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Kinases as drug targets in the treatment of bipolar disorder

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Bipolar disorder is one of the most severely debilitating of all medical illnesses, and is increasingly recognized as a major public health problem. For many patients with bipolar disorder, current pharmacotherapy is insufficient. Exciting recent data suggest that regulation of signaling molecules may be involved in the pathophysiology of the disorder, and in the mechanisms of action of mood stabilizers and antidepressants. Through our developing understanding of the biochemical targets of effective medications, several potential targets for new therapies have emerged. This short review will focus on two of the most promising such targets: glycogen synthase-3 and protein kinase C.

Bipolar disorder is a common, chronic, recurrent mental illness that affects the lives and functioning of millions of individuals worldwide. It is associated with significant morbidity and mortality, and diminished workplace productivity, and is increasingly recognized as a major public health problem. Patients with bipolar disorder generally experience high rates of relapse, chronicity, residual symptoms, cognitive and functional impairment, and psychosocial disability [1]. Current pharmacotherapy effectively reduces symptom burden and maintains remission in a subset of bipolar patients, but for many these medications are inadequate. Despite receiving treatment, many patients continue to have recurrent mood episodes, residual symptoms, functional impairment, and significant medical and psychiatric comorbidity. Nearly all the currently available treatments exhibit a several week lag period of onset of action. Finally, no currently available treatments represent a cure for this illness. The development of targeted therapies that are more effective, work more rapidly, and are better tolerated than existing treatments is therefore desperately needed.

Why target signaling cascades in the treatment of bipolar disorder? A growing body of data supports the contention that bipolar disorder arises from structural and functional impairments related to synaptic and neuronal plasticity in various regions of the central nervous system (CNS). In addition, psychotropic drugs used to treat these conditions target molecules and signaling cascades implicated in synaptic and neuronal plasticity. Bipolar disorder is, therefore, increasingly conceptualized as a genetically influenced disorder of synapses and circuits rather than simply the result of deficits or excesses in individual neurotransmitters. Supporting this theory, in a recent whole-genome association study of bipolar disorder, all of the highly significant associations implicated signaling cascades [2]. The role of cellular signaling cascades has the potential to explain much of the complex neurobiology of bipolar disorder [3]. Cellular signaling cascades regulate the multiple neurotransmitter and neuropeptide systems implicated in the disorder, and are targets for the most effective treatments. These cascades mediate affective, cognitive, motoric, and neurovegetative functions that are affected in the illness. Abnormalities in cellular signaling cascades that regulate diverse physiologic functions also likely explain the tremendous medical comorbidity associated with the disorder. Targeting these cascades may stabilize the underlying disease process by reducing the frequency and severity of the profound mood cycling that characterize this disorder.

In this article, we focus on signaling molecules that represent targets for novel therapies for bipolar disorder. We review the literature on two of the most promising such targets: glycogen synthase-3 (GSK-3) and protein kinase C (PKC). Both have been identified as therapeutically relevant biochemical targets of currently available and effective medications, and hold the possibility of mediating more refined and sophisticated treatment for bipolar disorder. We also discuss potential strategies and particular issues

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regarding the targeting of kinases in the treatment of central nervous system (CNS) disorders.

Clinical overview

Bipolar disorder has an approximate lifetime incidence of 1.5% [3] and is characterized by two seemingly opposite mood states: mania and depression. The manic stages are characterized by a hyperaroused state (either euphoric or dysphoric), racing thoughts, impaired judgment, and an apparent decreased need for sleep [3]. The depressive phases of the illness present with similar symptomatology as those seen in major depression, and, as with depression, suicide is the cause of death in up to 15% of individuals with bipolar disorder [3]. Bipolar disorder is traditionally, and still most commonly, treated with the class of medications known as mood stabilizers. The prototype of this class is lithium; others include the anticonvulsants valproate (Depakote) and lamotrigine (Lamictal). Although other types of medications, including atypical antipsychotics, are also used to treat the illness, most research has focused on lithium and valproate. Both have been used effectively for decades in the treatment of patients with bipolar disorder, but in a significant subset of patients their utility is limited by disabling side effects and/or inadequate efficacy. The development of novel therapies with better efficacy, and fewer side effects, is therefore critical.

