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Translating neurotrophic and cellular plasticity: from pathophysiology to improved therapeutics for bipolar disorder

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Abstract

Objective—Bipolar disorder (BD) likely involves, at a molecular and cellular level, dysfunctions of critical neurotrophic, cellular plasticity and resilience pathways and neuroprotective processes. Therapeutic properties of mood stabilizers are presumed to result from a restoration of the function of these altered pathways and processes through a wide range of biochemical and molecular effects. We aimed to review the altered pathways and processes implicated in BD, such as neurotrophic factors, mitogen-activated protein kinases, Bcl-2, phosphoinositol signaling, intracellular calcium and glycogen synthase kinase-3.

Methods—We undertook a literature search of recent relevant journal articles, book chapter and reviews on neurodegeneration and neuroprotection in BD. Search words entered were ‘brain-derived neurotrophic factor,’ ‘Bcl-2,’ ‘mitogen-activated protein kinases,’ ‘neuroprotection,’ ‘calcium,’ ‘bipolar disorder,’ ‘mania,’ and ‘depression.’

Results—The most consistent and replicated findings in the pathophysiology of BD may be classified as follows: i) calcium dysregulation, ii) mitochondrial/endoplasmic reticulum dysfunction, iii) glial and neuronal death/atrophy and iv) loss of neurotrophic/plasticity effects in brain areas critically involved in mood regulation. In addition, the evidence supports that treatment with mood stabilizers; in particular, lithium restores these pathophysiological changes.

Conclusion—Bipolar disorder is associated with impairments in neurotrophic, cellular plasticity and resilience pathways as well as in neuroprotective processes. The evidence supports that treatment with mood stabilizers, in particular lithium, restores these pathophysiological changes. Studies that attempt to prevent (intervene before the onset of the molecular and cellular changes), treat (minimize severity of these deficits over time), and rectify (reverse molecular and cellular deficits) are promising therapeutic strategies for developing improved treatments for bipolar disorder.

Keywords

brain-derived neurotrophic factor; Bcl-2; mitogen-activated protein kinases; neuroprotection; calcium; bipolar disorder; mania; depression

Introduction

Bipolar disorder (BD) likely arises from the complex interface among multiple susceptibility and protective genes and environmental factors. Its phenotype includes not only mood disturbances, but also a constellation of comorbidities, cognitive, motor, autonomic, neuroendocrine and neurovegetative alterations (1). This complex behavioural illness likely occurs through disturbances at multiple levels (systemic, cellular, molecular, and gene expression). On the basis of its polygenic origin, BD is characterized by the existence of diverse cellular and molecular targets associated not only with its pathophysiological basis, but also with its therapeutic profile. Most of these targets have been shown to critically regulate cellular plasticity and resilience (2). The objective of this study was to revise the evidences for the dysfunction of neurotrophic and cellular plasticity and resilience pathways in BD, with a particular focus on the disrupted process involved in neuroprotection.

Despite significant advances in the development of novel therapeutics during the last 20 years, the gold standard mood stabilizer lithium is still considered the most used and effective therapy for BD worldwide. Lithium exerts a wide range of effects at synapses and signal transduction pathways and has been used as an important tool in experimental paradigms of neuroprotection and neurotrophic effects; such paradigms are being used in the search of novel therapeutics for BD (1). It should be mentioned that most of these effects are associated with its chronic use at therapeutically relevant doses, which represents the key clinical paradigm when evaluating the predictive validity of lithium and other mood stabilizers.

Several direct targets of lithium have been identified and extensively studied, such as neurotrophic factors, mitogen-activated protein kinases, Bcl-2, phosphoinositol signaling, intracellular calcium, glutamate activity, and glycogen synthase kinase-3 (3–5). We proceed to review these targets of lithium in the following sections.

General concepts in neuroprotection and neuroplasticity: implications in BD

Neuroplasticity is characterized as the biological ability to induce and sustain important adaptative changes to internal and external stimuli in order to maintain the physiological functioning of the central nervous system (CNS). These changes aim to strengthen the synaptic signal and its efficacy through a direct regulation of neurotransmission (including receptor subunit phosphorylation and surface expression), intracellular signaling cascades in pre- and post-synaptic proteins as well as regulation of the expression of genes implicated in growth, survival, and synaptic transmission. These effects allow for a physiological remodeling of axonal and dendritic architecture. This remodeling is believed to be important to cellular resilience and at a clinical level, to mood stabilization.

Synaptic strength and cellular plasticity can be finely regulated over a short or even a long time scale by a combination of factors including previous activity of the network. Impairment of synaptic strength and cellular plasticity in mood disorders has been shown to involve changes in pathways regulating neurotrophic factors and neuroprotective proteins levels and expression. Neurotrophic factors, initially identified as modulators of neuronal growth and differentiation, have been currently considered critical regulators of plasticity and cell resilience in adult neurons and glia (1, 6). Activation of neuroprotective and

neurotrophic pathways has been also linked to the therapeutic effects of mood stabilizers. Even though lithium, valproate, and carbamazepine (CA) do not share similar chemical structure or all of the some biochemical targets, their neuroprotective effects have been shown to be the most replicated findings in both preclinical and clinical studies.

Aims of the study

This article will focus upon recent findings of cellular signaling abnormalities and impairments of cellular neurotrophic cascades that have been implicated in BD (Fig. 1).

Material and methods

We undertook a literature search of recent relevant journal articles, book chapter and reviews on this subject. Search words entered were ‘brain-derived neurotrophic factor,’ ‘Bcl-2,’ ‘GSK3,’ ‘IP3,’ ‘mitogen-activated protein kinases,’ ‘neuroprotection,’ ‘neurotrophic,’ ‘calcium,’ ‘bipolar disorder,’ ‘mania,’ and ‘depression.’

Results

Neuroimaging and neuropathological human studies: evidence of cellular dysfunction in BD

Reductions in volume, density, number and/or size of neurons and glial cells have been described in the subgenual prefrontal cortex (PFC), orbital cortex, dorsal anterolateral PFC, amygdala, and basal ganglia and dorsal raphe nuclei in BD (2, 7–9). Also, decreased glial cells density and increased nuclei size have been described in frontal cortical areas (1, 9–12). In parallel, reduced gray matter volumes in areas of the orbital and medial PFC, ventral striatum and hippocampus, and enlargement of third ventricles were observed in patients with BD. Significant reductions in the subgenual PFC glial number (41%) has also been reported in patients with a family history of BD (3–5, 10). A meta-analysis of imaging studies concluded that volumetric abnormalities of the subgenual PFC, striatum, hippocampus, and amygdala are present in first episode BD and children with BD (13). Other studies have found reductions in oligodendrocyte number and gene expression changes in the dorsolateral prefrontal cortex in individuals with BD (7–9, 14, 15). Interestingly, imaging data suggest that adolescents with BD who are taking mood stabilizers may be protected from the volume loss (16).

