Chapter 18

Intracellular signaling cascades in bipolar disorder

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18.1 Introduction

Intracellular signaling pathways in bipolar disorder (BD) represent complex, interconnected neurochemical communication systems that maintain a delicate balance. Evidence suggests that some or all of these pathways are disrupted in BD, leading to the pathophysiological and behavioral abnormalities seen in patients. These alterations are not unique to BD and do not apply to all BD patients universally, but rather represent individual heterogeneity. This chapter will describe several of these systems, their interactions, and expound upon the pharmacotherapeutic possibilities of modulating any of these systems, including Ca^{2+} signaling, GSK3-β/Wnt pathways, DAG/PKC pathways, brain-derived neurotrophic factor (BDNF), and mitochondria. See Fig. 18.1 for a visual overview of the interconnected concepts discussed here, and the impact lithium has on them.

18.2 Calcium signaling

Alterations in Ca^{2+} homeostasis were first observed in relation to BD in 1922 (Weston, 1922). Weston documented lower spinal fluid Ca^{2+} concentrations in individuals with BD compared to depressed counterparts—a finding that has since been replicated and expounded (Harrison, Hall, Mould, Al-Juffali, & Tunbridge, 2019). Recent controlled studies show elevated Ca^{2+}

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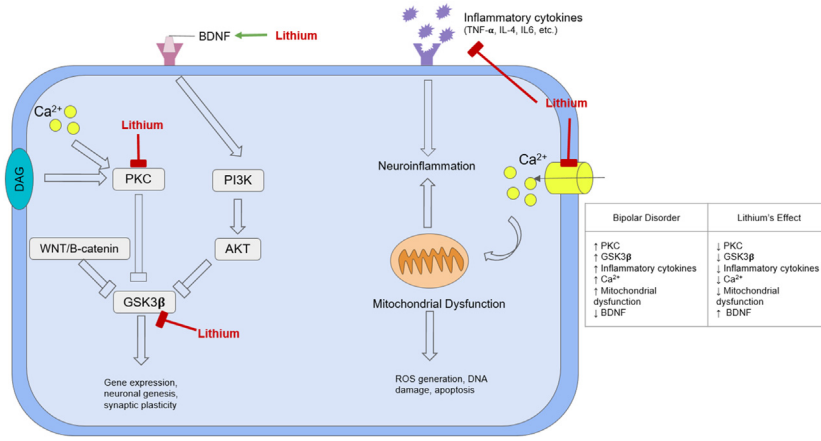

FIGURE 18.1 An illustration of various intracellular pathways involved in the pathogenesis of BD. Increased cellular permeability of Ca^{2+} channels results in mitochondrial dysfunction, resulting in generation of ROS, DNA damage, apoptosis, and increased neuroinflammation. Increased inflammatory cytokines further contribute to increased neuroinflammation. GSK3β functions in various cellular processes such as gene expression, neuronal genesis, and synaptic plasticity, but, in BD, GSK3β is overactive and causes dysfunction of these processes. BDNF is decreased in BD, resulting in the downregulation of the PI3K/AKT regulatory pathway and potentially contributing to the hyperactivity of GSK3β. PKC is overactive in BD, conversely leading to increased activity of GSK3β. Lithium treats BD using various mechanisms by inhibiting GSK3β, PKC, Ca^{2+} channel, and inflammatory cytokine activity and by increasing BDNF activity. (*BD*, Bipolar disorder; *BDNF*, brain-derived neurotrophic factor; *PKC*, protein kinase C; *ROS*, reactive oxygen species)

in lymphocytes and platelets as well as elevated Ca^{2+} ATPase activity in red blood cells (RBC) from unmedicated BD patients (Dubovsky, Murphy, Thomas, & Rademacher, 1992; Warsh, Andreopoulos, & Li, 2004). Calcium signaling appears to be a highly regulated process due to the dire consequences of imbalanced intra and extracellular Ca^{2+} concentrations, which can activate treatment-resistant cell death processes. The mitochondria and endoplasmic reticula are both essential to maintaining intracellular Ca^{2+} homeostasis via sequestering, buffering, and mobilization (Kato, 2017).

