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Mood stabilizer psychopharmacology

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Abstract

Mood stabilizers represent a class of drugs that are efficacious in the treatment of bipolar disorder. The most established medications in this class are lithium, valproic acid, and carbamazepine. In addition to their therapeutic effects for treatment of acute manic episodes, these medications often are useful as prophylaxis against future episodes and as adjunctive antidepressant medications. While important extracellular effects have not been excluded, most available evidence suggests that the therapeutically relevant targets of this class of medications are in the interior of cells. Herein we give a prospective of a rapidly evolving field, discussing common effects of mood stabilizers as well as effects that are unique to individual medications. Mood stabilizers have been shown to modulate the activity of enzymes, ion channels, arachidonic acid turnover, G protein coupled receptors and intracellular pathways involved in synaptic plasticity and neuroprotection. Understanding the therapeutic targets of mood stabilizers will undoubtedly lead to a better understanding of the pathophysiology of bipolar disorder and to the development of improved therapeutics for the treatment of this disease. Furthermore, the involvement of mood stabilizers in pathways operative in neuroprotection suggests that they may have utility in the treatment of classical neurodegenerative disorders.

Keywords

Mood stabilizer; Anticonvulsant; Antiepileptic; Neuroprotection; Neurotrophic; Depression; Mania; ERK; bcl-2; Protein kinase C; Bipolar disorder; valproate

1. Introduction

Mood stabilizers represent a class of drugs that have been found to be efficacious in the treatment of bipolar disorder. In addition to their effectiveness in treating acute mania, many of these medications appear to be useful for prophylaxis against future manic episodes and as adjunctive antidepressants [1]. The most established medications in this class are lithium, valproic acid (valproate, VPA), and carbamazepine.

Research on the action of these drugs originally concentrated on possible receptor mediated effects; however it has become clear that they likely do not exert their actions by interacting specifically with cell surface receptors [2,3]. The lack of interaction with cell surface receptors has prompted researchers to focus efforts on intracellular targets. This focus has led to numerous findings, including a few direct targets, for lithium, carbamazepine, and VPA [3–5]. However, it remains unclear which are the primary initial targets, and what the most therapeutically relevant downstream effects of these medications are [6].

It is very apparent, and also confounding, that the structures of the various mood stabilizers are vastly different: lithium is a monovalent cation; VPA an eight-carbon branched chain fatty acid; and carbamazepine is structurally related to the tricyclic antidepressants (Table 1). This observation suggests that the initial mechanism of action – or target – of mood stabilizers may not be maintained among these structurally different medications. However, because of their shared efficacy in treating bipolar disorder, it is likely that the intracellular and/or physiological effects may show convergence [7]. For this reason multiple laboratories are using biochemical and cellular methods to identify common targets of mood stabilizers [8–15].

The intent of this review is to describe research in this dynamic field, and to present the leading hypotheses regarding the mechanisms of action of mood stabilizers. Although it is not known for certain how any mood stabilizer exerts its therapeutic effects, there is suggestive evidence for various mechanisms. It appears likely that lithium exerts its initial effects by targeting the activity of an enzyme, or perhaps multiple enzymes, inside cells. Lithium has a hydrated ionic radius which is very similar to that of magnesium, and it inhibits some enzymes through competition for this required cofactor [16,17,248]. While lithium inhibits a number of enzymes [18], only a few are significantly inhibited at therapeutic concentrations (0.6–1.2 mM). These include a group of at least four related phosphomonoesterases [19], the metabolic enzyme phosphoglucomutase [20], and a crucial kinase that functions as an intermediary in numerous intracellular signaling pathways, namely glycogen synthase kinase-3 [21].

With respect to VPA and carbamazepine, the antiepileptic properties of these drugs may be the same targets as those that exert mood stabilizing properties [11,22,23]. However, in general, antiepileptic medications exert their effects quite rapidly, suggesting that their well-characterized effects on ion channels and excitatory and inhibitory amino acid neurotransmitters per se may play a major role in their antiseizure effects. By contrast, their therapeutic effects in the treatment of mood disorders displays a lag period for onset of action of at least 7–10 days; these temporal observations suggest that while carbamazepine and valproate may use the same *initial target* for the treatment of mood disorders as they do for epilepsy, interacting with these targets may bring about a cascade of downstream adaptations that are most relevant for the treatment of mood disorders. We attempt to briefly summarize the major findings with regard to possible therapeutic targets of lithium, VPA, and carbamazepine; first focusing on effects shared by multiple medications.