The presence of white matter abnormalities has been also described in imaging studies in BD. Although the cause of white matter hyperintensities in mood disorders is unknown, their presence particularly in the brains of young patients with BD suggests that importance in the pathophysiology of the illness (17, 18). In postmortem brain studies, reduced subcortical nuclei volumes in BD has been reported (19, 20). Neuronal density and size were found to be decreased in layers III, V, and VI in BD (8, 9, 11). Also, smaller pyramidal cell soma size was found in the hippocampal CA1 region (21).

Consistent with neurotrophic/neuroprotective properties of lithium and valproate, patients treated with chronic lithium or valproate exhibited subgenual PFC volumes that were significantly greater than non-treated patients, and not significantly different from controls (22). Also, in two elegant imaging studies, Moore et al. (23, 24) observed elevated N-acetyl-aspartate (NAA) (a mitochondrial marker of neuronal integrity) levels and gray matter volume in lithium-treated subjects. A subsequent MRI study by Sassi et al. (25) also showed an increased gray matter volume in lithium-treated BD subjects compared with untreated and healthy controls. Interestingly, the lithium-induced NAA increase showed a strong specificity to the gray matter. Other studies have noted similar effects with other mood stabilizers (16, 26).

Calcium dynamics, Bcl-2 regulation, and mitochondrial/endoplasmic reticulum (ER) activity

The calcium ion (Ca^{2+}) is a ubiquitous intracellular messenger controlling diverse critical biological functions in the human CNS. Calcium ions influence the synthesis and release of neurotransmitters and second-messenger cascades, thus affecting plasticity activation, intracellular signaling, energy metabolism, and synaptic consolidation (27–29). Mitochondria regulate different metabolic activities such as control of apoptosis, glutamate-mediated excitotoxic neuronal injury, and oxidative stress activity. Mitochondrial-encoded genes regulate synaptic activity related to long-lasting up-regulation of energy production (30, 31). Mitochondrial Ca^{2+} regulation also has a critical role in neuronal and glial activity, modulating both physiological and pathophysiological cellular responses (32). Decreased ATP and NAA levels in human studies have been associated with dysfunctions in mitochondrial metabolism. Inhibitors of the mitochondrial respiratory chain lead to a decrease in NAA levels, which is associated with deficits on ATP and oxygen availability (1, 33).

Impaired regulation of Ca^{2+} cascades is one of the most reproducible biological abnormalities described in BD research. It directly involves mitochondria and ER activity and has a critical role in neuroplasticity and cell survival. For instance, specific dysfunctions in store-operated calcium channel, ER function, and mitochondrial calcium uptake have been described in BD (2, 34). Elevated basal and agonist-stimulated intracellular Ca^{2+} levels in platelets and lymphocytes of bipolar I disorder (BD-I) have been widely described as well (1, 35–40). At therapeutically relevant doses, lithium attenuated agonist-stimulated intracellular Ca^{2+} responses (3–5, 41, 42). Furthermore, chronic lithium was shown to block an increase in calcium concentration, thus preventing oxidative stress and loss of mitochondrial membrane potential (6, 43, 44).

Mitochondrial dysfunction in BD was first proposed by Kato and Kato (45–47) and has been substantiated by others as well (see (9–12, 30). Konradi et al. (48) have also showed reduced expression of genes encoding mitochondrial proteins (including phosphorylation of mitochondrial inner membrane, subunits I and V). Decreased levels of NDUFV2 gene (a nuclear-encoded mitochondrial complex I subunit gene) was described in patients with BD (13, 49). Recently, Andreazza et al. reported a selective decrease in mitochondrial complex I subunit NDUF7 activity in BD subjects (7–9, 14, 15, 50). Also, decreased pH and increased lactate, with altered oxidative phosphorylation (16, 51) were observed in the brains of BD subjects, giving further evidence for this model. Other related findings includes altered expression of antioxidant genes and its levels in patients with BD (17, 18, 52, 53), as well as a significant increase in the number of proapoptotic genes in hippocampus from BD subjects (19, 20, 52). Interestingly, a downregulation in the proteins of the electron transfer chain in BD in glucose-deprived medium has also been described (8, 9, 11, 54).

Bcl-2 is a membrane-associated protein with both antiapoptotic and neuroprotective properties expressed preferentially in the limbic system (21, 55). Bcl-2 is mainly localized in the outer mitochondrial membrane and ER (22, 56–58) and activates neurotrophic pathways inducing neurite sprouting/outgrowth and axonal regeneration, thus preventing the deleterious effects of different insults (23, 24, 56, 57). Bcl-2 attenuates release of calcium from the ER and stabilizes mitochondrial membrane integrity thus limiting the release of cytochrome from mitochondria and activation of apoptotic pathways (25, 56, 59). Recently, the Bcl-2 rs956572 genotype AA was found to be associated with an abnormal Bcl-2 expression and to contribute to a dysfunctional Ca^{2+} homeostasis in BD, these effects were reversed by lithium (16, 26, 60). These effects seem to involve a direct regulation by inositol 1,4,5-triphosphate (IP3) receptors (27–29, 60). Also, chronic lithium treatment increased Bcl-2 expression and protein levels in the frontal cortex, hippocampus and striatum (30, 31,

61, 62). Repeated electroconvulsive treatment (ECT) administration in primates increased precursor cell proliferation in the dentate gyrus (DG) because of increased expression of Bcl-2 (32, 63). Bcl-2 knockout mice were found to have increased anxiety-like behaviours (64), supporting the role of this gene in mediating emotional-like behaviours.

The ER has also been shown to be critically involved in the regulation of intracellular calcium levels. Ca^{2+} is released from the ER mostly through IP_3 receptors. XBP1, a pivotal gene in ER stress response, has been considered a genetic risk factor for BD and its variant XBP1C/G has been associated with higher stress responses in lymphoblastoid cells lines (65). So et al. (66) observed impaired ER stress responses in BD subjects. Moreover, Hayashi et al. (67) reported that the induction of the spliced form of XBP1 and total XBP1 was significantly attenuated in patients with BD. Interestingly, chronic valproate and lithium regulate expression of ER stress proteins (68, 69). More recently, it was suggested that XBP1 116C/G would predict response to treatment with valproate (70).

