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Second messenger/signal transduction pathways in major mood disorders: moving from membrane to mechanism of action, part II: bipolar disorder

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Abstract

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In this second of two articles on second messenger/signal transduction cascades in major mood disorders, we will review the evidence in support of intracellular dysfunction and its rectification in the etiopathogenesis and treatment of bipolar disorder (BD). The importance of these cascades is highlighted by lithium's (the gold standard in BD psychopharmacology) ability to inhibit multiple critical loci in second messenger/signal transduction cascades including protein kinase C (involved in the IP₃/PIP₂ pathway) and GSK-3 β (canonically identified in the Wnt/Fz/Dvl/GSK-3 β cascade). As a result, and like major depressive disorder (MDD), more recent pathophysiological studies and rational therapeutic targets have been directed at these and other intracellular mediators. Even in the past decade, intracellular dysfunction in numerous neuroprotective/apoptotic cascades appears important in the pathophysiology and may be a future target for pharmacological interventions of BD.

Keywords: Bipolar disorder, signal transduction, second messenger, intracellular cascades, mood stabilizers, lithium

Introduction

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Like the other major mood disorder, major depressive disorder (MDD), pathophysiological and psychopharmacological research in bipolar disorder (BD) have encompassed monoamine (serotonin, norepinephrine, dopamine) and amino acid (γ -aminobutyric acid, glutamate)-based neurotransmission. However, as early as the 1970s, lithium (a cell-

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permeant cation with minimal reactivity at cell surface receptors) reduced brain inositol levels¹ [presumably via the inhibition of protein kinase C (PKC)] and was speculated to have state-specific, mood-stabilizing effects on second messenger/signal transduction cascades. Lithium is still the standard of care in the treatment of BD, especially in antimanic and maintenance therapies.² The antiepileptic drugs valproic acid and carbamazepine, although chemically dissimilar to lithium, also have profound effects on intracellular pathways to stabilize mood.³⁻⁶

Like other neuropsychiatric disorders, BD arises from complex and still poorly understood abnormalities at the molecular, cellular, and circuit levels. As in other neuropsychiatric disorders, these multitiered abnormalities are likely responsible for BD's signs and symptoms: elevated/expansive or irritable mood, impaired circadian rhythmicity, increased goal-directed activity, decreased cognitive control, increased impulsivity, and frequent risk-taking behaviors, eg, sexual indiscretions and reckless substance misuse. As was done with the first review in this series, this article will summarize our current state of knowledge of second messenger/signal transduction cascades in the etiopathogenesis of BD. We will then discuss what is known about the mechanism of action of the aforementioned mood stabilizers. Finally, we will illuminate potential future directions and rational therapeutic targets in BD.

Second Messenger/Signal Transduction Cascades

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The following second messenger/signal transduction cascades will be discussed in sequence: cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP-response element binding protein (CREB); extracellular regulated kinase (ERK)/mitogen-activated protein kinase (MAPK); phosphoinositide (PI)/protein kinase C (PKC); Wnt/frizzled (Fz)/disheveled (Dvl)/glycogen synthase kinase-3 beta (GSK-3β); and mitochondrial (pro- and anti-apoptotic) cascades. Although it certainly is as important in bipolar as in unipolar depression, we will not discuss neurotrophic signaling here in detail other than as an extracellular stimuli for intracellular cascades; the interested reader is referred to our extensive discussion of neurotrophins in the first article in this series. And, as in the first part, we will also not discuss extracellular neurotransmission (via classic neurotransmitters, neuropeptides, or other neuroendocrine mechanisms) except as the means of stimulating or inhibiting intracellular signal transduction/second messenger pathways.

cAMP/PKA/CREB

As may be surmised from the wealth of data in unipolar depression and preclinical models of despair, the cAMP/PKA/CREB pathway is also affected in BD. However, in contrast to preclinical models and unipolar depression, this cascade is upregulated/overactive in BD, especially in mania (Table 1). Levels of the stimulatory G protein linked to this cascade, G_s, are increased in postmortem bipolar brain (Table 1).^{7,8} As detected by coimmunoprecipitation with total brain homogenates, there is increased heterotrimeric G protein complex (Gαβγ) association relative to age, sex, and postmortem-interval matched controls.⁸ The increased levels/activity of this cascade have also been replicated in peripheral samples.⁹⁻¹¹ Unfortunately, some of the aforementioned studies report conflicting results both based on the phase of illness and the specific patient population. Next, adenylyl cyclase activity (both basal and stimulated) is enhanced in postmortem samples from bipolar patients, which increases production of the second messenger cyclic adenosine