2. G protein regulated cyclic AMP signaling

2.1. Lithium

A primary mechanism by which cell surface receptors transduce their signals to secondary signals within cells is via G proteins. G proteins are molecules in cells composed of three subunits (α , β , and γ , which are thereafter subdefined further) that interact to transfer a signal from extracellular membrane receptors to the interior of the cell. Thus, G proteins couple neurotransmitters – via their receptors – to intracellular signaling cascades that are involved in many cellular processes including growth, differentiation, metabolism, and synaptic plasticity [24] (Fig. 1).

A large amount of research implicates possible effects of lithium on G protein mediated signaling [13,25,26]. Lithium does not appear to change the density of G protein coupled receptors after chronic therapy [27]. However, there is evidence suggesting possible changes in G protein subunits. Lithium treatment in rats consistently decreases the mRNA level of a variety of G protein subunits [28–30]. Surprisingly, in spite of the mRNA changes, it has not been consistently found that lithium changes the total protein levels of G protein subunits.

Thus, in some reports, lithium slightly decreases the level of G protein subunits, in particular $G\alpha_s$, $G\alpha_{i1}$, and $G\alpha_{i2}$ [28,29]; however, other studies find no alterations [30,31].

A number of independent research laboratories have found that the ability of the receptor-mediated signal to be propagated via G proteins (G protein-receptor coupling) to decrease after lithium treatment [32–39]. This series of findings is also consistent with an animal model where cholera toxin (a stimulator of the G proteins, G_s and G_{olf}) induces hyperactivity when injected into the nucleus accumbens of rats. Cholera toxin induced hyperactivity is decreased by lithium administration [40], consistent with decreased G_s and/or G_{olf} activity during lithium treatment. In this context, it is noteworthy that a recent study found that 2 weeks (but not 1 week) of lithium, increased $G\alpha_{olf}$ protein levels by ~ 50% [41]. Furthermore, this group found that $G\alpha_{olf}$ returned to baseline levels 1 week after withdrawal of lithium. $G\alpha_{olf}$ is highly homologous to $G\alpha_s$, and in addition to its role in olfaction, is now known to be expressed in dopamine rich areas of the brain, including the caudate-putamen, nucleus accumbens, and olfactory tubercle [42]. It has been postulated that the increased $G\alpha_{olf}$ expression after chronic lithium represents a compensatory adaptation to the suppression of the adenylate cyclase system by lithium, and may be responsible (at least in part) for the ‘rebound’ increases in manic episodes observed after abrupt lithium discontinuation [41]. These results suggest that direct inhibitors of adenylate cyclase (e.g. carbamazepine, see below) may have clinical utility in the prevention of lithium-discontinuation emergence of mania.

However, while stimulated levels are decreased, there is evidence to suggest an increase in basal cyclic AMP activity [26,43–47]. Thus, the literature describing the effect of lithium on G proteins suggests that lithium both stimulates basal activity and inhibits stimulated adenylate cyclase, potentially resulting from stabilization of the inactive G protein ($\alpha\beta\gamma$) conformation [26,43,46–48]. Furthermore, chronic lithium has also been found to increase not only basal AMP levels [49], but also the levels of adenylate cyclase Type I and Type II mRNA and protein levels in frontal cortex [28], suggesting that lithium’s complex effects on the system may represent the net effects of direct inhibition of adenylate cyclase, upregulation of adenylate cyclase subtypes, and effects on the stimulatory and inhibitory G proteins. This is a role that theoretically corresponds with lithium’s effect of stabilizing spontaneous or stress (including drug/sleep deprivation)-induced affective episodes [50]. In spite of the effect of lithium on G protein signaling, no mutations in G proteins or G protein regulator sites have been found to correlate with mood psychopathology [51]. However, many transcriptional and posttranscriptional events regulate the expression and function of G proteins [26,46,47,52], resulting in a virtually unlimited number of possibilities whereby G protein activity can be modulated in cells. Thus, the changes observed in G protein coupled signaling may be due to indirect effects from other biological targets, for example enzymes discussed in a later section [3].

2.2. Valproic acid and carbamazepine

Evidence suggests that carbamazepine also effects cyclic AMP mediated signaling [2,50,53]. In mouse cerebral cortex and cerebellar tissue, carbamazepine decreases the basal concentration of cyclic AMP [54]. It also lowers cyclic AMP following stimulation by norepinephrine [54,55], adenosine [54,56,57], and the epileptogenic compounds ouabain [54] and veratridine [58,59]. Additionally, carbamazepine appears to attenuate β -adrenoceptor and muscarinic cholinergic coupling to G proteins in the rat cortex [60], decreases the levels of G_s and G_i and attenuates cyclic AMP mediated phosphorylation of CREB in C6 glioma cells [61]. Similarly, in pheochromocytoma (PC12) cells carbamazepine inhibits cyclic AMP mediated increases in *c-fos* gene expression [62].