In addition, patients presenting Darier's disease, a disease that involves a mutation in the ER Ca^{2+} pump (SERCA) also have high rates of comorbid BD and/or the presence of manic-like symptoms.

Overall, changes in the expression of diverse mitochondrial/ER and plasticity genes regulated by calcium and Bcl-2 have been shown to significantly affect cellular viability and lithium seems to rescue cells from these deleterious effects.

Neurotrophic signaling cascades: BDNF and extracellular signal-regulated kinase–mitogen-activated protein kinase (ERK/MAPK) pathway

Members of the neurotrophin family include nerve growth factor, *brain-derived neurotrophic factor* (BDNF), neurotrophins 3, 4, 5, and 6 and others. They bind to and activate a specific receptor tyrosine kinase (Trk) family. BDNF binds to the TrkB receptor with high affinity, thus activating diverse intracellular cascades involved in cellular survival and growth, such as the PI3K/Akt, MEK/ERK and phospholipase C (PLC)/PIP₂ signaling systems (71). BDNF exerts its biological effects through at least three key signaling pathways: phosphoinositide-3-kinase (PI3K)/Akt, PLC, or ERK–mitogen-activated kinase pathways. BDNF and the ERK pathways are considered key signaling cascades mediating neurotrophic actions and synaptic plasticity (7).

Altered BDNF levels and expression have been described in different animal models of depression and mania (72). Preclinical studies have also described that stress, which is involved in mood disorders, decreases the expression of BDNF (73). Interestingly, the interaction between BDNF and corticosteroids has been suggested to mediate the vulnerability to mood disorders (2). Chronic anti-depressant treatment increases BDNF expression in rat prefrontal cortex and hippocampus (74).

Peripheral levels of BDNF showed a significant decrease during manic and depressive episodes in mood disorders, which in some cases were shown to be significantly associated with the severity of symptoms and therapeutic response to antidepressants (53, 75). Furthermore, we recently reported that lithium monotherapy increases BDNF in acutely manic patients (76). Based on these findings of altered BDNF levels during mood episodes in peripheral cells and plasma/serum, it has been proposed that this neurotrophin may be a useful surrogate outcome measure of clinical improvement in mood disorder patients undergoing treatment (72).

The ERK/MAPK pathway has also been implicated in mediating some behavioural and pathophysiological facets of BD, presumably by mediating long-term cell plasticity events

(77). The ERK/MAPK pathway is a major intracellular signaling cascade mediating the biological effects of neurotrophic factors. Activated ERK phosphorylates diverse proteins involved in cellular plasticity (78). The regulatory effects of mood stabilizers on cell survival and resilience have been shown to be mediated by activation of the MAPK cascade. One target of the ERK/MAPK cascade is ribosomal S6 kinase (RSK), which activates cAMP response element-binding (CREB). RSK phosphorylates CREB, thus increasing the expression of the neuroprotective proteins involved in BD pathophysiology (64, 79) (see Fig. 1). Recently, it was demonstrated that ERK1 KO mice exhibit a behavioural excitement profile in several models of depression and mania (78).

Regarding therapeutics, the potential involvement of ERK cascade in the effects of mood stabilizers has been shown. Chronic lithium and valproate activate a major neurotrophic signaling pathway—the ERK/MAPK cascade, and its downstream effectors RSK and CREB. Studies have shown that therapeutic dose of lithium and valproate upregulate the ERK/MAPK cascade in human neuroblastoma cells (77, 80). Also, chronic lithium and valproate at therapeutically relevant concentrations robustly increase the levels of activated ERK and RSK (measured by the phosphorylation of ERK and RSK) in the anterior cingulate cortex, hippocampus, rodent cerebellum, and cortex (61, 80–82). Taken together, these data support an integrated role for the BDNF and ERK pathways in the pathophysiology and therapeutic action of mood stabilizers.

Phosphoinositol signaling pathway (IP₃/Inositol cascade)

The phosphoinositol signaling pathway (IP₃/Inositol cascade) has been linked to many cellular processes and pathological conditions (83). PLC produces diacylglycerol and IP₃, the latter of which binds IP₃ receptors on the ER to generate calcium mobilization from internal stores (84, 85). Binding IP₃ to its receptor induces release of ER calcium content. IP₃ binding sets forth downstream and is recycled back to PIP-2 by the enzymes IMPase and IPPase. It is important to mention that IMPA2 encoding IMPase is a candidate susceptibility gene for BD. One of the two human IMPase genes, *IMPA2* (86–89), was reported to be genetically associated with BD (87, 90). The ‘inositoldepletion hypothesis’ postulated that lithium, characterized as an uncompetitive inhibitor of inositol-1-phosphatase, generated its therapeutic effects by decreasing myoinositol levels. Lithium depletes IP₃ levels mediated by inhibiting of inositol monophosphatase and consequently decreases free inositol levels (87, 90).

Lithium has been shown to reduce inositol levels (1–4) by inhibiting IMPase *in vivo* (91), although the magnitude of inhibition is generally modest. However, it is not fully elucidated whether reduction in inositol is sufficient to limit PI or PIP₂ synthesis. Williams et al. (2002), using a tissue-culture assay that measures sensory neuron growth-cone stability, have demonstrated that mood stabilizers (lithium, carbamazepine and valproate) share a similar mechanism of action. These findings reinforce the neural development hypothesis for lithium effects (92). Overall, the concept that lithium inhibits the dephosphorylation of IP₃ at therapeutic concentrations, depleting cells of free inositol and bringing about its therapeutic effects has been questioned, but still remains an important reference in this area.

Glycogen synthase kinase (GSK-3)

GSK-3 is a kinase that acts as an intermediary in numerous intracellular signaling pathways and is regulated by serotonin, dopamine, psychostimulants, and antidepressants (3). GSK-3 is a key regulator of apoptosis and cellular plasticity/resilience, and this role has been postulated to be a key molecular target for lithium and valproate effects (5, 93). Lithium is considered a direct inhibitor of GSK-3, via competition with magnesium for a binding site

(94, 95). In mice, GSK-3 has also been shown to be inhibited by the structurally dissimilar valproate (96), and ECT, a non-pharmacologic therapy for mood disorders (97).

