation antipsychotics (SGAs), which are becoming increasingly important in the treatment of all phases of BD, have well-documented GSK3β inhibitory properties (Kalinichev and Dawson 2011; Pandey et al. 2015). Biased agonists such as aripiprazole have also been shown to increase the transcription of Wnt-related genes in the β-catenin pathway (de Bartolomeis et al. 2015). Lastly, conventional antidepressants have been shown to interact with several Wnt/GSK3 cellular cascades. GSK3β-mediated alterations in neuronal plasticity occur at the level of genetic transcription and are thus expected to take weeks before subjective improvement in symptoms occurs. This timeline thus concurs with the natural treatment course of SSRI therapies (Pilar-Cúellar et al. 2014).

Given the pervasive involvement of this pathway in a wide range of psychiatric disorders and medication classes, GSK3β inhibition stands as an attractive, albeit illusive therapeutic target. Over the past two decades, AstraZeneca has been at the forefront of GSK3β inhibitor development, with six novel candidates, only one of which progressed to phase II trials. Due to concerns over toxicity, safety margins, as well as various other issues, progress in this area has been slow (Bhat et al. 2018). Building on these efforts, Bhat et al. note that future GSK3 drug development should focus on increasing kinase selectivity as well as using novel conjugated-peptide technology to enhance tissue specificity.

6 Protein Kinase C (PKC) and Diacylglycerol (DAG)

Protein kinase C (PKC) is a family of calcium and phospholipid-dependent enzymes implicated in mood regulation. More specifically, PKC in the brain is present in high levels at presynaptic terminals and thought to play a role in the regulation of neuronal excitability, neurotransmitter release, and neuroplasticity (Zarate and Manji 2009). Conventional PKC (cPKC) isoforms (α, βI, βII, γ) require calcium and diacylglycerol (DAG) for activation, while novel PKC isoforms (δ, ε, η, θ, μ) only require DAG for activation (Zarate and Manji 2009). In CNS, cPKC isoforms are the most common and are highly expressed in several structures classically associated with mood regulation (prefrontal cortex, amygdala, and hippocampus) (Naik et al. 2000). This family of enzymes modulate neuronal transmission at several levels: short term (neurotransmitter/ion flux), intermediate (receptor regulation), and long term (synaptic remodeling, cell proliferation, genetic expression) (Amadio et al. 2006). PKC signaling underlies many of the pathologic mechanisms discussed throughout this chapter: neuronal excitability (Pahl et al. 2014), neurotransmitter release (Zarate et al. 2006), glutamate signaling (Zarate et al. 2003), neuroinflammation (Jun et al. 2014), neuroplasticity (Chu et al. 2014), and

mitochondrial dysfunction, especially as it pertains oxidative stress and apoptosis (Nam et al. 2015).

Multiple lines of animal and human evidence support the pervasive involvement of this family of enzymes in BD. PKC inhibition reduces manic-like behaviors and hippocampal cell degeneration in rat sleep deprivation mania models (Abrial et al. 2013). Compared to healthy controls, BD patients demonstrate increased levels of both central (cortical) and peripheral (platelet) PKC activity (Wang and Friedman 1996; Wang et al. 1999). Lastly, a meta-analysis of 8,700 patients with both unipolar and bipolar depression found that suicidality was significantly associated with the genetic locus for PKCε (Saxena et al. 2017).

In that regard, chronic lithium treatment has been shown to decrease PKC levels in platelets of BD patients (Soares et al. 2000). Both lithium and valproic acid inhibit PKC activity in vitro and in vivo (Zarate and Manji 2009; Chen et al. 1994, 2000). Chronic administration of quercetin, a non-specific PKC inhibitor, prevents methylphenidate-induced hyperlocomotion and lipid peroxidation in mice (Kanazawa et al. 2017). Tamoxifen, another potent PKC inhibitor, has demonstrated efficacy in acute manic or mixed episodes of BD as both adjunct and monotherapy (Talaei et al. 2016; Yildiz et al. 2016, 2008; Amrollahi et al. 2011).