Two signaling pathways are emerging as particularly promising targets for the development of new treatments for bipolar disorder: GSK-3 and PKC.

GSK-3

GSK-3 is a ubiquitous multi-substrate serine/threonine kinase that is a key component of many intracellular signaling pathways including the insulin, neurotrophin, and Wnt pathways (Figure 1). GSK-3 is encoded by two genes, GSK-3α and GSK-3β, whose protein kinase domains are 98% identical [4]. GSK-3 is regulated by many of the key players in mood disorder pathophysiology and treatment, including serotonin, dopamine, glutamate, psychostimulants, antidepressants and mood stabilizers [5]. GSK-3 plays a critical role in multiple cellular processes, such as metabolism, proliferation, differentiation, axonogenesis and synaptogenesis [6–14]. Its role in the regulation of apoptosis and cellular plasticity/resilience is thought to be the target of the mood stabilizers lithium and valproate [15,16].

GSK-3 in the pathophysiology and treatment of bipolar disorder

Initial interest in GSK-3 as a target for the treatment of mood disorders arose from the seminal observation that lithium directly inhibited the enzyme [17]. It is now clear that lithium inhibits GSK-3 through a combination of direct binding to GSK-3 and increased phosphorylation of the inhibitory N-terminal serine of GSK-3 [18]. In mice, GSK-3 has also been shown to be inhibited by the structurally dissimilar valproate [19] (although whether this is via direct or indirect action remains controversial [5]), and by electroconvulsive seizure treatment (ECT), a non-pharmacologic therapy for mood disorders [20].

Lithium directly inhibits GSK-3 at therapeutically relevant concentrations *in vitro* and *in vivo* in diverse cell types, including cultured neurons and rodent brain, and subsequently activates glycogen synthesis and Wnt/ß-catenin-dependent transcription [17,21–28]. As discussed below, GSK-3's role in the modulation of neurogenesis, neuronal survival, mood-related behaviors, and circadian rhythms position GSK-3 as a potential key mediator of lithium's clinical effects in these domains.

GSK-3 as a mediator of the neurotrophic and neuroprotective effects of mood stabilizers

Neuropathological and neuroimaging studies clearly document regional atrophic changes and impairment in neurogenesis in

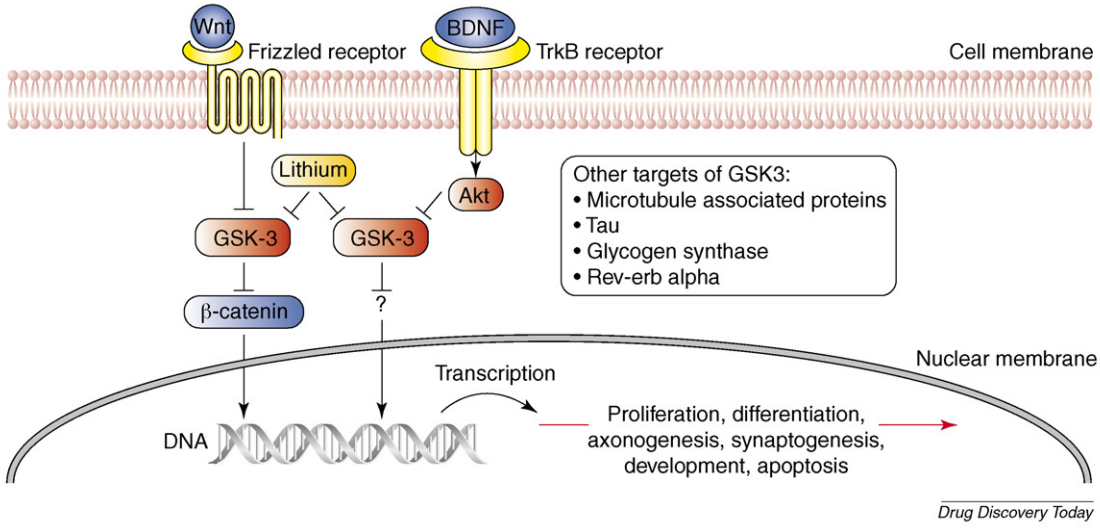

FIGURE 1

Wnt pathway and GSK-3. Mood stabilizers inhibit GSK-3. In the Wnt signaling pathway, Wnt glycoproteins interact with the frizzled family of receptors to stimulate the disheveled-mediated inactivation of GSK-3. Inhibition of GSK-3 prevents β-catenin phosphorylation and thereby inhibits degradation of this molecule that can act as a transcription factor binding to lef/tcf. Wnt proteins are implicated in the regulation of morphology, neurotransmission, and synaptogenesis. Reprinted with permission [80].