Intracellular Ca^{2+} mediates neuronal excitation, plasticity, toxicity, and survival, as well as neurotransmitter synthesis and release (Kato, 2017). It is therefore not surprising that abnormal calcium levels are shown to affect mood and behaviors (as in the case of hyperparathyroidism), and act as a therapeutic target of lithium in BD (Harrison et al., 2019). In clinical and preclinical paradigms, lithium directly and indirectly reduces Ca^{2+} by blocking NMDAR-stimulated Ca^{2+} signaling and enhancing Bcl-2 protein expression, which inhibits endoplasmic reticular Ca^{2+} release, resulting in increased neuronal survival (Nonaka, Hough, & Chuang, 1998; Rong & Distelhorst, 2008). Genetic variations on the *Bcl-2* gene associated with BD

development also correlate with elevated basal Ca^{2+} and enhanced cytosolic Ca^{2+} release (Machado-Vieira et al., 2011). Genomic studies also provide evidence in favor of aberrant intracellular Ca^{2+} in the pathogenesis of BD. Variants on genes encoding L-type calcium channel (LTCC) subunits, particularly the CACNA1C locus have been shown to enhance calcium signaling in neuron-like cells derived from BD patients (Yoshimizu et al., 2015). Similarly, iPSC from the hippocampal neurons of BD patients exhibits overactive Ca^{2+} signaling, which is reduced by lithium. Interestingly, the latter finding only occurs in cells derived from lithium-responsive patients, suggesting a conditional effect between normalization of Ca^{2+} signaling and symptom reduction/clinical efficacy (Mertens et al., 2015). However, further research is required before conclusions can be drawn.

Despite several lines of evidence (described earlier), intracellular Ca^{2+} hyperexcitability is not considered a biomarker of BD, in part, because free intracellular Ca^{2+} makes up just $<1\%$ of total cellular Ca^{2+} concentrations, with the majority being sequestered in organelles (Harrison et al., 2019). In keeping, therapeutic investigations of calcium antagonists acting on neuronal calcium channels, LTCC are inconclusive despite showing initial promise. Antihypertensive agents with LTCC activity, such as nimodipine, verapamil, and diltiazem were tested in BD mania and depression, but did not show sufficient monotherapeutic nor adjunctive efficacy in controlled trials, and may in fact have deleterious effects when administered in conjunction with certain mood stabilizers. Several studies reported that verapamil and diltiazem increased lithium activity and carbamazepine concentrations to the point of neurotoxicity (Jones, Rong, Shariq, Mishra, & Machado-Vieira, 2020).

18.3 Diacylglycerol and protein kinase C pathways

Diacylglycerol (DAG) is an enzyme that plays an important role in several signal transduction cascades and mediates membrane potentials and neuronal excitability (Thiruvengadam, 2021). Preclinical evidence suggests that it is through promotion of the DAG pathway that lithium exerts its control over these processes (Hokin, 1993). This pathway can also explain the mechanism by which many antidepressants induce mania in patients with BD (Pandey, Davis, Schwertz, & Pandey, 1991). Genome-wide association studies (GWAS) have implicated single nucleotide polymorphisms (SNPs) on a gene encoding DGKH, a protein within the PI pathway (which facilitates lithium's prophylactic mechanism) in the etiology of BD (Baum et al., 2008). DGK-β knockout mice demonstrate dysfunctional AKT-GSK3-β signaling and abnormal cortical spine formation, which likely account for manic-like behavioral abnormalities, such as hyperactivity and anxiety that are normalized with lithium but not antipsychotic, benzodiazepine, or serotonergic antidepressant medications (Kakefuda et al., 2010).

Protein kinase C (PKC) is a family of phospholipid-dependent enzymes that regulate protein function and act in various overlapping signal transduction cascades involved in neurotransmission, including neurotransmitter release, receptor regulation, synaptic modeling and genetic expression, and neuronal excitation (Amadio, Battaini, & Pascale, 2006; Chu, Fioravante, Leitges, & Regehr, 2014; Jun et al., 2014; Shin et al., 2019; Zarate, Singh, & Manji, 2006). Three novel subfamilies of PKC include the conventional type (α, βI, βII, γ) that require both DAG and Ca^{2+} to function, the novel type (δ, ε, η, θ, μ) that require only DAG, and the atypical type (ι/λ and ζ) that require neither DAG nor Ca^{2+} for activation (Abrial, Lucas, Scarna, Haddjeri, & Lambás-Señas, 2011; Pandey, Rizavi, & Ren, 2020; Shin et al., 2019; Wetsel et al., 1992). PKC isoforms, highly expressed in brain regions linked to cognitive and affective modulation (e.g., PFC, hippocampus, and amygdala) play a role in physiological processes relevant to neuronal genesis, plasticity, and survival (Naik et al., 2000; Saxena et al., 2017; Shin et al., 2019).