Animal behavioural data, from pharmacologic and genetic models, has shown that manipulation of GSK-3 produces both antidepressant and anti-manic effects (3, 98). Similarly, lithium has been demonstrated to exert both such effects. Also, it was found that lithium-induced behaviours in wild-type mice are phenocopied by overexpression of the GSK-3 target, β -catenin. GSK-3 inhibition results in a decrease in phosphorylation and degradation of its target β -catenin, and at therapeutically relevant concentrations, lithium increases β -catenin and Wnt-mediated gene expression in rodent brain. Notably, both lithium and β -catenin overexpression display mood stabilizing-like actions in prototypical animal models of mania (D-amphetamine hyperlocomotion) and depression (forced swim test) (99). It was therefore hypothesized that transgenic mice that over-express a constitutively active form of β -catenin would phenocopy lithium's behavioural effects. Further studies have been carried out to identify the GSK-3 target most relevant to lithium's behavioural effects.

Interestingly, GSK-3 has been found to play a critical role in regulating circadian rhythm, in preclinical models (100, 101). Patients with BD often demonstrate circadian disturbances, and lithium has been shown to increase circadian period in humans and animals (92, 102, 103), consistent with a consistent decrease in GSK-3 activity. Studies showing that psychomimetic drugs (amphetamine, Lysergic acid diethylamide (LSD), and Phencyclidine (PCP)) increase GSK-3 phosphorylation in frontal cortex and striatum (104) provide circumstantial support for the possibility of an underlying GSK-3 abnormality in BD. However, direct evidence for the role of GSK-3 in the etiology of BD has not been reported yet, and genetic studies have not reproducibly found GSK-3 polymorphisms to be associated with the disease. Therefore, it remains to be determined whether the pathophysiology of BD involves dysfunction of GSK-3 itself, or of other signaling molecules regulated by GSK-3. Nevertheless, in view of the role of GSK-3 in neural plasticity, survival, and circadian rhythms, and its involvement in the action of mood stabilizers, development of new selective GSK-3 inhibitors is actively underway by numerous pharmaceutical companies.

Discussion

The search for strategies aiming to improve neuroprotection and neurotrophic effects may represent a promising field for the development of improved treatments for BD. Regional reductions in brain volume are most likely a consequence of impairments of structure plasticity and resilience. While there is preclinical data describing neurotrophic and neuroprotective alterations in BD and reversal of these deficits with mood stabilizers, data linking these alterations to patients is lacking. Overall, the most consistent and replicated findings in the pathophysiology of BD may be classified as follows: i) calcium dysregulation, ii) mitochondrial/endoplasmic reticulum dysfunction leading to, iii) glial and neuronal death/atrophy and iv) loss of neurotrophic/plasticity effects in brain areas critically involved in mood regulation. These changes may be interconnected and studies examining these potential associations are needed. Studies that attempt to prevent (intervene before the onset of the molecular and cellular changes), treat (minimize severity of these deficits over time), and rectify (reverse molecular and cellular deficits) are promising therapeutic avenues for developing improved treatments for BD. Investigations are ongoing in these areas and may provide further insights into the complex pathophysiological basis of this illness with the goal of improved therapeutics.

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References

1. Machado-Vieira R, Manji HK, Zarate CA. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. *Bipolar Disord.* 2009; 11(Suppl 2):92–109. [PubMed: 19538689]
2. Manji HK, Quiroz JA, Sporn J, et al. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry.* 2003; 53:707–742. [PubMed: 12706957]
3. Gould TD, Manji HK. Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology.* 2005; 30:1223–1237. [PubMed: 15827567]
4. Gurvich N, Klein PS. Lithium and valproic acid: parallels and contrasts in diverse signaling contexts. *Pharmacol Ther.* 2002; 96:45–66. [PubMed: 12441177]
5. Li X, Bijur GN, Jope RS. Glycogen synthase kinase-3beta, mood stabilizers, and neuroprotection. *Bipolar Disord.* 2002; 4:137–144. [PubMed: 12071511]
6. Coyle JT, Manji HK. Getting balance: drugs for bipolar disorder share target. *Nat Med.* 2002; 8:557–558. [PubMed: 12042799]
7. Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. *Psychopharmacol Bull.* 2001; 35:5–49. [PubMed: 12397885]
8. Cotter DR, Pariante CM, Everall IP. Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain Res Bull.* 2001; 55:585–595. [PubMed: 11576755]
9. Rajkowska G. Cell pathology in mood disorders. *Semin Clin Neuropsychiatry.* 2001; 7:281–292. [PubMed: 12382210]
10. Ongür D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA.* 1998; 95:13290–13295. [PubMed: 9789081]
11. Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry.* 2000; 48:766–777. [PubMed: 11063973]
12. Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry.* 2001; 49:741–752. [PubMed: 11331082]
13. Hajek T, Carrey N, Alda M. Neuroanatomical abnormalities as risk factors for bipolar disorder. *Bipolar Disord.* 2005; 7:393–403. [PubMed: 16176432]
14. Tkachev D, Mimmachk ML, Ryan MM, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet.* 2003; 362:798–805. [PubMed: 13678875]
15. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res.* 2004; 67:269–275. [PubMed: 14984887]
16. Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A. Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005; 44:565–573. [PubMed: 15908839]
17. Lenox RH, Gould TD, Manji HK. Endophenotypes in bipolar disorder. *Am J Med Genet.* 2002; 114:391–406. [PubMed: 11992561]
18. Stoll AL, Renshaw PF, Yurgelun-Todd DA, Cohen BM. Neuroimaging in bipolar disorder: what have we learned? *Biol Psychiatry.* 2000; 48:505–517. [PubMed: 11018223]
19. Baumann B, Danos P, Krell D, et al. Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a postmortem study. *J Neuropsychiatry Clin Neurosci.* 1999; 11:71–78. [PubMed: 9990559]
20. Bielau H, Trübner K, Krell D, et al. Volume deficits of subcortical nuclei in mood disorders A postmortem study. *Eur Arch Psychiatry Clin Neurosci.* 2005; 255:401–412. [PubMed: 16080015]