subjects with mood disorders. Although the exact relationship between these impairments of structural plasticity (cell loss, cell atrophy, white matter changes) and the complex symptomatology of bipolar disorder remain to be fully elucidated, numerous studies at the anatomic, cellular and molecular levels provide evidence for the neurotrophic and neuroprotective actions of mood stabilizers. Several neuroimaging studies have demonstrated an increase in gray matter content in the brains of bipolar subjects on lithium [29]. Interestingly, a recent longitudinal study demonstrated that lithium responders, but not non-responders, showed region-specific increases in gray matter [30]. At the cellular level, lithium has been shown to promote neural viability and exert neuroprotective effects in a variety of preclinical cell-toxicity and injury paradigms *in vitro* and *in vivo* [31–33]. Although the mood stabilizer valproate has not been as extensively studied as lithium, several studies have found that it does indeed exert neuroprotective effects in injury and toxicity paradigms *in vitro* and *in vivo* [34–37].

GSK-3 is a major regulator of apoptosis and cellular plasticity and resilience. Generally, increased activity of GSK-3 is pro-apoptotic [15,38]. Treatment of cultured neurons with other GSK-3 inhibitors or transfection with GSK-3 small interfering RNAs (siRNA) mimic lithium's neuroprotective effects [39]. Further evidence supports the role of GSK-3 in mediating lithium's axonogenesis effects. N-terminal phosphorylated GSK-3ß localizes to growth cones, and agents that induce growth cone collapse also induce dephosphorylation of GSK-3 [40,41]. Local GSK-3 inactivation regulates axon site formation [42–44].

GSK-3 as a mediator of AMPA receptor trafficking and function

AMPA receptor-mediated plasticity may represent a relevant target for the treatment of severe mood disorders. Studies in rodents using the therapeutic agents used to treat mood disorders have found that AMPA receptor synaptic localization and phosphorylation are increased after antidepressant treatment and decreased after treatment with anti-manic agents *in vivo* [45]. GSK-3 inhibitors have been shown to block long-term depression in hippocampal slices [46]. Thus, regulating of AMPA receptor trafficking may represent a very important role of GSK-3 in the treatment of mood disorders.

GSK-3 as a mediator of the mood-related behavioral effects of mood stabilizers

Animal behavioral data, from pharmacologic and genetic models, has shown that manipulation of GSK-3 produces both antidepressant and antimanic effects [5,47,48]. Mice lacking one copy of GFK-3β, for example, exhibit antidepressant-like behavior in the forced swim test [27], and reduced amphetamine-induced locomotor activation [49]. To our knowledge, this is the only manipulation, other than that of lithium, that results in both antimanic-like and antidepressant-like effects. Further studies have been carried out to identify the GSK-3 target most relevant to lithium's behavioral effects. 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. Transgenic mice that overexpress a constitutively active form of β-catenin phenocopy lithium's behavioral effects. Notably, lithium and β-catenin overexpression have mood stabilizing-like actions in prototypical animal models of mania (D-amphetamine hyperlocomotion) and depression (forced swim test) [50].

GSK-3 as a mediator of circadian rhythms

Clinical features of bipolar disorder such as diurnal variation in mood, early morning awakening, and cyclicity and seasonality of recurrences have led to speculation that abnormalities in circadian rhythm play an important role in its pathophysiology [51,52]. A polymorphism in the human CLOCK gene has been associated with circadian mood fluctuation and illness recurrence in bipolar disorder [53]. GSK-3 has been found to play a role in regulating circadian rhythm, in Drosophila [54] and in mice [55]. Lithium has been shown to increase circadian period in many organisms including humans [56–58], consistent with a decrease in GSK-3 activity.