This evidence eventually led to studies suggesting that carbamazepine may directly inhibit adenylate cyclase [61]. Thus, Chen et al. reported that at therapeutic concentrations carbamazepine inhibited both basal and stimulated cyclic AMP production [61]. Carbamazepine exerted this effect regardless of whether adenylate cyclase coupled receptors, or adenylate cyclase itself was stimulated, thus suggesting the possibility of a direct inhibitory effect. Furthermore, these effects were found in adenylate cyclase extracts; suggesting that carbamazepine inhibits adenylate cyclase directly, or acts via a closely associated factor that purifies with the enzyme [61]. Most of the evidence discussed has been accumulated during acute treatment, and it remains to be seen if this action can be temporally associated with carbamazepine's therapeutic effects in treating mania. Interestingly, in addition to its putative role in the pathophysiology of mania [3], adenylate cyclase and the cyclic AMP signaling pathway has been postulated to play a role in epilepsy [53,63]. Thus, carbamazepine may exert both its antimanic and antiepileptic effects by inhibiting this enzyme and attenuating cyclic AMP mediated signaling.

In contrast to the multiple studies that describe the effects of lithium and carbamazepine on G protein coupled and/or cyclic AMP mediated signaling, only one published report exists for VPA [64]. This study found that at therapeutically relevant concentrations in a cell line model, VPA decreased the density of β ARs and attenuated both receptor- and post receptor-stimulated cyclic AMP production. These authors additionally reported that levels of $G\alpha_s$ 45, but none of the other G protein subunits examined were decreased [64]. Thus, VPA may exert an effect on cyclic AMP signaling at multiple levels, but more work needs to be done. The finding that lithium, carbamazepine, and VPA exert roughly similar effects on receptor stimulated cyclic AMP signaling suggests a common target of these two mood stabilizers [3,48,65] (Table 2).

3. Phosphoinositol/protein kinase C and mood stabilizers

3.1. Lithium inhibits enzymes involved in the phosphoinositol signaling pathway

Lithium inhibits a small group of magnesium dependent phosphomonoesterase enzymes that includes inositol polyphosphate 1-phosphatase (IPase) and inositol monophosphate phosphatase (IMPase, also discussed in a later section). Lithium's direct effect on IMPase and secondarily IPase led to the inositol depletion hypothesis of lithium's action [66,67]. IMPase is the final inositol polyphosphate phosphatase prior to conversion to inositol while IPase removes a phosphate from inositol-1, 4-bisphosphate, at a stage just prior to IMPase. Both are critical steps in the maintenance of the phosphoinositol-signaling cascade [66] (Fig. 1).

Following G protein coupled receptor-mediated activation of phospholipase C, phospholipase phosphoinositide 4,5-bisphosphate (PIP_2) is hydrolyzed to form diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3) [3,68]. IPase and IMPase are thereafter involved in recycling of diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3) back to PIP_2 [68] (Fig. 1).

Specifically, the inositol depletion hypothesis of lithium's action suggests that lithium, via inhibition of IMPase, decreases the availability of *myo*-inositol, and thus the amount of PIP_2 available for G protein mediated signaling events that rely upon this pathway [69]. It is hypothesized that the brain would be especially sensitive to lithium, due to *myo*-inositol's relatively poor penetration across the blood-brain barrier [69]. Furthermore, based on the inhibition profile of lithium (i.e. noncompetitive), more active brain regions may be affected to a greater degree [70]. In support of the hypothesis, lithium has consistently been shown to decrease free inositol levels in brain sections, and in the brains of rodents treated chronically with lithium [71,72]. Furthermore, in a recent clinical experiment lithium decreased

myo-inositol in human subjects [73]. However, the myo-inositol reduction was observed after only 5 days of treatment, suggesting that any decrease in PIP₂ signaling is upstream of the downstream therapeutically relevant targets [73].

Unfortunately, studies designed to address lithium's effects on PIP₂ signaling in rodent models have resulted in inconsistent results, and those positive results that exist suggest a small effect [3,72,74]. Thus, while lithium does appear across studies to lower inositol levels, there exists little direct evidence that PIP₂ mediated signaling is altered by lithium. In spite of these negative findings, inositol depletion remains a viable hypothesis for the mechanism of action of lithium. However, no clinically approved inhibitors of either IPPase or IMPase are available [75]; therefore, it remains difficult to test the inositol depletion hypothesis in patients with bipolar disorder.