A *meta*-analysis of 8700 mood disorder patients found a significant link between suicidality and a genetic locus for PKC (Saxena et al., 2017). GWAS have also associated BD with SNPs on PKC genes (Perlis et al., 2010). PKC dysfunction in the pathogenesis of BD is supported by several lines of evidence, although the direction of this associated appears unclear. Most studies observe central and peripheral PKC hyperactivity associated with BD (Hahn et al., 2005; Wang & Friedman, 1996; Wang, Markowitz, Levinson, Undie, & Friedman, 1999). Platelet analyses indicate decreased expression and activity of PKC isoforms following mood stabilizer administration, a finding in both medication free (Pandey et al., 2002) and acutely manic BD patients (Hahn et al., 2005), which was corroborated by a controlled postmortem analysis of cortical samples from medicated BD patients (Pandey et al., 2020).

Importantly, PKC alterations have been reported in a number of comorbid metabolic and cardiovascular conditions, possibly accounting for some of these discrepancies (Geraldes & King, 2010). In preclinical mania models, PKC inhibition decreases oxidative stress and hippocampal cell degeneration in conjunction with reducing manic-like behaviors (Abrial, Lucas, Scarna, Haddjeri, & Lambás-Señas, 2011; Valvassori et al., 2020). Similarly, lithium and valproate have been shown to inhibit PKC as part of the mood stabilizing mechanism (Chen, Manji, Hawver, Wright, & Potter, 1994; Chen, Masana, & Manji, 2000; Zarate & Manji, 2009).

PKC dysfunction is implicated in several neuropathologies, including unipolar and bipolar depression as well as Alzheimer's disease (Abrial, Lucas, Scarna, Haddjeri, & Lambás-Señas, 2011; Amiri, Azadmanesh, Shasaltaneh, Mayahi, & Naghdi, 2020). Indeed, PKC signaling underlies several pathologic mechanisms relevant to BD, such as neuroinflammation, apoptosis, plus mitochondrial dysfunction, and oxidative stress (Coyle & Duman, 2003;

Jun et al., 2014; Nam et al., 2015). In addition to currently available mood stabilizers, therapeutic investigations of novel PKC modulators are underway in BD with a number of promising candidates (Amrollahi et al., 2011; Talaei, 2016; Yildiz, 2016; Yildiz, Guleryuz, Ankerst, Ongür, & Renshaw, 2008). A systematic review and *meta*-analysis found that tamoxifen, a relatively selective PKC inhibitor, decreases symptoms of mania both as a monotherapy and adjunctive to lithium or valproic acid; however, due to antiestrogenic and other adverse effects, long-term use must be further evaluated (Kulkarni et al., 2006; Palacios, Yildiz, Young, & Taylor, 2019; Saxena et al., 2017; Zarate & Manji, 2009). Endoxifen, an active metabolite of tamoxifen with four times its inhibitory effect, shows antimanic efficacy for BD patients during acute mood episodes in phase III clinical trials (Ahmad et al., 2020; Ali et al., 2010). Research in ATP and DAG binding site inhibitors, protein inhibitors, and PKC substrate specific inhibitors are underway, but obstacles in selectivity, CNS permeability, adverse effects, and long-term efficacy impede the development of PKC inhibitors in BD pharmacotherapeutics (Mochly-Rosen, Das, & Grimes, 2012; Zarate & Manji, 2009).