GSK-3 and the pathophysiology of bipolar disorder

In the context of the evidence that GSK-3 mediates the therapeutic effects of mood stabilizers in bipolar disorder, it should be noted that direct evidence for the role of GSK-3 in the etiology of the disorder has not been reported, and genetic studies have not reproducibly found GSK-3 polymorphisms to be associated with the disease [59]. Nevertheless, it should be noted that a recent whole genome association study of bipolar disorder did identify polymorphisms in molecules in the overall GSK-3 signaling cascade to be associated with bipolar disorder [2]. Therefore, it remains to be determined if bipolar pathophysiology involves abnormalities of GSK-3 itself, or of other signaling molecules regulated by GSK-3. Nevertheless, in view of the role of GSK-3 in the actions of insulin, synaptic and neural plasticity, survival, and circadian rhythms, and its involvement in the action of mood stabilizers, development of GSK-3 inhibitors is actively underway by numerous pharmaceutical companies.

GSK-3 inhibitors in other CNS diseases

GSK-3 has emerged as a key target in the development of novel treatments for Alzheimer's disease, based on evidence that it is involved in formation of both amyloid plaques and neurofibrillary tangles, two pathological hallmarks of the disease. GSK-3 interacts with presenilin, which mediates the gamma-secretase cleavage step in the formation of amyloid-beta peptide [60]. GSK-3 also regulates the phosphorylation of the microtubule associated protein tau, which, in its hyperphosphorylated form, is a main component of neurofibrillary tangles [61]. Preclinical studies in animal models of Alzheimer's disease have shown that GSK-3 inhibition by lithium reduces beta-amyloid production [60]. Lithium lowers levels of phosphorylation at several epitopes of tau known to be hyperphosphorylated in Alzheimer's disease, and significantly reduces levels of aggregated, insoluble tau [26]. Most recently, it was demonstrated that lithium is neuroprotective in amyloid precursor protein (APP) transgenic mice [62]. These and other studies have raised considerable interest in the potential of GSK-3 inhibitors, and of lithium in particular, in the treatment of Alzheimer's and other neurodegenerative diseases and tauopathies.

Development of GSK-3 inhibitors

More than 30 inhibitors of GSK-3 have been identified to date [63], represented by such diverse classes of molecules as

pyridyl-oxadiazoles, malemides, thiadiazolidindiones, and pyrazolopyrimidines [18]. There are many considerations regarding selectivity and safety in the development and potential use of GSK-3 inhibitors. The need for substrate-selective modulators is critical, given that GSK-3 is known to phosphorylate at least 40 substrates [18]. The selectivity of most available GSK-3 inhibitors is poorly characterized [63], and many demonstrate overlapping interaction with the closely related kinases CDK2 and CDK5 [18]. AR-A014418, a thiazole, and SB-216763 and SB-415286, structurally distinct malemides, are ATP-competitive inhibitors that have been shown to be highly specific for GSK-3 [18]. AR-A014418 and SB-415286 demonstrate neuroprotective properties *in vitro* [64] and AR-A014418 demonstrates antidepressant properties in animal models [65]. In general, ATP-noncompetitive kinase inhibitors have the potential for greater target specificity than those that compete reversibly with ATP, which is the strategy of the majority of currently available inhibitors. 2,4-disubstituted Thiadiazolidiones (TDZDs) were the first class of ATP-noncompetitive inhibitors for GSK-3, and demonstrate high potency and selectivity [18]. TDZDs show neuroprotective properties in *in vitro* studies [18]. Thienylhalomethyl ketones represent a second class of ATP-noncompetitive GSK-3 inhibitors that has yet to be fully investigated [66]. Eldar-Finkelman and colleagues have developed a substrate competitive inhibitor, L803-mts, that demonstrates antidepressant properties in the forced swim test [48]. GSK-3's unusual substrate specificity provides an opportunity for the development of another class of highly selective ATP-noncompetitive inhibitors. In order to phosphorylate its target, GSK-3 requires a 'priming phosphorylation', carried out by another kinase which is substrate-dependent. Inhibitors that target the 'priming phosphate' have the potential for superior specificity. Cell-permeant phosphopeptides have been studied that bind to these sites and inhibit GSK-3 activity [67]. A further specificity challenge is the high sequence similarity (98%) between the catalytic domains of the two GSK-3 isoforms, making it difficult to develop isoform-selective inhibitors [18].