A number of more recent studies have investigated the possibility that mood stabilizers may regulate the phosphoinositol signaling pathway independently of inhibiting IMPase. In this context, studies have examined lithium's effects on the phosphoinositol system distal to the receptor since, as noted above, experimental evidence has shown that lithium may alter receptor coupling to phosphoinositol turnover. Since the fluoride ion will directly activate G protein coupled second messenger responses, efforts have been made to examine the effect of lithium on NaF stimulated phosphoinositol response in the brain [76]. Although Godfrey and colleagues reported a reduction of fluoride stimulated phosphoinositol response in cortical membranes of rats treated with lithium for three days, no change in response was observed in cortical slices from rats administered lithium for 30 days [76]. Additionally, using labeled phosphoinositol as a substrate (which should bypass any putative inositol depletion), Song and Jope reported an attenuation of phosphoinositol turnover in response to GTP analogs [77]. Taken together, these results suggest that although chronic lithium administration may affect receptor mediated phosphoinositide signaling, these effects are unlikely to be simply due to inositol depletion in the CNS [43,78,79]. Using a yeast model, it was reported that both lithium and VPA perturb regulation of the inositol biosynthetic pathway, albeit via different mechanisms [80,81]. A very interesting potential new target for the actions of structurally dissimilar mood stabilizers is the sodium/*myo*-inositol cotransport (SMIT), a high affinity *myo*-inositol transport system that has been characterized in various cell types, including those of neural origin [82]. Thus, it has recently been demonstrated that the activity of SMIT and the expression of its mRNA in cultured astrocytes are downregulated after chronic treatment with therapeutic concentrations of lithium [82,83]. Interestingly, downregulation of SMIT was also observed after VPA and carbamazepine. If replicated in vivo, these findings suggest that SMIT may represent a novel target for the development of new drugs. The most recent finding implicating phosphoinositol signaling in the actions of mood stabilizers comes from Williams and colleagues in 2002, who used a novel tissue-culture assay that measures sensory neuron growth-cone stability to conclude that mood stabilizers have a common mechanism of action – namely depletion of neuronal inositol-1,4,5-trisphosphate (IP₃) [14]. These investigators demonstrated that lithium, VPA and carbamazepine all inhibit the collapse of sensory neuron growth cones and increase growth cone area; effects which were reversed by inositol. The authors then used the slime mold, *Dictyostelium*, which relies on IP₃ for its development, to identify mutants that confer resistance to the drugs. Null mutations of a gene with unknown intracellular function that encodes prolyl oligopeptidase confer lithium resistance and elevate intracellular levels of IP₃. The authors drew a link between their slime-mold studies and mammals by showing that prolyl oligopeptidase inhibitors abolished the effects of lithium, carbamazepine and VPA on growth-cone collapse and area in their tissue culture assay [14]. Once again, if further validated in vivo, these observations will add to the body of data identifying CNS intracellular signaling cascades as targets for mood stabilizers, and may ultimately lead to the development of novel, more specific therapies for this devastating illness [84].

3.2. Both lithium and valproic acid target protein kinase C isozymes and MARCKS

Protein Kinase C (PKC) and PKC signaling appear to be a target of lithium and VPA [5,45,85] (Table 2). Reports have documented that chronic lithium treatment decreases the level of PKC isozymes α , and ϵ [86,87]. Thus, Manji et al. first reported – using a PKC radioligand – that total membrane PKC levels were decreased in regions of the hippocampus (primarily CA1 and subiculum) in rats treated with therapeutic concentrations for 5 weeks [87]. Using immunohistochemistry, this change was confirmed in the hippocampus, and extended to the frontal cortex. Furthermore, this decrease was identified to be due specifically to decreases of the α and ϵ isozymes [87], a finding also shown in cultured cells [87–89]. The precise mechanisms by which lithium exerts these isozymes-selective actions is unknown, but there is evidence that it may be due to lithium's effect on IMPase [85,86]. Further supporting the effect of lithium on PKC, lithium decreases the levels and phosphorylation of a major PKC substrate, myristoylated alanine-rich C kinase substrate (MARCKS), following chronic treatment in rats [90]. In cultured cells, it was found that this affect appears to be dependent on low media inositol concentrations, thus implicating lithium's inhibition of IMPase and/or IPPase as a causative factor [85,91].

Evidence also suggests that PKC is a target of VPA. In cultured cells, VPA reduces the PKC activity in both membrane and cytoplasmic fractions [8]. VPA also selectively reduces the protein levels of the same PKC isozymes reduced by lithium, α and ϵ , further suggesting possible importance in the treatment of bipolar disorder [8]. The reduction in the α isozyme has also been confirmed in the brains of rats treated chronically with VPA at therapeutically relevant concentrations [85]. Also, similar to the effects of lithium, VPA decreases the levels of MARCKS [92]. The mechanism by which VPA exerts these effects is unknown; however, they appear to be independent of myoinositol [92].