18.4 GSK3-β and Wnt pathways

With multiple regulators and more than 50 known substrates, GSK3-β is involved in numerous signaling pathways and plays an important role in a variety of neuronal functions, including cell proliferation, apoptic signaling, neuronal genesis and plasticity, as well as transcription regulation (Duda, Hajka, Wójcicka, Rakus, & Gizak, 2020). GSK3-β hyperactivity is associated with increased pro-inflammatory cytokine expression and has deleterious effects on BDNF production and circadian rhythms, and appears to inactivate the mechanisms by which medications lead to mood stabilization and neurogenesis (Ajmone-Cat et al., 2016; Duda et al., 2018; Duda et al., 2020; Porcu, Gonzalez, & McCarthy, 2019). This dysfunction may be linked to Wnt molecules, which are an important substrate that inhibit constituently active GSK3-β, causing β-catenin nuclear translocation, and ultimately resulting in neurotrophic generation, circadian regulation, and inflammatory modulation via activation of transcription factors and enhancers (Valvezan & Klein, 2012). Wnt pathways are active throughout the lifespan, and modulate neuronal morphology as well as cell patterning, differentiation, proliferation, and integration into established neuronal circuits (Duda et al., 2020).

Since 1996, when researchers discovered that lithium targets and inhibits GSK3-β, several lines of investigation have linked this enzyme to the pathogenesis of BD (Klein & Melton, 1996). Specific GSK3-β polymorphisms have been associated with lithium responsivity as well as manic/depressive episode severity in mood disorders (Bureau, Beaulieu, Paccalet, Chagnon, & Maziade, 2017; Iwahashi et al., 2014; Mitjans et al., 2015). Postmortem studies in BD patients show decreased β-catenin mRNA and protein content in

the dlPFC and temporal cortex compared to schizophrenic subjects and healthy controls, suggesting dysfunction in the upstream regulatory Wnt/GSK3-β pathway (Muneer, 2017; Pandey, Rizavi, Tripathi, & Ren, 2015). Compared to controls, those with BD show abnormal GSK3-β levels in peripheral blood mono-nuclear cells, which correlate with manic and depressive episode severity (Polter et al., 2010), as well as elevated GSK3-β transcripts in iPSC (O'Shea & McInnis, 2016). Transgenic mice overexpressing GSK3-β display manic-like behaviors, such as hyperactivity, hyperreactivity, and disturbed eating patterns (Prickaerts et al., 2006), while haploinsufficient mice lacking functional GSK3-β genes demonstrate behaviors akin to patients on chronic lithium therapy. Indeed, lithium administration nullifies manic-like behaviors in preclinical amphetamine-induced mania models (Kalinichev & Dawson, 2011; Valvassori et al., 2017).

Endogenously, GSK3-β inactivation can occur through several different intra and extracellular signaling pathways, including the Wnt pathways (described earlier), the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, or the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway (Duda et al., 2020; Hermida, Kumar, & Leslie, 2017; Muneer, 2017; Thornton et al., 2008). Thus dysfunction in these regulatory pathways can lead to GSK3-β overactivation, a trait associated with BD pathophysiology. Serotonin transmission also facilitates GSK3-β inhibition by activating the PI3K/AKT pathway, likely a key mechanism in the antidepressant efficacy of serotonergic medications (e.g., SSRI). In contrast, increased dopamine inhibits the AKT pathway, stimulating GSK3-β activity (Beaulieu et al., 2004; Cole, 2013), a mechanism observed with amphetamine administration. In the pathogenesis of BD, increased limbic stress may upregulate dopamine and pro-inflammatory cytokine levels, subsequently decreasing serotonin synthesis and activating GSK3-β (Ajmone-Cat et al., 2016; Magioncalda et al., 2016).

The mechanism by which lithium inhibits GSK3-β is modulated by magnesium competitive inhibition (Ryves & Harwood, 2001). However, other BD pharmacotherapies are still to be investigated in terms of GSK3-β activity. Anticonvulsants like carbamazepine and lamotrigine do not show inhibitory GSK3-β effects (Muneer, 2017), but valproate is a known histone deacetylase inhibitor with downstream effects that activate AKT, leading to indirect inhibition of GSK3-β (Kao et al., 2013; Muneer, 2017). Similarly, second generation antipsychotics (atypical antipsychotics), such as aripiprazole inhibit GSK3-β via increasing Wnt gene expression and AKT signaling (de Bartolomeis, Tomasetti, & Iasevoli, 2015; Kalinichev & Dawson, 2011; Li & Jope, 2010; Zheng et al., 2019). Conventional antidepressants have also shown indirect GSK3-β inhibition by targeting upstream regulators, the Wnt and PI3K/AKT pathways to affect gene expression in a time frame coinciding with their delayed therapeutic effects (Muneer, 2017; Pilar-Cúellar et al., 2014). Finally, the NMDA antagonist ketamine rapidly inhibits GSK3-β via