7 Neurotrophins

Neurotrophins are cellular growth factors involved in synaptic plasticity, neurogenesis, cell survival, and long-term memory formation (Grande et al. 2010). Within the neurotrophin family, brain-derived neurotrophic factor (BDNF) is the most extensively studied in BD (Fernandes et al. 2011; Rowland et al. 2018). Data from six meta-analyses have consistently demonstrated that BD patients have significantly lower levels of plasma BDNF compared to healthy controls, as do individuals with schizophrenia and unipolar depression (Rowland et al. 2018; Fernandes et al. 2015; Molendijk et al. 2014). Furthermore, BD patients in current manic or depressive episodes both demonstrate reductions in peripheral BDNF levels, unlike their euthymic counterparts (Fernandes et al. 2015; Rowland et al. 2018). The effect size is particularly large in bipolar depression (SMD − 0.86) and moderate in mania (SMD – 0.54) (Rowland et al. 2018).

BDNF plays a significant role in both GSK3β/Wnt and PKC activity (discussed in more detail in their respective sections). Briefly, BDNF transcription can be increased by various GSK3β inhibitors (including lithium) and through GSK3 gene silencing. Moreover, BDNF itself can inhibit GSK3β activity (Machado-Vieira et al. 2009). BDNF also mediates some of the genetic expression associated with synaptic plasticity via PKC signaling (Arevalo and Wu 2006). Beyond acting as a second messenger, PKC itself can also influence the expression of BDNF and other neurotrophins (Xu et al. 2013, 2015). The reciprocity and interdependence involved in both of these pathways underscores the pervasive and complex role that neurotrophins play in modulating a wide array of neuronal signaling mechanisms.

Some studies have suggested an association between polymorphisms in BDNF promoter genes and vulnerability for developing BD (D'Addario et al. 2012). Using a systems model of the human prefrontal transcriptional network, researchers have highlighted the importance of the early growth response gene 3 (EGR3) gene, which was previously shown to be modulated by BDNF (Pfaffenseller et al. 2016). A current proposal suggests a positive feedback loop wherein BDNF signaling dysfunction leads to reduced EGR3 expression, thus impairing neuroplasticity and resilience, increasing the vulnerability to stress, and further lowering BDNF expression (Pfaffenseller et al. 2018). Moreover, using a multisystem analysis of BDNF genes and other loci, researchers were able to identify bipolar patients with a sensitivity of 73% and a specificity of 71% (Munkholm et al. 2019). Building on this success, recent findings indicate that measuring BDNF in conjunction with TNF-α may provide even greater fidelity in distinguishing manic/depressed individuals from euthymic patients (Rowland et al. 2018). All of these studies suggest that BD pathogenesis is highly connected to many BDNF-related pathways. As with the "triple test" in Down syndrome and diagnostic tests for thyroid-related illnesses, BDNF measurements may be of greatest use when combined with other known biomarkers in BD. Given its pervasive influence on neuronal activity, BDNF may also have great potential as future therapeutic target.

Currently, no pharmacological agent used in BD directly targets the neurotrophins; however, antidepressants, lithium, electroconvulsive therapy (ECT), and glutamatergic agents like ketamine and memantine all increase peripheral levels of BDNF in patients with major depressive disorder (MDD) (Molendijk et al. 2014; Duncan and Zarate 2013; Haile et al. 2014; Lu et al. 2012). The pervasive, reciprocal interactions of neurotrophins with many other pathways present significant confounding obstacles for investigators. For now, BDNF may be of greatest utility as biomarker for disease severity and treatment response.

8 Glutamatergic System

Alterations in the glutamatergic system have been extensively implicated in the pathophysiology of BD. Likewise, the glutamate-modulating capability of conventional BD treatments such as lithium, valproate, lamotrigine, and antidepressants is well-documented (Machado-Vieira et al. 2012). Glutamate is the most abundant excitatory neurotransmitter in the brain. It acts in three different cellular compartments – pre/postsynaptic neurons and glia – characterized as the "tripartite glutamatergic synapse."