3.3. PKC signaling in animal models of mood disorders

Two current models of mania that have been used and have reasonable heuristic value in the study of mood disorders have been kindling and behavioral/amphetamine sensitization [93–95]. Considerable evidence implicates long-term alterations in midbrain dopaminergic transmission in the development of behavioral sensitization, but the cellular mechanism(s) underlying the long-term changes in excitability observed in kindled or stimulant sensitized animals have not been fully elucidated. However, a growing body of evidence suggests alterations in both PKC and certain G proteins (especially G_i and G_o) [96–104] in these models. In particular dramatic increases in membrane-associated PKC have been observed in the bilateral hippocampus up to 4 weeks and in the amygdala/pyriform cortex at 4 weeks after kindled seizures [105,106]. Studies have also implicated alterations in PKC activity as mediators of long-term alterations in neuronal excitability in the brain following chronic stimulant use. Thus, several independent laboratories have now demonstrated that both acute and chronic amphetamine produce an alteration in PKC activity, its relative cytosol to membrane distribution, as well as the phosphorylation of a major PKC substrate, GAP-43 which has been implicated in long term alterations of neurotransmitter release [100–104]. Furthermore, PKC inhibitors have been shown to block the acute responses to both amphetamine [107] and cocaine (as assessed by both behavioral and in vivo microdialysis studies) as well as cocaine-induced sensitization [98,99].

Abnormalities of circulating glucocorticoids are well known to be associated with affective symptomatology [108], and interestingly, elevated glucocorticoids have been associated with *both* depressive and manic symptomatology [109,110]. It is thus noteworthy that a recent study found that the repeated administration of dexamethasone for 10 days caused a significant increase in B_{max} of [3H]PDBu binding to PKC, increased PKC activity, and increased the levels of PKC α and ϵ in the rat hippocampus [111]. It is indeed striking that

behavioral sensitization and kindling (models which have been postulated to represent models of BD and mania) as well as dexamethasone administration *all* produce robust alterations in the PKC signaling pathway in critical limbic structures, since lithium and VPA also target the very same biochemical targets. Thus, although considerable caution obviously needs to be employed when extrapolating from rodent brain, the fact that these two models and glucocorticoid administration are associated with opposite effects on PKC signaling to those observed with chronic lithium or VPA is compelling indeed. Interestingly, there is also evidence suggesting that chronic antidepressants may also modulate PKC activity in limbic and limbic-associated areas of rat brain [112,113]. Moreover, PKC has recently been demonstrated to regulate the activity of norepinephrine, dopamine and serotonin transporters [114–117]. Whether these complex effects of antidepressants on PKC activity underlies their apparent ability to trigger manic episodes, and perhaps promote rapid cycling in susceptible individuals [118], remains to be determined.

In view of the pivotal role of the PKC signaling pathway in the regulation of neuronal excitability, neurotransmitter release, and long term synaptic events [119–121], it was postulated that the attenuation of PKC activity may play a role in the antimanic effects of lithium and valproate. These original findings led to a clinical trial investigating possible antimanic properties of the PKC inhibitor tamoxifen [122]. While best known for its anti-estrogenic properties, tamoxifen is also a potent PKC inhibitor at high concentrations [123,124]. Initial results are encouraging, finding that tamoxifen treatment resulted in a significant decrease in manic symptoms rated by the Young Mania Rating Scale, with a greater than 50% decrease in the Young Mania Rating Scale score occurred in five of seven patients enrolled in the initial trial [122]. Larger double-blind placebo-controlled studies of tamoxifen are currently underway.

4. Glycogen synthase kinase and the Wnt signaling pathway

4.1. A Wnt pathway enzyme, glycogen synthase kinase, is a target of lithium

Glycogen synthase kinase-3 (GSK-3) is a highly conserved enzyme in evolution, and is found in two nearly identical isoforms in mammals, α and β [125–127]. This enzyme was first discovered (and named) based upon its ability to phosphorylate, and thereby inactivate the enzyme glycogen synthase, an action that leads to a decrease in the synthesis of glycogen. While older literature suggests that lithium interacts with glycogen synthase [128–130], it was not until 1996, when Klein and Melton discovered that lithium inhibited the action of GSK-3, that the direct inhibition of this enzyme by lithium was identified [21]. Lithium's inhibition of GSK-3 appears to be by competition with magnesium for a binding site [17,248].

The effect appears specific, as no other kinases are known to be inhibited by lithium to such a degree [18,21]. GSK-3 is rather unique among kinases in that it is constitutively active. Thus, most intracellular signals to GSK-3 inactivate the enzyme. In addition to its role in mediating signals from insulin/PI₃-kinase that effect glycogen synthesis, signals deactivating GSK-3 arise from numerous growth factors (for example those which activate PI₃-kinase), and developmental signals (such as the Wnt pathway) [125,127,131]. A number of endogenous growth factors (e.g. nerve growth factor and brain derived neurotrophic factor (BDNF)) utilize the PI₃-kinase signaling cascade as a major effector system. Thus, growth factors may bring about many of their neurotrophic/neuroprotective effects, at least in part, by GSK-3 inhibition [132] (Fig. 2).