21. Liu L, Schulz SC, Lee S, et al. Hippocampal CA1 pyramidal cell size is reduced in bipolar disorder. *Cell Mol Neurobiol.* 2007; 27:351–358. [PubMed: 17235693]
22. Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog Brain Res.* 2000; 126:413–431. [PubMed: 11105660]
23. Moore GJ, Bebchuk JM, Hasanat K, et al. Lithium increases N-acetyl-aspartate in the human brain: *in vivo* evidence in support of bcl-2's neurotrophic effects? *Biol Psychiatry.* 2000; 48:1–8. [PubMed: 10913502]
24. Moore GJ, Bebchuk JM, Wilds IB, CHEN G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet.* 2000; 356:1241–1242. [PubMed: 11072948]
25. Sassi RB, Nicoletti M, Brambilla P, et al. Increased gray matter volume in lithium-treated bipolar disorder patients. *Neurosci Lett.* 2002; 329:243–245. [PubMed: 12165422]
26. Yucel K, Mckinnon MC, Taylor VH, et al. Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. *Psychopharmacology.* 2007; 195:357–367. [PubMed: 17705060]
27. Kato T. Role of mitochondrial DNA in calcium signaling abnormality in bipolar disorder. *Cell Calcium.* 2008; 44:92–102. [PubMed: 18177933]
28. Török TL. Neurochemical transmission and the sodium-pump. *Prog Neurobiol.* 1989; 32:11–76. [PubMed: 2563913]
29. Wolff DJ, Poirier PG, Brostrom CO, Brostrom MA. Divalent cation binding properties of bovine brain Ca²⁺ + -dependent regulator protein. *J Biol Chem.* 1977; 252:4108–4117. [PubMed: 193856]
30. Quiroz JA, Gray NA, Kato T, Manji HK. Mitochondrially mediated plasticity in the pathophysiology and treatment of bipolar disorder. *Neuropsychopharmacology.* 2008; 33:2551–2565. [PubMed: 18235426]
31. Mattson MP. Mitochondrial regulation of neuronal plasticity. *Neurochem Res.* 2007; 32:707–715. [PubMed: 17024568]
32. Simpson PB, Russell JT. Role of mitochondrial Ca²⁺ + regulation in neuronal and glial cell signalling. *Brain Res Brain Res Rev.* 1998; 26:72–81. [PubMed: 9600625]
33. Bates TE, Strangward M, Keelan J, Davey GP, Munro PM, Clark JB. Inhibition of N-acetylaspartate production: implications for 1H MRS studies *in vivo* . *NeuroReport.* 1996; 7:1397–1400. [PubMed: 8856684]
34. Kato T, Ishiwata M, Mori K, et al. Mechanisms of altered Ca²⁺ + signalling in transformed lymphoblastoid cells from patients with bipolar disorder. *Int J Neuropsychopharmacol.* 2003; 6:379–389. [PubMed: 14604453]
35. Dubovsky SL, Christiano J, Daniell LC, et al. Increased platelet intracellular calcium concentration in patients with bipolar affective disorders. *Arch Gen Psychiatry.* 1989; 46:632–638. [PubMed: 2735813]
36. Dubovsky SL, Murphy J, Thomas M, Rademavher J. Abnormal intracellular calcium ion concentration in platelets and lymphocytes of bipolar patients. *Am J Psychiatry.* 1992; 149:118–120. [PubMed: 1728159]
37. Tan CH, Javors MA, Seleshi E, Lowrimore PA, Bowden CL. Effects of lithium on platelet ionic intracellular calcium concentration in patients with bipolar (manic-depressive) disorder and healthy controls. *Life Sci.* 1990; 46:1175–1180. [PubMed: 2342403]
38. Emamghoreishi M, Schlichter L, LI PP, et al. High intra-cellular calcium concentrations in transformed lymphoblasts from subjects with bipolar I disorder. *Am J Psychiatry.* 1997; 154:976–982. [PubMed: 9210749]
39. Hough C, Lu SJ, Davis CL, Chuang DM, Post RM. Elevated basal and thapsigargin-stimulated intracellular calcium of platelets and lymphocytes from bipolar affective disorder patients measured by a fluorometric microassay. *Biol Psychiatry.* 1999; 46:247–255. [PubMed: 10418700]
40. Suzuki K, Kusumi I, Sasaki Y, Koyama T. Serotonin-induced platelet intracellular calcium mobilization in various psychiatric disorders: is it specific to bipolar disorder? *J Affect Disord.* 2001; 64:291–296. [PubMed: 11313098]
41. Wasserman MJ, Corson TW, Sibony D, et al. Chronic lithium treatment attenuates intracellular calcium mobilization. *Neuropsychopharmacology.* 2004; 29:759–769. [PubMed: 14970832]

42. Andreopoulos S, Wasserman M, Woo K, Li PP, Warsh JJ. Chronic lithium treatment of B lymphoblasts from bipolar disorder patients reduces transient receptor potential channel 3 levels. *Pharmacogenomics*. 2004; 4:365–373.
43. Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. *Neuropharmacology*. 2002; 43:1173–1179. [PubMed: 12504924]
44. Tseng WP, Lin-Shiau SY. Long-term lithium treatment prevents neurotoxic effects of beta-bungarotoxin in primary cultured neurons. *J Neurosci Res*. 2002; 69:633–641. [PubMed: 12210829]
45. Kato T, Kato N. Mitochondrial dysfunction in bipolar disorder. *Bipolar Disord*. 2000; 1(3 Pt 1): 180–190. [PubMed: 11256685]
46. Kato T, Kunugi H, Nanko S, Kato N. Mitochondrial DNA polymorphisms in bipolar disorder. *J Affect Disord*. 2001; 62:151–164. [PubMed: 11223103]
47. Murashita J, Kato T, Shioiri T, Inubushi T, Kato N. Altered brain energy metabolism in lithium-resistant bipolar disorder detected by photic stimulated 31P-MR spectroscopy. *Psychol Med*. 2000; 30:107–115. [PubMed: 10722181]
48. Konradi C, Eaton M, Macdonald ML, Walsh J, Benes FM, Heckers S. Molecular evidence for mitochondrial dysfunction in bipolar disorder. *Arch Gen Psychiatry*. 2004; 61:300–308. [PubMed: 14993118]
49. Washizuka S, Kakiuchi C, Mori K, et al. Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2003; 120B: 72–78. [PubMed: 12815743]
50. Andreazza AC, Shao L, Wang JF, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. *Arch Gen Psychiatry*. 2010; 67:360–368. [PubMed: 20368511]
51. Stork C, Renshaw PF. Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance spectroscopy research. *Mol Psychiatry*. 2005; 10:900–919. [PubMed: 16027739]
52. Benes FM, Matzilevich D, Burke RE, Walsh J. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. *Mol Psychiatry*. 2006; 11:241–251. [PubMed: 16288314]
53. Machado-Vieira R, Dietrich MO, Leke R, et al. Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. *Biol Psychiatry*. 2007; 61:142–144. [PubMed: 16893527]
54. Naydenov AV, Macdonald ML, Ongur D, Konradi C. Differences in lymphocyte electron transport gene expression levels between subjects with bipolar disorder and normal controls in response to glucose deprivation stress. *Arch Gen Psychiatry*. 2007; 64:555–564. [PubMed: 17485607]
55. Bernier PJ, Parent A. The anti-apoptosis bcl-2 proto-oncogene is preferentially expressed in limbic structures of the primate brain. *Neuroscience*. 1998; 82:635–640. [PubMed: 9483524]
56. Adams JM, Cory S. The Bcl-2 protein family: arbiters of cell survival. *Science*. 1998; 281:1322–1326. [PubMed: 9735050]
57. Bruckheimer EM, Cho SH, Sarkiss M, Herrmann J, McDonnell TJ. The Bcl-2 gene family and apoptosis. *Adv Biochem Eng Biotechnol*. 1998; 62:75–105. [PubMed: 9755641]
58. Merry DE, Korsmeyer SJ. Bcl-2 gene family in the nervous system. *Annu Rev Neurosci*. 1997; 20:245–267. [PubMed: 9056714]
59. Murphy DG, Decarli C, Mcintosh AR, et al. Sex differences in human brain morphometry and metabolism: an *in vivo* quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Arch Gen Psychiatry*. 1996; 53:585–594. [PubMed: 8660125]
60. Machado-Vieira R, Pivovarova NB, Stanika RI, et al. The Bcl-2 gene polymorphism rs956572AA increases inositol 1,4,5-trisphosphate receptor-mediated endoplasmic reticulum calcium release in subjects with bipolar disorder. *Biol Psychiatry*. 2011; 69:344–352. [PubMed: 21167476]
61. Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? *Biol Psychiatry*. 1999; 46:929–940. [PubMed: 10509176]