Particularly through its action at ionotropic AMPA and NMDA receptors, glutamatergic signaling plays a crucial role in excitatory neurotransmission, synaptic function, neuroplasticity, and neurogenesis. Indeed, AMPA (GluA1 subunit) knockout mice provide a successful model for depression, and NMDA receptor antagonists have repeatedly demonstrated antidepressant efficacy (Papp and Moryl 1994; Chourbaji et al. 2008). Interestingly, Du et al. (2010) showed that the GSK3 inhibitor

AR-A014418 regulates AMPA-induced GluR1 and GluR2 internalization via phosphorylation of kinesin light chain 2 (KLC2), the key molecule of the kinesin cargo delivery system (Du et al. 2010). As previously discussed, neurotrophins modulate the activity of GSK3 (Bartzokis 2012). Thus, glutamate seemingly acts as a molecular intermediary between many of the signaling pathways discussed throughout this chapter.

Candidate gene and genome-wide association studies (GWAS) have also implicated glutamate signaling in BD pathophysiology, albeit with some conflicting results. In a recent systematic review, de Sousa et al. found a positive association between BD and glutamate-related genes in 12 of 34 (35%) studies (Nurnberger et al. 2014; de Sousa et al. 2017). Overall, these genetic findings warrant deeper investigation, especially for the glutamatergic genes which have repeatedly demonstrated associations with BD (*GRIA3*, *GRIK2*, *GRIK4*, and *GRM7*). Moreover, researchers have demonstrated alterations in mRNA expression as well as induction of depressive-like behaviors in genetically altered animal models, further implicating these candidate genes in the disease process (Beneyto et al. 2007; Catches et al. 2012; Cryan et al. 2003; Duric et al. 2013).

Separate genetic analysis has also uncovered a significant association between BD and the glia-astrocyte pathway (Duncan et al. 2014). In addition to being the primary mediators of neuroinflammation, glial cells are integral to the glutamate recycling process. In that regard, investigation into glutamate/glial modulators has substantially increased in recent years. Ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, has been placed in the spotlight due to its rapid antidepressant action in both unipolar and bipolar depression (Sanacora et al. 2017). While previous data did not demonstrate effective remission rates in bipolar depression (McCloud et al. 2016), a more recent double-blind, randomized placebo-control study phase 1 trial found that repeated ketamine infusions were effective in treating bipolar depression (Chen et al. 2019). Research suggests that ketamine's NMDA receptor antagonism increases BDNF-mediated synaptic protein synthesis via downstream glutamate-stimulation of AMPA receptors (Duman et al. 2012). Ketamine has also demonstrated a significant degree of interaction with glia-astrocyte-mediated inflammatory signaling (Miller 2013). Thus, beyond its therapeutic efficacy, ketamine potentially represents a paradigm-shifting convergence of the inflammatory and glutamate hypotheses of depression.

Approved by the FDA for the treatment of amyotrophic lateral sclerosis, riluzole (2-amino-6-trifluoromethoxy benzothiazole), is a glutamatergic modulator with both neuroprotective and anticonvulsant properties. Riluzole inhibits voltage-dependent sodium channels in neurons with subsequent inhibition of glutamate release, enhancing AMPA trafficking and membrane insertion of GluR1 and GluR2 and also increasing glutamate reuptake (Bellingham 2011). While early studies showed promise of riluzole in bipolar depression (Machado-Vieira et al. 2012), a more recent double-blind, placebo-controlled trial failed to show efficacy (Park et al. 2017). Another NMDA agent, memantine, is approved for dementia; it acts as a low-affinity NMDA receptor antagonist (Rammes et al. 2008). Like riluzole, initial clinical trials and case reports generated relatively positive results as an add-on to

mood stabilizers in both mania (Koukopoulos et al. 2010; Serra et al. 2013) and bipolar depression (Stevens et al. 2013). However, a recent meta-analysis of randomized, double-blind controlled trials failed to demonstrate efficacy (Zheng et al. 2019). Especially given recent findings in relation to NMDA signaling, targeted modulation of glutamate neurotransmission will likely be an area of great clinical potential in the near future.