The Wnt signaling pathway is an evolutionarily highly maintained pathway that is recognized as playing a major role in cell fate determination during early embryonic development [133]. Secreted Wnt glycoproteins interact with the frizzled family of receptors

to deactivate GSK-3, thus preventing the phosphorylation and subsequent degradation of β -catenin by this constitutively active enzyme. When not degraded, β -catenin interacts with tcf/lef transcription factors acting on tcf/lef promoters. In addition to its role in early development, recent evidence suggests that the Wnt pathway is operative in adult organisms, and in the adult nervous system [127]. Indeed, there is evidence that the Wnt pathway plays an important role in synaptic plasticity [134]. Thus, while the other pathways regulated by GSK-3 should not be overlooked, Wnt pathway regulation could play an important role in the treatment of bipolar disorder [135].

GSK-3 phosphorylates – and thereby inactivates – many other targets including transcription factors and cytoskeletal proteins such as the Alzheimer's protein tau (a previous name for GSK-3 was tau kinase) (Fig. 2). Inhibition of GSK-3 thus results in the release of this inhibition, and activation of multiple cellular targets [125,127,131]. A rapidly increasing amount of evidence suggests that GSK-3 plays important roles in regulating neuronal survival and synaptic plasticity [133–135,136]. GSK-3's eminent role as an intermediary in a multiplicity of cellular processes suggests that many of the effects documented for lithium may be due to lithium's inhibition of this key enzyme. Furthermore, as discussed elsewhere in this review, accumulating evidence suggest that lithium may have some neuroprotective effects – possibly due to inhibition of GSK-3 [137].

4.2. Effect of VPA on GSK-3 and the Wnt signaling pathway

Lithium's activation of the Wnt signaling pathway is well established to be through inhibition of GSK-3 [21,135,138]. However, there is also evidence that VPA is an activator of the Wnt signaling pathway/deactivator of GSK-3 [135,139,140]. For example, in human neuroblastoma SH-SY5Y cells, incubation with 0.6 mM VPA resulted in a decrease in phosphorylation of GSK-3 substrates [139]. Similarly, VPA treatment prevents the phosphorylation of a GSK-3 target MAP1B in developing neurons in culture [15]. Furthermore, one-day (and longer) treatment of SH-SY5Y cells with a therapeutically relevant concentration of VPA resulted in a significant increase in both nuclear and cytoplasmic β -catenin protein levels [139]. Finally, VPA increases lef/tcf mediated reporter gene expression in Neuro 2A cells [140] (Table 2).

The mechanism by which VPA exerts these effects is unknown. Some studies suggest that VPA – similar to lithium – may be a direct inhibitor of GSK-3 [135,138]. Specifically, Chen et al. reported that VPA inhibited GSK-3 phosphorylation of a CREB peptide in vitro [139] and Grimes and Jope found that VPA inhibits the ability of immunoprecipitated GSK-3 to phosphorylate recombinant human tau in vitro [141]. In contrast, Phiel and colleagues reported that VPA did not inhibit the in vitro phosphorylation of glycogen synthase peptide or the in vivo phosphorylation of tau [140]. VPA also inhibits the phosphorylation of MAP-1B by GSK-3 in vivo, but not in vitro [15]. Thus, the effect of VPA on GSK-3 may be substrate specific, or possible due to differences in assay conditions [135,138]. In spite of these discrepancies, there is a general consensus that VPA inhibits the function of GSK-3 – and/or GSK-3 mediated pathways – in vivo [135]. Furthermore, VPA exerts effects on other pathways regulated by GSK-3; specifically it prevents GSK-3 mediated cell death [136] and counteracts the effects of GSK-3 on CREB DNA binding activity [141].

5. Arachidonic acid turnover is decreased by both lithium and VPA

Arachidonic acid (AA) functions as an important mediator of second messenger pathways within the brain [142,143]. It is released from membrane phospholipids via receptor/G protein-initiated activation of phospholipase A2 [144]. This action results in release of AA from the cellular membrane and subsequent formation of a number of eicosanoid metabolites such as prostaglandins and thromboxanes. These metabolites mediate numerous

subsequent intracellular responses and, due to their lipid permeable nature, trans-synaptic responses.

Arachidonic acid metabolism as a target of mood stabilizers is suggested by studies done by Chang et al. in 1996 and 2001 showing that chronic lithium and VPA treatment of rats results in selective reductions in the turnover rate in the brain phospholipids of AA [145–147] (Table 2). In the case of lithium the reduction was 80%, and it was also subsequently demonstrated that lithium down-regulated the gene expression and protein levels of an AA-specific phospholipase A2 (cPLA2) [148,149]. VPA also decreased the turnover of AA by 33%, with no effect on cPLA2 protein levels [145]. These findings suggest that effects of mood stabilizers on cell membranes – and specifically AA turnover – might be relevant to the pharmacological action of lithium and VPA [143,147].