Postmortem cerebral cortex Gs alpha-subunit levels are elevated in bipolar affective disorder [Brain Res. 1991]

Receptor-mediated activation of G proteins is increased in postmortem brains of [J Neurochem. 1996]

Mononuclear leukocyte levels of G proteins in depressed patients with bipolar [Am J Psychiatry. 1994]

Abnormal G protein alpha(s) - and alpha(i2)-subunit mRNA expression in bipolar affective disorder [Mol Psychiatry. 1998]

Increased cyclic AMP-dependent protein kinase activity in postmortem brain from [J Neurochem. 1999]

Altered cAMP-dependent protein kinase subunit immunolabeling in post-mortem brain [J Neurochem. 2003]

Protein kinase A activity in platelets from patients with bipolar disorder. [J Affect Disord. 2003]

The cAMP-dependent protein kinase A and brain-derived neurotrophic factor expression in [J Affect Disord. 2004]

Gene expression analysis of bipolar disorder reveals downregulation of the ubiquitin-proteasome system [Mol Psychiatry. 2006]

Genetic association of cyclic AMP signaling genes with bipolar disorder. [Transl Psychiatry. 2012]

Chronic treatment with mood stabilizers increases membrane GRK3 in rat frontal cortex [Biol Psychiatry. 2007]

Review Signaling: cellular insights into the pathophysiology of bipolar disorder [Biol Psychiatry. 2000]

Review Physiological roles for G protein-regulated

monophosphate (cAMP). The catalytic subunit of protein kinase A (PKA) and cAMP-stimulated PKA activity are also increased in BD brain.^{12,13} Like linked G proteins, increased PKA activity has been observed in peripheral blood platelets and lymphoblasts, even in the absence of mood stabilizers.^{14,15} CREBP1 [a cAMP-response element binding (CREB) protein interactor] expression is reduced in BD postmortem orbitofrontal cortex,¹⁶ but, to date, there have been no reports of CREB levels and/or transcriptional activity in BD or animal models of the disorder, eg, psychostimulant-induced hyperlocomotion. Finally, a recent multiple rare variant genetic analysis identified several single nucleotide polymorphisms (SNPs) in related signaling genes [including several variants of phosphodiesterase (PDE)10A] in bipolar I disorder (BDI). Moreover, several SNP × SNP interactions among these signaling genes multiplicatively increased the genetic risk of BDI in this sample.¹⁷ However, the relationship of these PDE10A SNPs is speculative at best without evidence of dysregulation in cAMP levels and impairment in cAMP-stimulated PKA activity.



Table 1
Pathophysiological impairments of second messenger/signal transduction cascades in bipolar disorder (BD)

Traditional mood stabilizers normalize activity in the cAMP/PKA/CREB second messenger/signal transduction cascade. Lithium and the antiepileptic drug carbamazepine promote the cytosol-to-plasma membrane translocation of G-protein receptor kinase-3 (GRK3), a serine/threonine kinase implicated in the homologous desensitization of G-protein coupled receptors.⁵ GRK3's plasma membrane translocation may dampen receptor overactivation in bipolar brain. Chronic lithium administration also affects adenylyl cyclase activity, ie, an increase in basal activity while inhibiting receptor-mediated overactivation.¹⁸ (Of note, these are total cytosolic AC activity assays and may not reflect differences in activity in specific AC subtypes and/or in different subcellular microdomains.¹⁹) There are conflicting results of lithium's effect on CREB in preclinical studies.^{20,21} (This intersects with our discussion of the ERK/MAPK second messenger/signal transduction cascade below to affect CREB phosphorylation, nuclear translocation, and CRE-mediated gene transcription.)