9 Dopaminergic System

Dopaminergic neurotransmission and its dysregulation in the development of BD are shown at different levels of evidence: behavioral, biomarker, and pharmacological proof-of-concept studies. Increasing dopamine activity is known to produce mania-like clinical presentations (Cousins et al. 2009). Specifically, amphetamine inhibits dopamine transporter-mediated reuptake and increases dopamine synaptic stimulation in the striatum, nucleus accumbens, and the frontal cortex. Predictably, it induces mood elevation, goal-directed activities, and motor hyperactivity and decreases the need for sleep. Likewise, L-dopa, a dopamine precursor, can induce manic or hypomanic states when used as a treatment for Parkinson's disease (PD). Homovanillic acid (HVA), a metabolite of dopamine, is decreased in the CSF of untreated individuals with bipolar depression. Conversely, treated and manic subjects have normal or increased HVA (Zarate et al. 2004). A recent meta-analysis of 26 studies supports this claim that decreased HVA is found in those with depressive disorders (Ogawa et al. 2018).

Measurements of in vivo availability of dopamine receptor binding using single-photon emission computed tomography (SPECT) radiotracer [^{123}I] iodobenzamide (IBZM) have generated mixed results. One study demonstrated reduced D_1 receptor binding potentials in the frontal cortex when compared to healthy controls, while D_2 receptor density was normal in all phases of non-psychotic BD individuals (Gonul et al. 2009). Using SPECT radiotracer [^{99m}Tc], a different study found increased dopamine transporter (DAT) availability in euthymic bipolar patients when compared to healthy subjects (Chang et al. 2010). Furthermore, another study used positron emission tomography (PET) and found that unmedicated BD subjects had significantly lower DAT availability and possibly higher dopamine concentrations in the dorsal caudate (Anand et al. 2011). In contrast, a different study found greater DAT density in unipolar and bipolar depressed vs non-depressed subjects (Amsterdam et al. 2012). More studies are needed to elucidate the role of dopamine receptor binding in mania and depression.

As increasing evidence reinforces the role of dopamine in BD pathophysiology, prescriptions of atypical antipsychotics are increasing. One cohort of 343 patients with bipolar depression who received olanzapine monotherapy significantly improved from their symptoms when compared to 171 bipolar depression patients receiving placebo in a randomized, double-blind placebo-controlled trial (Tohen et al. 2012). A separate randomized, double-blind placebo-controlled trial of

802 subjects with acute bipolar depression, which compared two dosages of quetiapine with lithium and placebo, found quetiapine more effective than both (Young et al. 2010). Recently, another randomized, double-blind placebo-controlled trial found cariprazine, a different atypical antipsychotic, to be effective, well-tolerated, and safe in depressive symptoms in adults with bipolar I (Earley et al. 2019). One proposed theory is that the atypical antipsychotics have 5-HT_{2A} antagonism and some D_2 receptor antagonism/partial D_2 agonism, which balances the dopamine signaling and leads to anti-manic effects (Kato 2019). This could partially explain the aforementioned mixed findings regarding dopamine receptor activity in BD.

Pramipexole, an aminothiazole derivative D_2/D_3 agonist, approved for use in PD, has been employed in proof-of-concept clinical trials in bipolar depression. Its theoretical utility as an antidepressant is derived in part from its D_3 receptor activity, which modulates several neuronal circuits implicated in depressive states (Zarate et al. 2004). It also increases anti-apoptotic Bcl-2 expression (Inden et al. 2009), suggesting an added neuroprotective benefit (Shaltiel et al. 2007). Previously, a cohort of 23 patients were followed, and 60.9% of patients showed sustained remission of a depressive episode (defined as a $>$ 50% on the Montgomery-Asberg Depression Rating Scale score) (Cassano et al. 2004). Using similar criteria, a subsequent meta-analysis showed that pramipexole had a response rate of 52.5%, a long-term response rate of 62.1%, and a long-term remission rate of 39.6% in 504 patients (Tundo et al. 2019). Randomized clinical trials have also demonstrated superiority compared to placebo in major depressive episodes (Tundo et al. 2019). While pramipexole showed beneficial as a therapeutic option for depression in BD patients, the authors suggest having an RCT of a higher power to confirm its benefit (Tundo et al. 2019).