6. Lithium and VPA activate a major signaling cascade utilized by endogenous growth factors: the ERK MAP kinase pathway

Neurotrophins (such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), NT4/5 and NT6) are a family of regulatory factors that mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity [150,151]. These molecules bind to and activate specific receptor tyrosine kinases belonging to the Trk family of receptors, including TrkA, TrkB, TrkC and a panneurotrophin receptor, P75 [150,151]. One of the primary pathways activated by neurotrophins is the ERK MAP kinase pathway (Fig. 2). Among the targets of ERK are the ribosomal S6 kinases (RSKs). RSK activates CREB and other transcription factors. Recent studies have also demonstrated that the activation of the MAP kinase pathway by RSK can inhibit apoptosis by inducing the phosphorylated inactivation of BAD (Bcl-xl/Bcl-2 Associated Death promoter), and increasing the expression of the anti-apoptotic protein Bcl-2: the latter effect appearing to involve activation of CREB [152,153] (Fig. 2).

ERK MAP kinases are abundantly present in brain, and in recent years evidence has suggested that they play a major role in a variety of neuroplastic events in the brain, both in the developing and mature CNS [154–158]. Additionally, ERK MAP kinase pathways have recently been demonstrated to regulate the responses to environmental stimuli and stressors in rodents [159], and to couple PKA and PKC to CREB phosphorylation in area CA1 of hippocampus [160,161]. These recent studies suggest the possibility of a broad role for the ERK signaling cascade in regulating gene expression in long-term forms of synaptic plasticity [160]. Thus, neurotrophin signaling and activation of the ERK MAP kinase pathway plays a major role in regulating various forms of neuronal and synaptic plasticity, as well as neuronal survival. It is in this context that recent evidence showing that the ERK signaling cascade is a target for the actions of two structurally highly dissimilar mood stabilizing agents is of great interest.

6.1. Lithium and valproate activate the ERK signaling cascade and upregulate the cytoprotective protein bcl-2

In studies in our laboratory, chronic treatment of rats with doses of lithium and valproate that are similar to those used clinically produced a doubling of bcl-2 levels in the frontal cortex, effects which were primarily due to a marked increase in the number of bcl-2 immunoreactive cells in layers II and III of the frontal cortex [162]. Chronic lithium also markedly increased the number of bcl-2 immunoreactive cells in the dentate gyrus and striatum [163], and increases bcl-2 levels in C57BL/6 mice [162], in human neuroblastoma SH-SY5Y cells in [50], and in rat cerebellar granule cells in culture [164]. This latter work found that lithium produced a remarkable increase in bcl-2 protein and mRNA levels. Thus,

overall the data clearly shows that chronic lithium robustly increases the levels of the neuroprotective protein bcl-2 in areas of rodent frontal cortex, hippocampus, and striatum in vivo; and in cultured cells of both rodent and human neuronal origin in vitro. Since a primary pathway regulating the transcription of bcl-2 is the ERK MAP kinase pathway, these data suggest that this pathway may be a target of lithium and VPA. Further suggestive evidence that lithium and VPA activate the ERK MAP kinase pathway and/or targets of this pathway comes from the finding that both mood stabilizers increase the expression of BDNF in rodent brain following chronic treatment [165] (in addition to activating the ERK MAP kinase pathway, the ERK MAP kinase pathway also initiates – via CREB – the transcription of BDNF).

Hence, in view of the important role of the ERK signaling cascade in mediating long-term neuroplastic events and mediating bcl-2 and BDNF gene expression, we have undertaken a series of studies designed to investigate the effects of lithium and VPA on this signaling cascade [166,167]. These studies have shown that lithium and VPA, at therapeutically relevant concentrations, activate the ERK MAP kinase cascade in human neuroblastoma SH-SY5Y cells, primary cortical cells, and in the cortex of intact animals [166,167] (Fig. 2). In addition to finding that VPA and lithium activate ERK, we have also found that downstream targets of the ERK pathway such as RSK and CREB are activated, while the proapoptotic protein BAD is deactivated. Furthermore, an inhibitor of the enzyme that phosphorylates ERK, MEK, attenuates the VPA and lithium-induced increase in ERK and RSK1 phosphorylation (unpublished observations). Thus, recent evidence suggests that both lithium and VPA activate the ERK MAP kinase pathway, and the transcription of downstream molecules bcl-2 and BDNF (Table 2).