Although structurally dissimilar to lithium, valproic acid's antimanic effects may also result from alterations in the cAMP/PKA/CREB second messenger/signal transduction cascade. Chronic valproic acid administration decreased the expression of β_1 -adrenergic receptors and postreceptor-mediated cAMP generation.³ In a microarray study of rats exposed to intraperitoneal valproic acid (200 mg/kg), many genes implicated in G-protein-mediated signaling (including the catalytic subunit of PKA and CREB) were up- or downregulated at least 1.4-fold relative to untreated controls.⁴ Real-time quantitative polymerase chain reaction (PCR) in an independent sample validated these microarray expression differences. Nonetheless, the aforementioned studies were conducted in cell lines and rodents, and these results have yet to be

adenylyl cyclase isoforms: insight [Neurosignals. 2009]
Lithium increases transcription factor binding to AP-1 and cyclic AMP-responsive element [J Neurochem. 1997]
Reduced CREB phosphorylation after chronic lithium treatment is associated [Int J Neuropsychopharmacol. 2007]

Effects of valproic acid on beta-adrenergic receptors, G-proteins, and adenylyl cyclase [Neuropsychopharmacology. 1996]
Microarray analysis of rat brain gene expression after chronic administration of sodium [Brain Res Bull. 2005]

Inhibitory effects of anticonvulsant drugs on cyclic nucleotide accumulation in brain. [Ann Neurol. 1979]
Carbamazepine distinguishes between adenosine receptors that mediate different effects [Eur J Pharmacol. 1991]
Chronic carbamazepine administration attenuates dopamine D2-like receptor-initiated responses [Neurochem Res. 2008]
Effect of carbamazepine on cyclic nucleotides in CSF of patients with affective illness. [Biol Psychiatry. 1982]

Comparative analysis of the effects of four mood stabilizers in SH-SY5Y cells and primary neurons [Bipolar Disord. 2005]
The role of p38 MAPK in valproic acid induced microglia apoptosis. [Neurosci Lett. 2010]
Selective G2/M arrest in a p53(Val135)-transformed cell line induced by lithium is mediated [Life Sci. 2012]
The role of the extracellular signal-regulated kinase signaling pathway in mood modulation [J Neurosci. 2003]

Reduced frontal cortex inositol levels in postmortem brain of suicide victims and patients with bipolar disorder [Am J Psychiatry. 1997]
The phosphoinositide signal transduction system is impaired in bipolar affective disorder [J Neurochem. 1996]
Elevated platelet membrane phosphatidylinositol-4,5-bisphosphate in bipolar mania [Am J Psychiatry. 1993]
A genome-wide association study implicates diacylglycerol kinase ϵ (DGK ϵ) in bipolar disorder [Mol Psychiatry. 2008]

translated into bipolar patients. Therefore, valproic acid's antimanic mechanism of action in humans still remains poorly understood.

Albeit equally dissimilar in structure to lithium and valproic acid, carbamazepine has analogous biochemical and cell biological effects. In addition to promoting the cytosol-to-cell membrane translocation of GRK-3, carbamazepine has been shown to decrease basal and stimulated cAMP production in rodents.^{22,23} Also, like valproic acid, chronic administration in rodents decreased dopamine (D₂) receptor activity (as displayed by quinpirole-mediated inhibition of arachidonic acid production/signaling).²⁴ Finally, in mania, carbamazepine decreased cAMP levels in cerebrospinal fluid.⁶

ERK/MAPK

The ERK/MAPK pathway has also been investigated in BD and preclinical models. As mentioned, there is significant overlap in the cAMP/PKA/CREB and ERK/MAPK second messenger/signal transduction cascades to converge on CREB phosphorylation and CRE-mediated gene transcription. Unfortunately, there has been minimal research to date on ERK/MAPK dysregulation in the pathophysiology of BD (Table 1). However, there have been numerous *pharmacological* investigations into the mechanism of action of mood stabilizing medications. In an immortalized human cell line (SH-SY5Y) and in primary neuronal cultures, both lithium and valproic acid stimulate the ERK/MAPK cascade in contrast to other mood stabilizers (carbamazepine and lamotrigine).²⁵ Valproic acid induces microglial apoptosis in vitro, which relies on p38-stimulated MAPK phosphorylation [in contrast to other MAPK isoforms, phospho-ERK and phospho-Jun activated kinase (JNK)].²⁶ Lithium also enhances the phosphorylation of p38-MAPK, p53 downregulation, and the reversal of cell cycle arrest at G2/M in rat fibroblasts and an immortalized p53 mutant cell line.²⁷ Next, lithium and valproic acid increased levels of phospho-ERK in the rodent frontal cortex and hippocampus, and ERK inhibitors have stimulatory effects similar to D-amphetamine administration (a rodent model of mania) that are reversed by lithium pretreatment.²⁸ As in other psychiatric and nonpsychiatric disorders, eg, oncology, the ERK/MAPK cascade is a central regulator of cell survival and proliferation, which provides novel hypotheses into the mechanistic underpinnings of the neuroprotective and mitogenic effects of mood stabilization.