10 Neurohormonal System

Circadian abnormalities have been recently associated with BD (Melo et al. 2017). Rhythm disruption can both precipitate and exacerbate mood episodes (Hirata et al. 2007). It is suggested that causality of this phenomenon is bidirectional, with circadian disruptions also being a consequence of affective disorders themselves (Bechtel 2015). Even in the euthymic state, BD patients have more alterations in their sleeping patterns than healthy controls (Ng et al. 2015). Circadian rhythms are regulated primarily by the secretion of melatonin from the suprachiasmatic nucleus (SCN) and subsequent binding to MT1 and MT2 receptors in the posterior hypothalamus. Normally, melatonin secretion reaches its peak during the night and trough during the day. BD patients characteristically show a delayed onset and lower evening peak of melatonin secretion compared to healthy controls (Robillard et al. 2013; Nurnberger et al. 2000). Mutant mice, deficient in the MT1 receptor encoding gene, display behavioral alterations that resemble some symptoms of depression (Comai et al. 2015).

Corticotropin-releasing hormone (CRH), secreted by the hypothalamus, stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then enables the secretion of cortisol by the adrenal glands. Circulating cortisol exerts a negative feedback effect at multiple levels within the hypothalamic-pituitary-adrenal (HPA) axis. In healthy individuals, cortisol displays the opposite circadian pattern to melatonin: peaking early in the morning and lowest at night. In addition to secreting melatonin, the SCN also modulates cortisol secretion and cognitive performance, both of which are altered in mania and depression (Linkowski et al. 1994). Both hypercortisolemia and a flattening of circadian cortisol variation are seen in depressed individuals (Carroll et al. 1976). Elevated cortisol response to dexamethasone suppression and CRH (DEX/CRH test) at the time of discharge from an inpatient treatment is also predictive of relapse in depressed individuals (Zobel et al. 2001). As with depression, newly diagnosed bipolar patients display elevated baseline cortisol (Coello et al. 2019).

Additionally, changes in CRH secretion may have potential as a future biomarker, as they can be detected before the clinically observable onset of manic or hypomanic symptoms (Daban et al. 2005). Previous research indicates that cortisol secretion is elevated in the manic and the depressed phases of bipolar disorder, suggesting that aberrant stress responsiveness plays a role in both phases of the disease (Cervantes et al. 2001). Higher cortisol concentrations have also been demonstrated in both remitted and non-remitted bipolar patients, implying a persistence of HPA axis abnormalities beyond symptomatic control (Watson et al. 2004). Ellenbogen et al. found that offspring of parents with bipolar disorder have elevated cortisol compared to those with no parental history of mental illness (Ellenbogen et al. 2004). The heritability of basal cortisol secretion level is estimated to be 60% (Bartels et al. 2003). Taken together, this implicates hormonal axis dysfunction as a core mechanism underlying the pathogenesis and transmission of BD. Aberrancies precede, are passed on, and may persist beyond a patient's detectable symptomatic course.

In addition to hormone secretion, the glucocorticoid receptor (GR) function plays an intricate role in the pathophysiology of mood disorders. Cortisol diffuses through cellular membranes and binds to both GR and mineralocorticoid (MR) intracellular receptors. The human stress response increases glucocorticoid secretion, preferentially causing MR saturation first. GR binding thus becomes the primary mediator of feedback inhibition on the HPA axis (Pariante et al. 2001). Both glucocorticoids and stress have been shown to impair neurogenesis and promote atrophy of dendritic processes in the hippocampus (Kempermann 2002; McEwen 2005). GR antagonists block the detrimental effects of hypercortisolism and increase the expression of GRs, exerting a more powerful negative feedback effect on the HPA axis.