Several strategies for reducing toxicity may be combined with the above methodologies in the development of signaling molecule-targeted drugs for psychiatric disorders. The use of partial inhibitors can be a preferred strategy in cases in which the targeted kinases are essential for life, as is the case for GSK-3. The GSK-3β knockout mouse is embryonic lethal, indicating that its function is essential and non-redundant, at least during development [68]. Partial inhibition may not only be necessary to reduce toxicity, but may also be optimal for therapeutic effect, on the basis of the fact that lithium only partially (20–25%) inhibits GSK-3. Animal studies that show that 25% inhibition of GSK-3 is sufficient to account for lithium's behavioral effects [69]. An additional toxicity issue with regard to GSK-3 is the theoretical increase in the risk of cancer, via activation of its target, the pro-oncogenic β-catenin. However, decades of clinical experience with lithium have shown it does not increase the risk of cancer [70]; partial inhibition of GSK-3 may account (at least in part) for this lack of oncogenic effect. Another potential strategy for reducing toxicity is the use of uncompetitive inhibitors, that is, agents that demonstrate increased inhibition when the system is more active. This may make more physiologic sense, as well as triggering less toxicity, and is the mechanism by which lithium inhibits inositol monophosphatase (IMPase) and GSK-3. Finally, CNS-selective delivery, for example, delivery of inactive prodrug with conversion to the active drug only in the CNS, is a widely used strategy to minimize systemic toxicity. This may be an effective strategy in the case of GSK-3. GSK-3β knockouts die in late embryogenesis with the primary defect found in hepatocytes [68]. Targeted delivery to CNS may bypass non-CNS toxicity.

PKC

PKC is a family of serine/threonine kinases that are involved in the transduction of signals for cell proliferation, differentiation, apoptosis, senescence and angiogenesis. The family is comprised at least 12 isoforms, which are subdivided into three classes (classical/conventional, novel and atypical) on the basis of calcium- and diacylglycerol (DAG)-dependence. PKC isoforms differ in structure, subcellular localization, tissue specificity, mode of activation, and substrate specificity [71]. Activation of PKC results in its translocation, and subcellular localization is thought to regulate accessibility to activators and substrates [71]. PKC is activated by such varied upstream signals as G protein-coupled receptors (GPCRs), receptor tyrosine kinases (RTKs), and non-RTKs via DAG activation (Figure 2). Several PKC isoforms are independently activated by the phospholipase C (PLC) and phosphoinositide-3 kinase (PI3K) pathways [71]. Of PKC's numerous substrates, a major target is the MEK/ERK pathway [71]. The activation of MEK and the MAPK cascade is thought to involve activation of Raf1 [71].

PKC has been identified as a potential target for the treatment of several medical diseases, including diabetes, cancer and bipolar disorder. With respect to its potential role in bipolar disorder, it is significant that lithium and valproate bring about strikingly similar effects on the PKC signaling cascade [72], as discussed below.

PKC in the pathophysiology and treatment of bipolar disorder

Evidence from numerous studies using widely varying methodologies implicates PKC in the pathophysiology and treatment of bipolar disorder [3]. Peripheral blood cell studies show altered PKC isozyme levels and activity in bipolar subjects. Postmortem studies similarly demonstrate altered PKC levels and activity in subjects with bipolar disorder. Lithium and valproate decrease PKC levels in an isozyme-specific manner and decrease PKC activity. Lithium interacts with the PI/PKC pathway via the inhibition of inositol mono-phosphatase (IMPase), resulting in decreased free myo-inositol and the subsequent production of DAG, with the downstream effect of decreasing PKC levels and activity. The structurally dissimilar mood stabilizer valproate appears to inhibit PKC via a distinct mechanism, suggesting that this action is important to the common therapeutic effects of these medications.