PI/PKC

Phosphoinositide (PI) levels are decreased in BD postmortem prefrontal cortex,²⁹ and stimulated PI turnover is reduced (~50% at all tested concentrations of GTPγS) in fractionated occipital cortical membranes from BD vs. controls (Table 1).³⁰ There is evidence of altered PI signaling in peripheral tissue as well. Interestingly, medication-free bipolar subjects in a current manic or depressive episode display *higher* phosphatidylinositol-4,5-bisphosphate (PIP₂) levels in platelets.³¹ A genetic association between BD and the PI/PKC pathway has also been suggested. In a genome-wide association study (GWAS) of common SNPs there was a strong correlation between BD diagnosis and the first intron of diacylglycerol kinase eta (DGKH),³² a regulator of PIP₂ and diacylglycerol (DAG) production to stimulate PKC and modulate the expression of members of the transient receptor potential cation channel family.^{33,34} Total PKC levels, cytosol-to-plasma membrane

TRPM2 variants and bipolar disorder risk: confirmation in a family-based association study [Bipolar Disord. 2009]

Association of the iPLA2β gene with bipolar disorder and assessment of its interaction with the 5-HTT gene [Psychiatr Genet. 2013]

Enhanced protein kinase C activity and translocation in bipolar affective disorder brain [Biol Psychiatry. 1996]

Increased association of brain protein kinase C with the receptor for activated C kinase [Biol Psychiatry. 2001]

Altered platelet protein kinase C activity in bipolar affective disorder, manic episode [Biol Psychiatry. 1993]

Increased membrane-associated protein kinase C activity and translocation in bipolar disorder [J Psychiatr Res. 1999]

Protein kinase C and phospholipase C activity and expression of their mRNAs in bipolar disorder [Neuropsychopharmacology. 2002]

Reduced CREB phosphorylation after chronic lithium treatment is associated with increased risk for bipolar disorder [Int J Neuropsychopharmacol. 2007]

Altered IMPA2 gene expression and calcium homeostasis in bipolar disorder. [Mol Psychiatry. 2001]

Lithium decreases membrane-associated protein kinase C in hippocampus: selective effects of lithium [J Neurochem. 1993]

Review: Lithium regulates PKC-mediated intracellular cross-talk and gene expression [Bipolar Disord. 2000]

Chronic lithium administration alters a prominent PKC substrate in rat hippocampus. [Brain Res. 1992]

Glutamate receptors as targets of protein kinase C in the pathophysiology of bipolar disorder [Neuropharmacology. 2009]

Chronic sodium valproate selectively decreases protein kinase C alpha and epsilon [J Neurochem. 1994]

Sodium valproate down-regulates the myristoylated alanine-rich C kinase substrate [J Pharmacol Exp Ther. 1998]

Chronic carbamazepine treatment increases myristoylated alanine-rich C kinase substrate [Brain Res. 2003]

Protein kinase C inhibition by tamoxifen antagonizes manic-like behavior in rats [Neuropsychobiology. 2007]

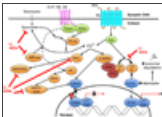
A preliminary investigation of a protein kinase C inhibitor in the treatment of bipolar disorder [Arch Gen Psychiatry. 2000]

A pilot study of hormone modulation as a new treatment for bipolar disorder [J Affect Disord. 2003]

translocation, and enzymatic activity were also increased in postmortem BD frontal cortex.³⁵ The same research group also discovered a facilitated interaction of PKC with the receptor for activated protein kinase C (RACK-1) in the frontal cortex.³⁶ PKC activity and membrane translocation are also increased in platelets from patients in a current manic episode.^{37,38} Other groups, however, have reported conflicting observations of PKC. PKC isozyme levels and activity were decreased with concomitant increases in other members of this pathway, ie, myristoylated alanine-rich C-kinase substrate (MARCKS), in membrane and cytosolic fractions from platelets of unmedicated bipolar patients relative to unmedicated MDD and nondepressed healthy volunteers.³⁹ In pediatric BD, peripheral PKC isozyme levels were reduced at baseline with concomitant increased activity alone (not isozyme levels) after successful mood stabilization.³⁷