The extensive involvement of the HPA axis in affective disorders makes this system an attractive target for therapeutic interventions. Tricyclic antidepressants increase glucocorticoid receptor protein binding and capacity in vivo. This effect was also seen in rats when submitted to lithium therapy or electroconvulsive therapy. In humans, elevated diurnal cortisol is dampened with chronic lithium prophylaxis (Colla et al. 2009). Thus, it is suggested that part of the overall therapeutic

mechanism in the treatment of BD may involve a gradual reinstatement of appropriate glucocorticoid receptor function and some degree of HPA axis normalization.

As follows, several other therapeutic interventions have been attempted, targeting various aspects of HPA/circadian homeostasis. Exogenous melatonin has well-documented hypnotic properties and has been shown to improve sleep disturbances in the context of depression (Satyanarayanan et al. 2018). However, administering melatonin on its own to patients fails to display any antidepressant efficacy. Conversely, agomelatine, a MT1 and MT2 agonist but also a 5-HT2c antagonist, displayed clear antidepressant activity in animal models of depression (Thomas et al. 2016). A single dose of agomelatine can restore sleep architecture in severely depressed individuals. The compound also induces a faster symptomatic improvement in depressed patients than the SSRI sertraline (Kasper and Hamon 2009). This finding was bolstered by a subsequent systematic review which concluded that agomelatine is a viable treatment for depression (Fornaro et al. 2010). With regard to bipolar disorder, an open-label study for agomelatine enrolled 21 patients with bipolar I depression. Patients received 25 mg/day for 6–46 weeks, with 81% of subjects showing substantial improvement (>50% improvement in HAM-D scores) (Calabrese et al. 2007).

Researchers have also investigated the efficacy of the GR antagonist mifepristone (RU-486) in proof-of-concept trials. In one double-blind, placebo-controlled crossover study, patients with psychotic depression experienced rapid improvement of their symptoms following 4 days of mifepristone therapy (Belanoff et al. 2001). Authors replicated this result in a larger study which also found that elevated dosages (>600 mg/day) may be the optimal therapeutic range (Belanoff et al. 2002). Young et al. conducted a mifepristone trial (600 mg/day vs placebo) in 20 patients with bipolar depression. Spatial recognition/memory, verbal fluency, and HAM-D rating scores all significantly improved in the intervention group. Notably, improvements in cognition were inversely correlated with baseline cortisol levels, further implicating an anti-glucocorticoid effect as the therapeutic mechanism (Young et al. 2004). Gallagher et al. conducted a placebo-controlled, 7-day mifepristone trial of 19 individuals with bipolar disorder and 20 with schizophrenia. There was a significant elevation in cortisol secretion directly following mifepristone administration. However, at 21 days post-treatment, cortisol levels decreased significantly, falling below baseline level in both treatment subgroups. Conversely, cortisol levels for both bipolar and schizophrenic patients in the placebo group remained unchanged. This reinforces the notion that GR antagonists cause normalization of the HPA axis through long-term, receptor-mediated negative feedback. More recently, Watson et al. conducted a RDBPCT evaluating a 7-day course of mifepristone (600 mg/day) vs placebo as an adjunct therapy in 60 patients with bipolar depression. Though patients experienced no antidepressant efficacy, spatial working memory showed substantial improvement, which was sustained 7 weeks after cessation of treatment. Consistent with previous findings, the magnitude of cortisol response to mifepristone directly correlated with the magnitude of memory improvement (Watson et al. 2012).

Glucocorticoid synthesis inhibitors such as ketoconazole and metyrapone have also shown some antidepressant efficacy in clinical and preclinical models. In a double-blind, randomized, controlled trial for MDD, metyrapone was superior to placebo as add-on therapy to conventional antidepressants and accelerated the onset of symptomatic relief (Jahn et al. 2004). Gallagher et al. evaluated five trials conducted with ketoconazole in either MDD or BD, finding a significant difference in HAM-D scores favoring treatment (Gallagher et al. 2008). However, the risks associated with long-term use of these agents may limit their applicability in mood disorders. Nevertheless, these proof-of-concept studies show promise for more-targeted approaches in the future.