62. Chen G, Zeng WZ, Yuan PX, et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *J Neurochem.* 1999; 72:879–882. [PubMed: 9930766]
63. Perera TD, Coplan JD, Lisanby SH, et al. Antidepressant-induced neurogenesis in the hippocampus of adult non-human primates. *J Neurosci.* 2007; 27:4894–4901. [PubMed: 17475797]
64. Einat H, Manji HK. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. *Biol Psychiatry.* 2006; 59:1160–1171. [PubMed: 16457783]
65. Kakiuchi C, Iwamoto K, Ishiwata M, et al. Impaired feedback regulation of XBP1 as a genetic risk factor for bipolar disorder. *Nat Genet.* 2003; 35:171–175. [PubMed: 12949534]
66. So J, Warsh JJ, Li PP. Impaired endoplasmic reticulum stress response in B-lymphoblasts from patients with bipolar-I disorder. *Biol Psychiatry.* 2007; 62:141–147. [PubMed: 17217928]
67. Hayashi A, Kasahara T, Kametani M, Toyota T, Yoshikawa T, Kato T. Aberrant endoplasmic reticulum stress response in lymphoblastoid cells from patients with bipolar disorder. *Int J Neuropsychopharmacol.* 2009; 12:33–43. [PubMed: 18771604]
68. Bown CD, Wang JF, Chen B, Young LT. Regulation of ER stress proteins by valproate: therapeutic implications. *Bipolar Disord.* 2002; 4:145–151. [PubMed: 12071512]
69. Shao L, Sun X, Xu L, Young LT, Wang JF. Mood stabilizing drug lithium increases expression of endoplasmic reticulum stress proteins in primary cultured rat cerebral cortical cells. *Life Sci.* 2006; 78:1317–1323. [PubMed: 16236328]
70. Kim B, Kim CY, Lee MJ, Joo YH. Preliminary evidence on the association between XBP1–116C/G polymorphism and response to prophylactic treatment with valproate in bipolar disorders. *Psychiatry Res.* 2009; 168:209–212. [PubMed: 19564049]
71. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog Neurobiol.* 2005; 76:99–125. [PubMed: 16099088]
72. Kapczinski F, Frey BN, Kauer-Sant'anna M, Grassi-Oliveira R. Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder. *Expert Rev Neurother.* 2008; 8:1101–1113. [PubMed: 18590480]
73. Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat Neurosci.* 2007; 10:1089–1093. [PubMed: 17726474]
74. Molteni R, Calabrese F, Bedogni F, et al. Chronic treatment with fluoxetine up-regulates cellular BDNF mRNA expression in rat dopaminergic regions. *Int J Neuropsychopharmacol.* 2006; 9:307–317. [PubMed: 16035958]
75. Cunha AB, Frey BN, Andreazza AC, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neurosci Lett.* 2006; 398:215–219. [PubMed: 16480819]
76. De Sousa RT, Van De Bilt MT, Diniz BS, et al. Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study. *Neurosci Lett.* 2011; 494:54–56. [PubMed: 21362460]
77. Chen G, Manji HK. The extracellular signal-regulated kinase pathway: an emerging promising target for mood stabilizers. *Curr Opin Psychiatry.* 2006; 19:313–323. [PubMed: 16612219]
78. Engel SR, Creson TK, Hao Y, et al. The extracellular signal-regulated kinase pathway contributes to the control of behavioral excitement. *Mol Psychiatry.* 2009; 14:448–461. [PubMed: 18227838]
79. Hashimoto K, Koizumi H, Nakazato M, Shimizu E, Iyo M. Role of brain-derived neurotrophic factor in eating disorders: recent findings and its pathophysiological implications. *Prog Neuropsychopharmacol Biol Psychiatry.* 2005; 29:499–504. [PubMed: 15866349]
80. Yuan PX, Huang LD, Jiang YM, Gutkind JS, Manji HK, Chen G. The mood stabilizer valproic acid activates mitogen-activated protein kinases and promotes neurite growth. *J Biol Chem.* 2001; 276:31674–31683. [PubMed: 11418608]
81. Einat H, Manji HK, Gould TD, Du J, Chen G. Possible involvement of the ERK signaling cascade in bipolar disorder: behavioral leads from the study of mutant mice. *Drug News Perspect.* 2003; 16:453–463. [PubMed: 14668941]
82. Chuang DM, Chen RW, Chalecka-Franaszek E, et al. Neuroprotective effects of lithium in cultured cells and animal models of diseases. *Bipolar Disord.* 2002; 4:129–136. [PubMed: 12071510]