Reduced inositol monophosphatase (IMPase) activity and elevated basal intracellular calcium (iCa²⁺) have been observed in B lymphoblast cell lines (BLCLs) in BDI. Interestingly, BDI males with higher basal serum Ca²⁺ have lower levels of IMPase mRNA relative to male BDI subjects with normal serum Ca²⁺, female BDIs, and healthy volunteers. Postmortem IMPase levels in the temporal cortex, in contrast, were higher in male BDI subjects relative to age-matched male postmortem temporal cortex.⁴⁰ PKC overactivation (both increased activity and membrane localization) and phosphorylation of downstream targets, eg, GAP43, have been observed in psychostimulant-induced psychomotor activation. Although these observations are excitingly suggestive of PI dysfunction, it is important to note that all studies to date have been performed on relatively small numbers of subjects. It is therefore imperative to obtain in vivo evidence of pathway dysfunction in the bipolar brain before definitive conclusions can be drawn.

As mentioned above, mood stabilizer pharmacology has been intimately tied to the PI/PKC cascade. Lithium-mediated reduction in central inositol levels has been one of the most formative observations in BD pharmacology. Lithium was shortly thereafter discovered to be a potent PKC inhibitor with concomitant decreased phosphorylation of downstream targets (Figure 1). Preclinical studies have elucidated some of the molecular players involved in lithium and other mood stabilizers' biochemical and molecular effects. Chronic lithium treatment reduced PKC isozymes (α and ϵ) in the hippocampus and the frontal cortex.^{41,42} Next, downstream levels and/or activity of PKC substrates are reduced with chronic lithium treatment, eg, MARCKS.⁴³ Lithium decreased PKC-induced phosphorylation of neurogranin and excitatory glutamatergic N-methyl-D-aspartate (NMDA) receptors and 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) receptors in the prefrontal cortex of psychostimulant-exposed rodents. Consistent with the "kindling hypothesis" of BD pathophysiology, lithium may exert antimanic effects partially by decreasing excessive glutamatergic neurotransmission.⁴⁴ Finally, valproic acid had similar biochemical effects to lithium,^{45,46} but chronic carbamazepine treatment has been reported to increase neocortical MARCKS expression.⁴⁷



treatment for mania [Psychoneuroendocrinology. 2006]
Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a [Bipolar Disord. 2007]
Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-c [Arch Gen Psychiatry. 2008]
Review Nutrient-based therapies for bipolar disorder: a systematic review. [Psychother Psychosom. 2013]

Review The high affinity inositol transport system--implications for the pathophysiol [Bipolar Disord. 2000]
Sodium-myo-inositol co-transporter (SMIT-1) mRNA is increased in ne [Int J Neuropsychopharmacol. 2007]
SMIT1 haploinsufficiency causes brain inositol deficiency without affecting lit [Mol Genet Metab. 2006]

A molecular mechanism for the effect of lithium on development. [Proc Natl Acad Sci U S A. 1996]
The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase [J Neurochem. 1999]
Biphasic changes in the Ser-9 phosphorylation of gh [Prog Neuropsychopharmacol Biol Psychiatry. 2003]
Deficiency in the inhibitory serine-phosphorylation of glycogen synthase [Neuropsychopharmacology. 2010]

Beta-catenin overexpression in the mouse brain phenocopies lithium [Neuropsychopharmacology. 2007]

The expression of proapoptosis genes is increased in bipolar disorder, but not in schiz [Mol Psychiatry. 2006]
Altered expression of apoptotic factors and synaptic markers in postmortem brain fron [Neurobiol Dis. 2010]
Phosphorylation status of glucocorticoid receptor, heat shock protein 70, cy [Psychoneuroendocrinology. 2009]
The Bcl-2 gene polymorphism rs956572AA increases inositol 1,4,5-trisphosphate rece [Biol Psychiatry. 2011]
Bcl-2 rs956572 polymorphism is associated with

GSK-3 β phosphorylation in stressed wild-type mice and peripheral samples from bipolar patients.⁶⁰ GSK-3 β also plays a crucial role in circadian rhythmicity, which is often impaired in the earliest stages of hypo/mania. Therefore, like lithium itself, pharmacologic or genetic manipulations of GSK-3 β may have antimanic, antidepressant, and/or maintenance effects depending on type of episode.