Although far from ideal, amphetamine and cocaine-induced behavioral alterations in rodents are used as experimental models of mania. The models are based on the clinical observation that psychostimulants worsen manic symptoms in hypomanic patients and induce manic relapses in subjects with a personal or family history of bipolar disorder. Lithium treatment prevents these forms of psychostimulant-induced behaviors, which validates these models for mania. Notably, the behavioral alterations induced by psychostimulants in rodent models are associated with changes in PKC [3]. Furthermore, pharmacologic inhibitors of PKC

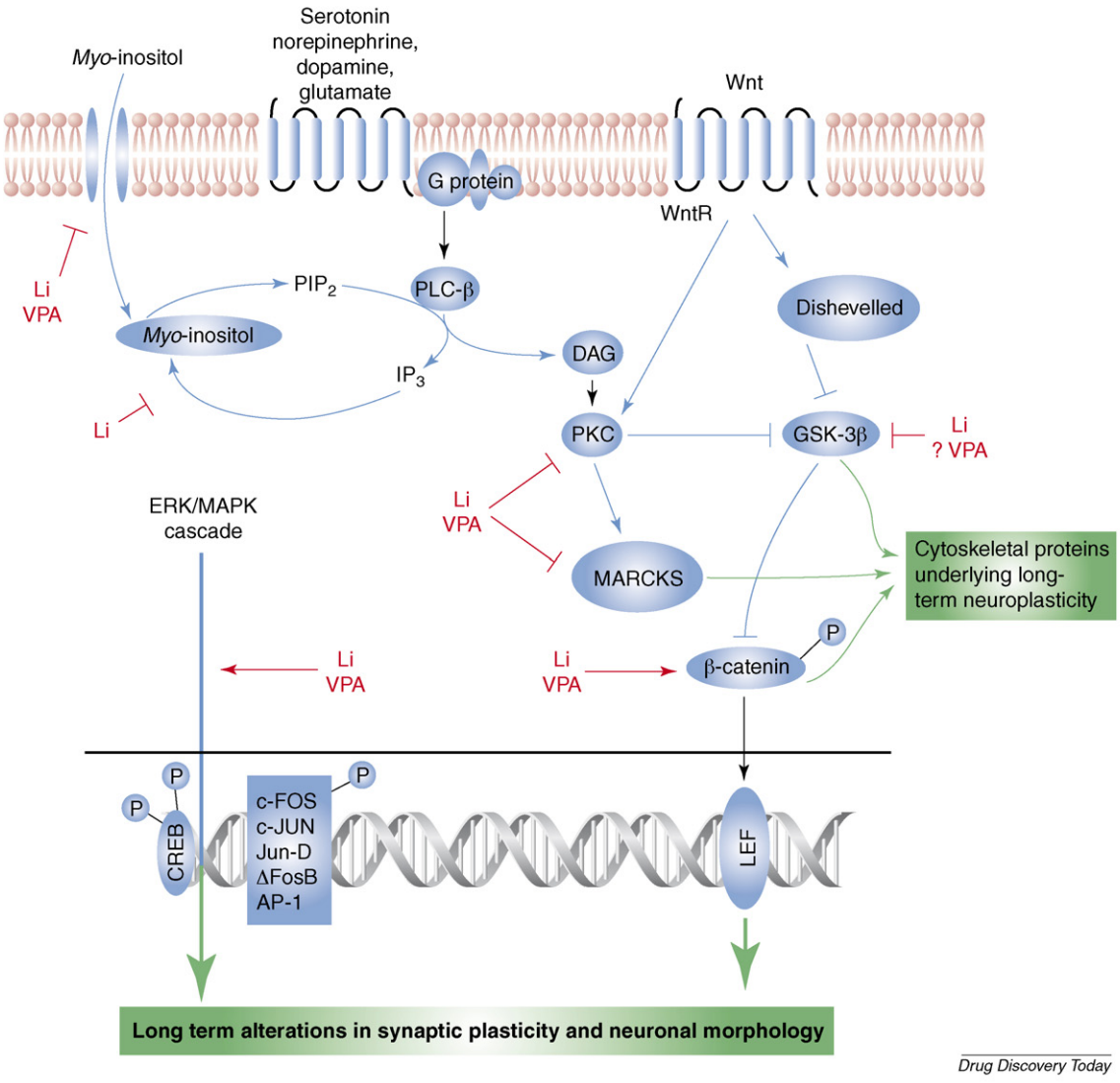

FIGURE 2

Intracellular signaling cascades involved in long term stabilization of mood by lithium (Li) and valproic acid (VPA). Activation of receptors coupled to PI hydrolysis results in the breakdown of phosphoinositide 4,5-biphosphate (PIP_2) into two second messengers: IP_3 and diacylglycerol (DAG), which is an endogenous activator of PKC. Lithium is an uncompetitive inhibitor of inositol monophosphatases, whereas both lithium and VPA, upon chronic administration, decrease *myo*-inositol uptake. These perturbations by mood stabilizers likely contribute to the reduction in PKC activity and the reduced levels of PKC-α, PKC-ε and myristoylated alanine-rich C kinase substrate (MARCKS), a major PKC substrate in the CNS. In the Wnt signaling pathway, binding of the Wnt signal to the Wnt receptor (WntR) activates an intermediary protein, Dishevelled, which regulates GSK-3β. GSK-3β regulates cytoskeletal proteins, and also has an important role in determining cell survival and cell death. Lithium (and possibly VPA) directly inhibits GSK-3β, which may underlie, at least in part, the increases in β-catenin that occur after chronic treatment with these agents. The ERK MAP kinase cascade regulates several important transcription factors, most notably CREB and activator protein-1 (AP-1). Recent studies have demonstrated that both lithium and VPA activate the ERK MAP kinase cascade, which may contribute to the long-term changes in synaptic plasticity and morphology that follow chronic treatment. Together, the regulation of these signaling pathways brings about an enhancement of synaptic connectivity potentially necessary for long-term stabilization of mood. Reproduced with permission from [81].