83. Schlecker C, Boehmerle W, Jeromin A, et al. Neuronal calcium sensor-1 enhancement of InsP3 receptor activity is inhibited by therapeutic levels of lithium. *J Clin Invest*. 2006; 116:1668–1674. [PubMed: 16691292]
84. Finch EA, Augustine GJ. Local calcium signalling by ino-sitol-1,4,5-trisphosphate in Purkinje cell dendrites. *Nature*. 1998; 396:753–756. [PubMed: 9874372]
85. Takechi H, Eilers J, Konnerth A. A new class of synaptic response involving calcium release in dendritic spines. *Nature*. 1998; 396:757–760. [PubMed: 9874373]
86. Yoshikawa T, Turner G, Esterling LE, Sanders AR, Detera-Wadleigh SD. A novel human myo-inositol monophosphatase gene, IMP.18p, maps to a susceptibility region for bipolar disorder. *Mol Psychiatry*. 1997; 2:393–397. [PubMed: 9322233]
87. Sjöholt G, Ebstein RP, Lie RT, et al. Examination of IMPA1 and IMPA2 genes in manic-depressive patients: association between IMPA2 promoter polymorphisms and bipolar disorder. *Mol Psychiatry*. 2004; 9:621–629. [PubMed: 14699425]
88. Arai R, Ito K, Ohnishi T, et al. Crystal structure of human myo-inositol monophosphatase 2, the product of the putative susceptibility gene for bipolar disorder, schizophrenia, and febrile seizures. *Proteins*. 2007; 67:732–742. [PubMed: 17340635]
89. Ohnishi T, Yamada K, Ohba H, et al. A promoter haplotype of the inositol monophosphatase 2 gene (IMPA2) at 18p11.2 confers a possible risk for bipolar disorder by enhancing transcription. *Neuropsychopharmacology*. 2007; 32:1727–1737. [PubMed: 17251911]
90. Ohnishi T, Ohba H, Seo KC, et al. Spatial expression patterns and biochemical properties distinguish a second myo-inositol monophosphatase IMPA2 from IMPA1. *J Biol Chem*. 2007; 282:637–646. [PubMed: 17068342]
91. Hedgepeth CM, Conrad LJ, Zhang J, Huang HC, Lee VM, Klein PS. Activation of the Wnt signaling pathway: a molecular mechanism for lithium action. *Dev Biol*. 1997; 185:82–91. [PubMed: 9169052]
92. Iwahana E, Akiyama M, Miyakawa K, et al. Effect of lithium on the circadian rhythms of locomotor activity and glycogen synthase kinase-3 protein expression in the mouse suprachiasmatic nuclei. *Eur J Neurosci*. 2004; 19:2281–2287. [PubMed: 15090054]
93. Gould TD, Manji HK. The Wnt signaling pathway in bipolar disorder. *Neuroscientist*. 2002; 8:497–511. [PubMed: 12374432]
94. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci USA*. 1996; 93:8455–8459. [PubMed: 8710892]
95. Ryves WJ, Harwood AJ. Lithium inhibits glycogen synthase kinase-3 by competition for magnesium. *Biochem Biophys Res Commun*. 2001; 280:720–725. [PubMed: 11162580]
96. Chen G, Huang LD, Jiang YM, Manji HK. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. *J Neurochem*. 1999; 72:1327–1330. [PubMed: 10037507]
97. Roh MS, Kang UG, Shin SY, et al. Biphasic changes in the Ser-9 phosphorylation of glycogen synthase kinase-3beta after electroconvulsive shock in the rat brain. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; 27:1–5. [PubMed: 12551719]
98. Jope RS, Roh MS. Glycogen synthase kinase-3 (GSK3) in psychiatric diseases and therapeutic interventions. *Curr Drug Targets*. 2006; 7:1421–1434. [PubMed: 17100582]
99. Gould TD, Einat H, O'donnell KC, Picchini AM, Schloesser RJ, Manji HK. Beta-catenin overexpression in the mouse brain phenocopies lithium-sensitive behaviors. *Neuropsychopharmacology*. 2007; 32:2173–2183. [PubMed: 17299510]
100. Martinek S, Inonog S, Manoukian AS, Young MW. A role for the segment polarity gene shaggy/GSK-3 in the *Drosophila* circadian clock. *Cell*. 2001; 105:769–779. [PubMed: 11440719]
101. Kaladchibachi SA, Doble B, Anthopoulos N, Woodgett JR, Manoukian AS. Glycogen synthase kinase 3, circadian rhythms, and bipolar disorder: a molecular link in the therapeutic action of lithium. *J Circadian Rhythms*. 2007; 5:3. [PubMed: 17295926]
102. Johnsson A, Pflug B, Engelmann W, Klemke W. Effect of lithium carbonate on circadian periodicity in humans. *Pharmakopsychiatr Neuropsychopharmacol*. 1979; 12:423–425. [PubMed: 538086]

103. Jolma IW, Falkeid G, Bamerni M, Ruoff P. Lithium leads to an increased FRQ protein stability and to a partial loss of temperature compensation in the *Neurospora* circadian clock. *J Biol Rhythms*. 2006; 21:327–334. [PubMed: 16998153]
104. Svenningsson P, Tzavara ET, Carruthers R, et al. Diverse psychotomimetics act through a common signaling pathway. *Science*. 2003; 302:1412–1415. [PubMed: 14631045]

Clinical recommendations

- Neuroprotection and neurotrophic effects may represent a promising field for the development of improved treatments for bipolar disorder (BD).
- New therapeutic targets beyond monoamines are expected to involve intracellular signaling cascades involved in cell survival. Once the disrupted pathways are identified, therapeutic strategies would be aimed to prevent, treat, or rectify the identified altered cellular and molecular processes in BD
- Lithium represents an important tool to better understand the presumed targets involved in BD through its effects on neuroprotection, such as neurotrophic factors, mitogen-activated protein kinases, phosphoinositol signaling, intracellular calcium, energy metabolism (mitochondria and endoplasmic reticulum), and glycogen synthase kinase-3.

Additional comments

- The preclinical data showing neurotrophic and neuroprotective effects of mood stabilizers will need to be extended to the clinic to ascertain that they truly have a major role in the pathophysiology of BD.
- A major problem in neuropharmacological research is the difficulty in precisely ascribing therapeutic relevance to any observed biochemical finding, especially in the absence of suitable animal models (and unclear direct targets) for BD.