GSK-3 β inhibition results in decreased phosphorylation/stabilization of β -catenin. This normalizes transcription of multifarious messenger ribonucleic acids (mRNAs) that affect synaptic transmission, postsynaptic signaling, and cytoskeletal reorganization in BD brain. Like GSK-3 β modulation, the over-expression of dephosphorylated β -catenin in rodents had mood stabilizing effects analogous to lithium.⁶¹ As a result of these findings, more selective GSK-3 β inhibitors, agents to promote dephosphorylated β -catenin accumulation, and/or the manipulation of upstream targets in this cascade, ie, Wnt-neutralizing antibodies, and/or Fz receptor antagonists, are potentially novel molecular targets in BD treatment.

Mitochondria/cell survival

In the past decade, there has been a burst of interest in mitochondrial-based cell signaling pathways in BD (Table 1). BD is associated with increased intracellular Ca²⁺, which may be released from intracellular stores, eg, endoplasmic reticulum and mitochondria, and/or influx through the stimulation of cell surface receptors. Excessive NMDA receptor activation via glutamate promotes neuronal cell death (“excitotoxicity”) (Figure 2). A recent microarray screen in postmortem BD hippocampus identified the upregulation of numerous pro-apoptotic genes and downregulation of antioxidant and anti-apoptotic genes^{62,63} (Table 1). In an independent sample of BD patients, the phosphorylation of the glucocorticoid receptor was decreased (pro-apoptotic), heat shock protein (Hsp-70) levels were decreased (pro-apoptotic), cytosolic Bax expression was decreased (anti-apoptotic), and cytosolic cytochrome C protein was increased (pro-apoptotic) in manic, depressed, and euthymic cohorts, which suggests a complex relationship to intracellular apoptotic cascades.⁶⁴ The anti-apoptotic gene B-cell lymphoma-2 (Bcl-2), a mitochondrial CREB-responsive gene that prevents the release of cytochrome C and concomitant caspase (proteolytic enzyme) activation, has been genetically associated with BD in several studies by our group. First, lymphoblasts from bipolar subjects with the Bcl-2 SNP rs956572AA displayed decreased Bcl-2 expression and increased IP₃-mediated Ca²⁺-release relative to the AG/GG genotypes.⁶⁵ The same SNP was also associated with increased Glx (combined glutamate and glutamine)/creatinine ratio in the anterior cingulate cortex in euthymic BDI,⁶⁶ which again supports the kindling hypothesis with a further provocative hypothesis that there may be ongoing excitotoxic cell damage even when not manic or depressed. Next, a polymorphism in the promoter (−116G/C) of the Ca²⁺-responsive endoplasmic reticulum stress gene, *XBPI*, has been implicated in the pathophysiology and treatment of BD.⁶⁷ This polymorphism affects transcription in response to stress; valproic acid induces the transcription of the upstream gene *ATF6*, which may result in the downregulation of *XBPI* expression with effective treatment.⁶⁷ Although several other studies have confirmed decreased stress-induced *XBPI* expression in peripheral samples from bipolar patients,^{68,69} there is conflicting data on the *XBPI* −116G/G SNP and impaired stress-related transcription in BD.^{68,70}

The expression of proapoptosis genes is increased in bipolar disorder, but not in schiz [Mol Psychiatry. 2006]

Altered expression of apoptotic factors and synaptic markers in postmortem brain from [Neurobiol Dis. 2010]

Review Homeostatic functions of BCL-2 proteins beyond apoptosis. [Adv Exp Med Biol. 2010]

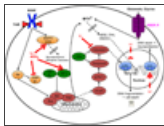


Figure 2

Neuroprotective/apoptotic intracellular cascades at baseline and as mitigated by mood stabilizers in BD. The canonical brain-derived neurotrophic factor (BDNF)/TrkB signaling pathway is presented to highlight its potent neurotrophic/mitogenic effects, ...