The neurohormonal modulator, liraglutide, a glucagon-like peptide 1(GLP-1) analog, has already shown promise in preclinical models of Alzheimer's disease, Parkinson's disease, and stroke. Weina et al. found that liraglutide successfully decreased behavioral symptoms of depression and anxiety in a corticosterone-induced mouse model of depression. Importantly, these findings were associated with a reduction in ACTH-mediated stress responsiveness. The drug was shown to preserve neuronal plasticity and increase the density of immature neurons in the hippocampus (Weina et al. 2018). Further investigation regarding its clinical efficacy in humans is highly warranted, especially given the strong association between metabolic disease, insulin resistance, and BD.

Non-pharmacologic interventions targeting the neurohormonal/circadian system, including sleep manipulation/deprivation and light therapy, have also been investigated. Total sleep deprivation and partial sleep deprivation during the second half of the night have shown the most antidepressant efficacy (Wirz-Justice et al. 2005). Sleep deprivation, in combination with SSRI, has been proven to accelerate the improvement of depressive symptoms compared to SSRI alone (Benedetti et al. 1997). Light therapy has also shown promise in certain mood disorders, especially seasonal depression. Like sleep deprivation, best results have been demonstrated when used in combination with antidepressants (Lanfumey et al. 2013). Tseng et al. conducted a meta-analysis regarding the use of light therapy and sleep deprivation in patients with bipolar depression. The results of 9 studies, including 489 patients, indicated that adjunct light therapy significantly reduced disease severity in medicated patients (Tseng et al. 2016).

As the primary arbiters of circadian rhythm and stress responses, neurohormones such as cortisol and melatonin play a significant role in the development and transmission of BD. Whether through genetic, epigenetic, or direct signaling mechanisms, circadian and HPA axis dysfunction seems to underlie most mood disorders, making the pathway an attractive target for therapeutic interventions going forward. Successful treatment of BD seems to entail a certain degree of normalization both in GR function and the HPA axis overall. Supporting this hypothesis, therapeutic efficacy, especially in the cognitive domain, is consistently associated with beneficial alterations in cortisol secretion. Currently, however, therapeutic interventions have been mostly limited to proof-of-concept studies and non-pharmacologic modalities, which may not be broadly applicable in real-world clinical settings. Given the

significant association between metabolic syndrome and BD, further investigation of hormonal modulators, particularly those which affect insulin signaling, is warranted.

11 Purinergic System and Mania

In 1921, Kraepelin indirectly implicated the purinergic system in the parthenogenesis of BD by suggesting an association between manic symptoms, hyperuricemia, and gout (Ketter 2009). Clinicians have since observed that patients being treated with lithium see improvements not only in their mood disturbances but also in their gout/hyperuricemia (Shorter 2009). This association has subsequently been confirmed by several studies showing elevated uric acid (UA) levels in drug-naïve patients experiencing their first manic episode, as well as nationwide, population-based data indicating an increased risk of gout in patients with BD (Salvadore et al. 2010; Chung et al. 2010). Uric acid modulates a variety of endogenous functions, including sleep, appetite, cognition, memory, motor activity, and social interaction (Machado-Vieira et al. 2002; Lorenzi et al. 2010). Elevated UA levels have been associated with specific manic traits such as impulsivity, irritability, increased drive, disinhibition, and hyperthymia (Machado-Vieira et al. 2002; Lorenzi et al. 2010; Sutin et al. 2014). Manic patients demonstrate increased serum UA compared to those with bipolar depression or MDD (Bartoli et al. 2017b). Higher serum UA is also predictive of bipolar conversion in currently depressed patients (Oliveira et al. 2019). Indeed, hyperuricemia appears to be highly selective for mania in BD (Berardis and De Berardis 2008), whereas low UA levels have been linked to depressive mood scores in BD, independent of current disease phase (Albert et al. 2015; Muti et al. 2015). Reductions in mania are associated with a concurrent decrease in serum uric acid levels, and enhanced urinary excretion of UA has been observed during lithium-induced remission from hypomania (Machado-Vieira et al. 2017a).