MEK/ERK and PI3K/AKT pathways in animal models (Beurel, Song, & Jope, 2011; Duman, Li, Liu, Duric, & Aghajanian, 2012; Réus et al., 2014; Snitow, Bhansali, & Klein, 2021).

Clinical development for novel GSK3-β modulators, such as ATP binding site inhibitors, is underway in several diseases. Based on GSK3-β's constitutive expression and near-universal involvement in signaling pathways, these avenues may be GAME CHANGING; however, developing safe and effective pharmacotherapies with minimal offshoot effects is a slow, yet highly anticipated front (Noori et al., 2019; Saha, Pal, & Nimse, 2021). Peptide-conjugated GSK3-β inhibitors and substrate competitive inhibitors may increase selectivity and specificity in GSK3-β targeting in order to combat these limitations (Bhat et al., 2018; Rippin & Eldar-Finkelman, 2021). In addition, machine learning techniques can identify new and FDA-approved drugs acting on GSK3-β (Vignaux, Minerali, Foil, Puhl, & Ekins, 2020).

18.5 Brain-derived neurotrophic factor

Neurotrophins act as cellular growth factors facilitating cell survival, neurogenesis, synaptic plasticity, and long-term memory formation. In mood disorders, the most well-studied neurotrophin is BDNF, which plays an essential role in several pathways discussed in this chapter. BDNF and PKC appear to have reciprocal regulatory mechanisms by which PKC directly and indirectly modulates expression of BDNF and other neurotrophins. Meanwhile, BDNF facilitates PKC signaling-related synaptic plasticity via modulation of genetic expression (Xu et al., 2013; Xu, Czerwinski, Xia, Forstermann, & Li, 2015). BDNF can also obstruct GSK3-activity, and acts as a downstream target of GSK3-inhibition via lithium (Machado-Vieira, Manji, & Zarate, 2009). BDNF and neurotrophins as a class play a complex and interdependent role in various aspects of neuronal signaling, genetic expression, and disease states.

Stressor are known to reduce BDNF, and in BD, lower BDNF levels increases with treatment at a rate relative to clinical improvement (Post, 2007). *Meta*-analyses consistently support decreased plasma BDNF concentrations in BD patients compared to controls, while peripheral levels are associated with mood state and cognitive function. BD patients experiencing euthymia demonstrate lower peripheral BDNF levels than controls, while those experiencing mania/depression demonstrate lower levels than controls and euthymic counterparts (Rowland et al., 2018). In controlled studies, BDNF levels are positively correlated with executive functioning, memory, and overall cognitive ability, but negatively correlated with markers of oxidative stress and inflammation, such as IL-6 (Mora et al., 2019). Although no pharmacotherapies target BDNF directly, many (e.g., lithium, antidepressants, ECT, and ketamine/NMDA antagonists) increase peripheral concentrations. Due to its highly reciprocal interactions with signaling pathways and

overall neuronal activity, BDNF is a challenging and potentially unrealistic treatment target, but may be an effective biomarker for severity, state, and treatment response in BD (Jones et al., 2020).