attenuate amphetamine-induced hyperlocomotion [73]. Birnbaum and associates demonstrated that excessive activation of PKC dramatically impaired the cognitive functions of the prefrontal cortex, exposure to stress activated PKC, and inhibition of PKC protected cognitive function [74], suggesting that PKC plays a role in some of the cognitive features of mania.

The first study in humans with a fairly selective PKC inhibitor was conducted by Bebchuck *et al.* [75]. In this small, open-label study, tamoxifen resulted in a greater than 50% decrease in manic symptoms in five of seven subjects [75]. This effect was recently confirmed in a 3-week, double-blind, placebo-controlled study of 16 manic patients [76]. Antimanic effects were found as early as day 5 in this study.

The potential role of the PKC signaling pathway in the pathophysiology of bipolar disorder has been further strengthened by the identification of a bipolar susceptibility gene which is an upstream regulator of PKC. Two recent independent genome-wide association studies identified diacylglycerol kinase eta (DGKH) as a risk gene for

bipolar disorder [2,77]. DGKH is a major regulator of DAG, which activates all known classical and novel isoforms of PKC.

Development of PKC inhibitors

A large number of structurally distinct PKC inhibitors have been identified or developed, mostly for use in cancer treatment [71]. As mentioned above, the anti-estrogen tamoxifen has been investigated and found efficacious in three independent clinical trials for bipolar disorder. PKC inhibitors that are used in treatment or have undergone clinical trials for cancer include tamoxifen (treatment for estrogen receptor-positive breast cancer); the lipid analogs safingol (Phase I trial with doxorubicin for solid tumors) and miltefosine (Phase II trial of topical treatment for cutaneous breast cancer metastases); the indolocarbazoles UCN-01 (Phase II trials for several cancers) and PKC412 (Phase II trials for solid tumors); the bisindolylmalemide enzastaurin (Phase II trials for glioblastoma and B-cell lymphoma); and the PKCα-specific antisense oligonucleotide ISIS3521 (several Phase II and Phase III trials) [71]. The PKC inhibitors that have been investigated thus far, with the exception of the antisense oligonucleotides, are relatively non-specific. The potential of isoform-, cell type-, and substrate-selective PKC inhibitors has, therefore, not been fully explored.