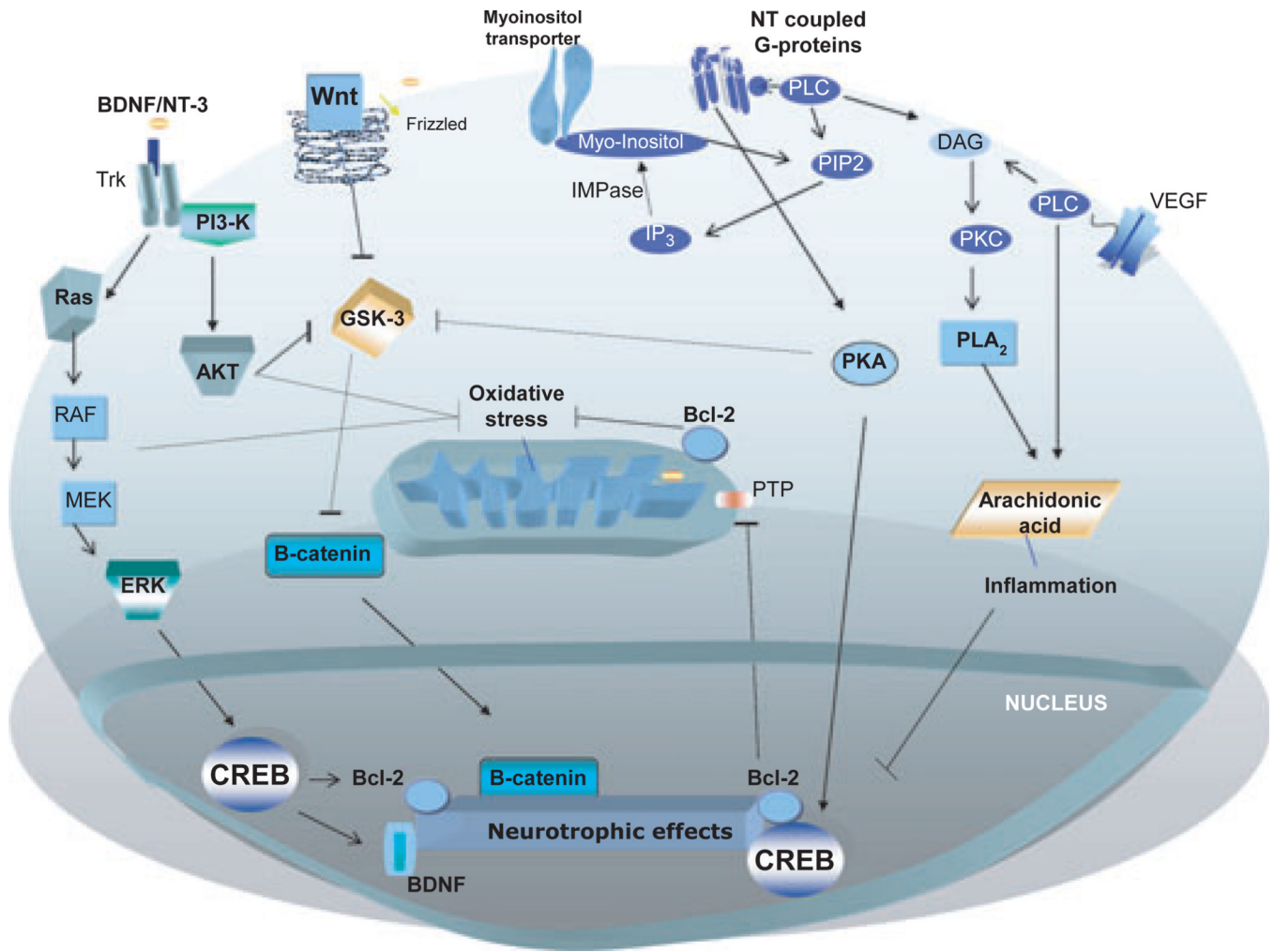


Fig. 1. Signaling abnormalities and impairment of neurotrophic cascades that underlie the neurobiological basis of bipolar disorder. Lithium increases their expression and/or levels, thus inducing neuroprotective and neurotrophic effects. Activation of brain neurotransmitter-coupled G-proteins induces PLC hydrolysis of PIP₂ to IP₃ and DAG (not shown), which activates PKC. IP₃ binds to the IP₃R, thus inducing the release of ER calcium stores. Elevated intracellular calcium levels have been described in bipolar disorder and may increase the risk of apoptosis. The neuroprotective protein Bcl-2 downregulates ER calcium release through an IP₃R-dependent mechanism. The same effect is induced by lithium treatment, which also increases Bcl-2 levels. IP₃ is recycled by IMPase, another of lithium's targets. Cellular signaling through Wnt glycoproteins and frizzled receptors result in GSK-3 β inhibition, a critical cellular target and effector for diverse proteins. Inhibition of GSK-3 β prevents β -catenin phosphorylation and stimulates its translocation to the nucleus, thus targeting transcription of specific genes activating neurotrophic effects and synaptogenesis. Activation of the BDNF receptor (Trk-B) activates the ERK/MAPK pathway, which inhibits GSK-3 β and BAD. Activation of the extracellular signal-regulated kinase-mitogen-activated protein kinase pathway by BDNF increases the expression of nuclear CREB, which facilitates the expression of neurotrophic/neuroprotective proteins such as Bcl-2 and BDNF. BDNF also activates the PI3K pathway, which indirectly inhibits GSK-3 β and BAD. Mitochondrial Bcl-2 and Bcl-x1 also inhibit pro-apoptotic activation of

BAD, as well as consequent mitochondrial increase in calcium influx and cytochrome C release. *Bcl-2* = *B-cell lymphoma-2*; *BDNF* = *brain-derived neurotrophic factor*; *CREB* = *cAMP response element binding protein*; *DAG* = *diacylglycerol*; *ERK* = *extracellular regulated kinase*; *GSK* = *glycogen synthase kinase*; *IMPase* = *inositol monophosphatase*; *IP₃* = *inositol 1,4,5-triphosphate 3*; *PI3K* = *phosphatidylinositol-3 kinase*; *PIP₂* = *phosphoinositide 4,5-biphosphate*; *PKC* = *protein kinase C*; *PLC* = *phospholipase C*; *PTP* = *permeability membrane pore*; *TrkB* = *tyrosine receptor kinase B*; *RAS* = *RA_t Sarcoma*; *AKT* = *B*; *PLA2* = *Phospholipase A2*; *PLC* = *Phospholipase C*; *VEFG* = *Vascular endothelial growth factor*; *NT-3* = *Neurotrophin-3*.