Furthermore, plasma uric acid level abnormalities are typically absent during euthymic periods (Berardis and De Berardis 2008). This evidence strongly suggests that purinergic system dysfunction plays an important role, especially early in the development of BD (Machado-Vieira et al. 2008). Given the positive association between peripheral and central uric acid levels (Bowman et al. 2010), UA holds significant potential as a state-dependent biomarker and outcome indicator in BD.

The purine adenosine is decreased in the serum of euthymic bipolar patients when compared to healthy controls, and lower levels confer a higher degree of functional impairment (Gubert et al. 2016). Adenosine receptor agonists characteristically display anti-aggressive, anticonvulsant, and antipsychotic properties, whereas antagonists (caffeine, theophylline) can enhance irritability, anxiety, and insomnia (Lara et al. 2006). This suggests that, beyond acting as surrogate markers for other cellular processes (i.e., nucleic acid turnover), purinergic constituents independently contribute to the overall disease process in BD. Machado-Vieira et al. previously demonstrated the efficacy of allopurinol in treatment-resistant mania associated

with hyperuricemia (Machado-Vieira et al. 2001). By inhibiting xanthine oxidase, it is suggested that allopurinol may increase CNS levels of adenosine and other purine metabolites in addition to decreasing UA formation (Marro et al. 2006). Several trials have subsequently demonstrated the efficacy of allopurinol as an adjunct to standard therapy in improving manic symptoms (Machado-Vieira et al. 2002, 2008; Akhondzadeh et al. 2006). Moreover, a 2017 systematic review and meta-analysis of 5 RCTs using adjuvant purine-modulators confirmed their anti-manic efficacy compared to placebo (Bartoli et al. 2017a). Of note, allopurinol can also effectively treat aggressive behavior in patients with dementia, further solidifying the association between UA and the aggression/impulsivity (Lara et al. 2003).

Genetic studies have recently revealed a specific SNP in the P2X7 gene, which encodes a CNS-expressed purine receptor associated with both BD and MDD in animal models (Sperlagh et al. 2012). P2X7 expression is also increased by sleep deprivation and rapid cycling in humans (Backlund et al. 2012). P2X7 receptor-associated neuroinflammation has also been implicated in the parthenogenesis of BD (Masuch et al. 2016). Recently, significant attention has been directed towards developing targeted therapies for P2X7 in BD and MDD, though robust clinical trials have not yet been executed (Bhattacharya et al. 2013; Dodd et al. 2015).

In conclusion, beyond acting as surrogate markers, evidence strongly implicates purinergic system constituents as a priori disease modulators in BD. The diversity of metabolites and downstream interactions associated with this pathway espouse significant potential for future therapeutic and biomarker development.

12 Conclusion

Our evolving understanding of BD weaves an ever-expanding web of conceptual integration. Complexities notwithstanding, several key entities (cortisol, BDNF, PKC, GSK3, calcium, glutamate, and inflammatory cytokines) seem to underlie and connect many of the seemingly disparate concepts discussed in this chapter. Through these elements, we can see how oxidation and mitochondrial function, for example, ultimately affect neurotransmission, plasticity, apoptosis, and even the inflammatory milieu. Despite our limited understanding of the microbiome, we can already appreciate this same dynamic. Small alterations in the gut seem to affect everything from neurotransmitter metabolism, to neuroinflammation, and even the HPA axis. From a therapeutic standpoint, lithium perfectly exemplifies this concept. Its efficacy stems from its ability to modulate so many aspects of this disease from oxidative stress, mitochondrial function, apoptosis, and calcium signaling to inflammation, hormonal activity, glutamate signaling, and even the purinergic system. Likewise, we see how novel therapies like ketamine simultaneously integrate both the glutamate and inflammatory hypotheses of depression through final common pathways. It is no coincidence that emerging biomarkers such as BDNF, TNF-α, UA, and others seem to act as molecular conduits between so many different pathways and systems. Moving forward, clinicians and scientists must build on

this ethic: making connections that emphasize a holistic context for every specific discovery, increasing patient screening with objective markers, and implementing multi-modal, tailored approaches to treatment.

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