As discussed above with respect to GSK-3, the development of highly selective PKC inhibitors is critical for the possibility of novel therapies with good efficacy, tolerability and safety profiles. Strategies such as the use of non-ATP-competitive inhibitors, or inhibitors that target binding proteins or substrates that are less promiscuous than the target kinase, may prove useful in the development of anti-PKC agents. A substrate-competitive inhibitor has been designed for PKCα [78], and peptides corresponding to PKC anchoring proteins like RACK (receptors for activated C kinases) selectively inhibit specific PKC isozyme activity [79]. A related strategy is to target PKC in specific subcellular locations. Because PKC isoforms are translocated upon activation, targeting location-specific anchoring proteins may produce isoform- and/or substrate-specific inhibition. Finally, combination strategies may prove beneficial for increasing specificity, increasing sustained therapeutic effectiveness, and reducing resistance. Examples of target combinations might include kinase-targeted agents with: (a) binding or scaffolding proteins that are location- and/or isoform-specific (such as RACK); (b) up/downstream molecules within the same signaling pathway to accomplish a synergistic effect with increased specificity; or (c) functionally related molecules with narrower expression profiles. Bisubstrate inhibitors might combine, for example, ATP and a particular kinase substrate for a higher degree of specificity. Ideally, combinations of therapies are designed such that they accomplish increased effectiveness to a greater degree than increased side effects. Disadvantages of this strategy include the increased likelihood of drug–drug interactions and the potential of decreased compliance. Therapies combining PKC modulators with other anti-cancer agents have been investigated at the preclinical level and in clinical trials [71].

Drug discovery: the feasibility of developing modulators of signaling molecules in the CNS

There is now compelling data to support the notion that targeting intracellular signaling cascades may have considerable utility in the treatment of bipolar disorder. The use of modulators of ubiquitous kinases in the CNS, however, still raises concerns of specificity, tolerability and safety. Is it, in fact, feasible to develop such drugs? At least 50 drugs that target kinases are in clinical development for various medical illnesses, and many more are being investigated at the preclinical level [18]. The success of several kinase-targeted drugs in cancer treatment, including Gleevec (Imatinib, an inhibitor of tyrosine kinase BCR-Abl), Iressa (Gefitinib, an inhibitor of tyrosine kinase EGFR) and Herceptin (Trastuzumab, an antibody against tyrosine kinase receptor HER2), has proved the feasibility of this strategy, at least outside the CNS. Modulators that target the brain are, for the most part, still in the preclinical stages of development. However, lithium, a mood stabilizer which targets signaling cascade molecules including GSK-3, has been a mainstay of treatment for bipolar disorder for almost 60 years, providing a key example of a safe and effective modulator of signaling systems in the CNS. Tamoxifen, as discussed above, is another (albeit less specific) regulator of CNS signaling molecules with an acceptable efficacy and safety profile. Although both drugs modulate signaling pathways that are involved in diverse brain functions, and possibly other CNS disorders, they demonstrate relatively circumscribed clinical effects. Developing other therapies that target the CNS is therefore entirely possible, albeit challenging. Several strategies, a number of which have been mentioned above in the context of the discussion of GSK-3- and PKC-specific inhibitors, may prove useful in the development of CNS kinase-targeted drugs with adequate specificity and tolerability.

Conclusion

A novel pharmacotherapy has not been developed for bipolar disorder since lithium, over 50 years ago, and the currently available therapies, mostly anticonvulsants and antipsychotics, are inadequate for many patients. Recent data suggest that regulation of signaling molecules is probably involved in mechanisms of action of mood stabilizers and antidepressants, and the possibility of targeting signaling molecules for treatment, particularly kinases such as GSK-3 and PKC, holds great promise. The debate regarding whether protein kinases can be safely targeted for directed medical therapies has focused primarily on concerns of specificity and safety. The success of several kinase inhibitors in cancer treatment, as well as the use of lithium for almost six decades, demonstrates the realistic potential of using kinase inhibitors safely and efficaciously. As discussed here, several strategies may be employed to increase specificity and limit toxicity with the goal of developing novel treatments with improved efficacy, tolerability and safety for this devastating illness.

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