Several converging lines of evidence support a role for BDNF in the pathophysiology of BD and BD subtypes (Chiou & Huang, 2019). A number of different BDNF biomarkers (e.g., serum concentrations, multisystem genetic analysis, machine learning, and genomic variations) have been shown to accurately differentiate between BD patients and controls in long- and short-term studies (Chiou & Huang, 2019), indicating that BDNF is a consistent trait marker of BD. Genetic analyses suggest an association between vulnerability to developing BD with variants on BDNF promoter genes (D'Addario et al., 2012). The *EGR3* gene, which is regulated by BDNF is implicated in a proposed positive feedback loop explaining BD vulnerability/risk using a systems model of the transcriptional network in the human PFC. Researchers posit that alterations in BDNF signaling reduce *EGR3* expression, resulting in impaired neuroplasticity and resilience, subsequently increasing vulnerability to cellular stressors, which further reduces BDNF expression (Pfaffenseller et al., 2016; Pfaffenseller, Kapczinski, Gallitano, & Klamt, 2018). Overall, BDNF and related pathways seem to play a clear role in BD pathogenesis, and, due to its widespread involvement in neuronal function, could act in conjunction with other biomarkers to increase efficacy. Some findings suggest that combining measurements of BDNF and TNF-α can better distinguish between mood states in BD patients, based on two independent mechanisms (Rowland et al., 2018).

18.6 Mitochondrial dysfunction

Mitochondria produce a majority of the cell's energy in the form of ATP as well as nearly all endogenous reactive oxygen species (ROS). On a cellular level, mitochondria play a role in neuronal development, synaptic plasticity, intrinsic apoptic signaling, inflammatory signaling, calcium homeostasis, and mediation of cellular stress. Even slight alterations in morphology or function can decrease efficiency of ATP production by generating more oxidative byproducts and reduce antioxidant capacity (Clay, Sillivan, & Konradi, 2011; Dager et al., 2004; Machado-Vieira, Zanetti, et al., 2017). The presence of mitochondrial disease appears to predispose BD compared to the general population (this association is likely bidirectional but deserves further investigation) (Goodwin & Jamison, 2007). Meanwhile, BD is associated with abnormalities in mitochondrial structure, membrane potential, and distribution within the cell (Scaini et al., 2021; Zuccoli, Saia-Cereda, J.M., & Martins-de-Souza, 2017).

In regard to BD pathogenesis, there is evidence that a reactive upsurge of antioxidant enzymes occurs early in the course of the disease, and particularly during phases of depression. Thus oxidative damage may take part in

both pathogenesis and neuroprogression of BD, potentially accounting for cognitive and neurodegeneration, progressive shortening of interepisode euthymic periods, diminishing treatment response over time, and rising cardiovascular mortality associated with the longitudinal course of BD (Brown, Andreazza, & Trevor Young, 2014; Machado-Vieira et al., 2007).

Several lines of investigation support this notion. Younger age of onset, longer duration of illness, and increasing episodic frequency are correlated with elevated peripheral markers of oxidative and nitrosive stress (Jones et al., 2020). Indeed, BD patients show increased lipid peroxidation and nitric oxide levels in serum and RBC with the resulting impairment corroborated in postmortem brain tissue and peripheral blood (de Sousa et al., 2014). This suggests that BD is associated with chronic system oxidative and nitrosive stress that increase over time. Mitochondrial Complex I dysfunction, which reduces intracellular and extracellular BDNF concentrations may help account for decreased plasticity and neurocognitive decline (Andreazza, Shao, Wang, & Young, 2010; de Sousa, Streck, & Zanetti, 2015). Other markers of mitochondrial function and neuronal variability (e.g., intracellular pH and lactate levels) are altered in BD, increasing energy demand and decreasing supply (de Sousa et al., 2014); however, lithium administration appears to increase Complex I activity while decreasing TBARS, SOD, hydrogen peroxide, and lipid peroxidation. This neuroprotective mechanism reduces mitochondrial dysfunction and neuronal oxidative damage in addition to aiding prophylaxis (Andreazza et al., 2010; de Sousa et al., 2015; Jones et al., 2020).

18.7 Conclusion

Alterations in calcium signaling appear to be mediated by mitochondrial abnormalities. Both of these indirectly and directly affect other intracellular signaling pathways discussed earlier, increasing GSK3-β and PKC activity, both pathways known to be involved in the pathogenesis of BD. The concepts discussed in this chapter—Ca^{2+} signaling, GSK3-β/Wnt pathways, DAG/PKC pathways, BDNF, and mitochondrial abnormalities—are interconnected systems, making pharmacotherapeutic targeting difficult due to adverse downstream effects and a large number of unknown factors. However, targeting any of these systems involved in the pathophysiology of BD will be crucial for therapeutics in the future, due to the high number of patients not responding to available treatments.

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