Although there are reports of pro-apoptotic effects of lithium in rodents,^{71,72} the preponderance of data support a neuroprotective role. In valinomycin (a potassium ionophore)-treated human SY5Y neuroblastoma cells, lithium decreased the expression of the pro-apoptotic caspase-3.⁷³ In a recent microarray study, lithium responders were found to selectively downregulate pro-apoptotic transcription, ie, Bax1 and Bad, and upregulate anti-apoptotic gene expression, ie, Bcl-2 and IRS2, after only one month of treatment.⁷⁴ Interestingly, the expression profile of lithium-resistance was the converse.⁷⁴ Pramipexole, a dopamine receptor agonist and downstream inducer of Bcl-2, had efficacy over placebo in a randomized, double-blind, placebo-controlled trial in BDII patients maintained on therapeutic levels of lithium or valproic acid.⁷⁵ Several pharmaceutical companies are attempting to develop inhibitors of apoptosis for many neuropsychiatric and medical disorders, which may ultimately find utility in the treatment of BD. Next, pro- and anti-apoptotic gene regulation may be a useful pharmacogenetic biomarker of treatment response, which warrants further investigation earlier in the course of lithium and anti-epileptic mood stabilizer therapy.

Conclusions/Future Directions

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In this second of two articles, we have reviewed our current understanding of intracellular second messenger/signal transduction pathways in the pathophysiology and treatment of BD. We have surveyed evidence in support (and, in some cases, in refutation) of dysfunction in the following intracellular second messenger/signal transduction cascades: cAMP/PKA/CREB, ERK/MAPK, PI/PKC, Wnt/Fz/Dvl/GSK-3 β , and anti- and pro-apoptotic pathways. There are several nodes of overlap and discrepancy with MDD and mouse models of despair, ie, PKC down-regulation in MDD/preclinical models and upregulation in BD. These differences warrant future diagnostic exploration and may eventually be exploited by novel treatments such as more selective PKC inhibitors. As a potential caveat, there have been relatively few studies *directly* demonstrating signal transduction impairment in the bipolar brain and/or response to effective treatment. Many of these studies have been conducted with rodent models, eg, psychostimulant-induced hyperlocomotion, or, when studied in humans, have occurred in small samples with carefully selected patients, eg, on a particular mood stabilizer, preserved psychosocial functioning, and no comorbid substance abuse. Therefore, although promising, these animal and clinical samples may not pertain to typical community bipolar patients. Moreover, our current technologies also limit our ability to directly test intracellular pathway dysfunction in the living human brain.

Apoptotic signaling cascades may be uniquely impaired in BD relative to

other neuropsychiatric disorders such as schizophrenia.⁶² Nevertheless, there have been few studies that have demonstrated apoptosis in the human bipolar brain, ie, Kim et al's⁶³ revelation of increased Bax/Bak and decreased Bcl-2 expression in postmortem BD brain. Expression differences, however, do not necessarily translate to increased apoptosis, which has been exemplified by non-apoptotic roles for Bcl-2.⁷⁶

In conclusion, our increasing understanding of intracellular second messenger/signal transduction pathway dysfunction in BD may eventually lead to improved diagnostic markers, better predictors of treatment response, and exciting future therapeutic targets. As a single example, the genetic manipulation of and/or small-molecule, membrane-permeant inhibitors of apoptosis are such novel therapeutic targets for future drug discovery and development.

Clinical Implications

- Bipolar disorder (BD) is a complex, highly-heritable major mood disorder characterized by episodes of hypo/mania and depression. Intracellular second messenger/signal transduction dysfunction in BD was first suggested by lithium's ability to inhibit protein kinase C (PKC).
- Including the aforementioned, some of the intracellular second messenger/signal transduction cascades that have been implicated in BD are the following: cAMP/PKA/CREB, ERK/MAPK, p11, PI/PKC, and Wnt/Fz/Dvl/GSK-3(beta).
- Apoptotic/cell survival dysfunction in BD has excited much interest in mitochondrial-based mechanisms of disease. Albeit preliminary, BCL-2 and XBP1 polymorphisms may be influential in BD.
- As in the other major mood disorder, major depressive disorder (MDD), intracellular second messenger/signal transduction abnormalities in BD and their reversal with successful treatment may be nosological endophenotypes and biomarkers of response to, respectively, improve diagnostics and further development of mood stabilizers with novel mechanisms of action.

Acknowledgments

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Footnotes

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Disclosures

Drs. Niciu, Ionescu, Mathews, and Richards have no potential financial conflicts of interest to disclose.

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