7. Neuroprotective mechanisms of lithium and other mood stabilizers

Emerging preclinical and clinical evidence suggest that lithium may have neuroprotective qualities [137,168,169]. Reports in the early 1990s suggested that lithium exerted protective effects on neuronal cells [170–174]. These results led numerous labs to investigate this finding in more detail, and to determine if there are changes in the brains of patients with mood disorders that could possibly be reversed or prevented with neurotrophic therapy. Indeed, interest has increased with further evidence that VPA also activates neuroprotective pathways and is neuroprotective in some models [136,137,175].

Postmortem and in vivo neuroimaging evidence suggests that alterations in neuroplasticity and cellular resiliency may play a role in the pathophysiology of bipolar disorder. Collectively, postmortem analysis of brains from patients with bipolar disorder indicates decreases of volume in several regions, and region- and layer-specific reductions in the number, density, and size of neurons and/or glial cells when compared to control subjects [176–179]. Similarly – taken in toto – in vivo imaging studies from patients with bipolar disorder describe enlargement of the third and lateral ventricles, as well as reduced gray matter in areas of the prefrontal cortex and temporal cortex, the ventral striatum, and mesiotemporal cortex [6,180]. Recent studies have also documented decreases in *N*-acetylacetate (NAA), a putative marker of neuronal viability, in the hippocampus and in the dorsolateral prefrontal cortex in patients with bipolar disorder compared to healthy control subjects [6,180]. These results suggest that changes in neuronal volume may underlie a cause of bipolar disorder, or in the very least be a marker of the disease.

Lithium is protective in numerous pro-apoptotic paradigms in cell culture [169], and in animal models [168] (Table 3). Among the most convincing experiments include the studies by Chuang and colleagues, which report that lithium protects against damage status-post middle cerebral artery occlusion in the rat and suppresses the quinolinic acid induced

excitotoxicity-induced striatal lesions in a rat model of Huntington's disease (Fig. 3) [168,181,182].

The data on the effect of VPA and carbamazepine in neuroprotective paradigms is not as well developed as it is for lithium. However, some evidence does exist [175,183–186]. In a direct comparison, Manji et al. reported the neuroprotective effects of lithium and VPA to be similar [175]. Lithium and VPA protected human neuroblastoma SH-SY5Y cells from both thapsigargin- and MPP⁺-induced apoptosis at therapeutically relevant concentrations. Furthermore, at therapeutic concentrations, the degree of protection from both drugs was similar [175]. VPA and lithium also protect SH-SY5Y cells from staurosporine-induced apoptosis in cells stably transfected with GSK-3 [136,187] and protect cortical neurons from glutamate toxicity [186]. VPA, lithium, and carbamazepine also attenuate β -amyloid induced cell death in cultured rat hippocampal neurons [184,188] and carbamazepine has been reported to protect against some of the toxic effects of brain ischemia [189].

Based on this evidence, our group undertook several clinical studies to ascertain if lithium had effects consistent with neurotrophic actions in humans. Using magnetic resonance spectroscopy, Moore et al. documented increased levels of NAA, a putative marker of neuronal viability, in brains of patients and controls receiving lithium for a four-week period [190]. There was a strong positive correlation between the change in NAA and the amount of gray matter per voxel. This led to a more recent study, using magnetic resonance imaging where increases in the gray matter volume of patients with bipolar disorder undergoing treatment with lithium was found [191]. These reports suggest the potential for lithium – and possible other mood stabilizers – to reverse the neuroimaging and neuropathological findings in bipolar disorder [137,192]. The relationship between these changes and variations in mood remains unknown.

Thus, the changes in neuroplasticity seen with lithium may reverse the alterations in neural structure and volume observed in postmortem specimens and in vivo studies. These findings also suggest the possibility that lithium may be useful for the treatment of other 'classic' neurodegenerative disorders.

8. Targets unique to individual mood stabilizers

8.1. Direct targets of lithium

Lithium has been in clinical use for over 50 years, and provided the first pharmaceutical treatment available for the manic phase of bipolar disorder [193]. Indeed, its introduction has helped to further our understanding of bipolar disorder as a biological illness, and to begin to explore lithium's mechanism of action in the hope of developing more specific therapies [118]. However, despite extensive research, we do not, as yet, know precisely how it exerts its delayed therapeutic effects in this complex neuropsychiatric disorder. Nevertheless, research has identified a number of *initial targets* for the actions of lithium, two of which have been undergoing investigation for the development of potential new medications for bipolar disorder [138]. It appears likely that lithium exerts its initial effects by targeting the activity of an enzyme, or perhaps multiple enzymes, in cells. Lithium has a hydrated ionic radius which is very similar to that of magnesium, and it inhibits some enzymes through competition for this required cofactor [16,17,248]. Many in the field believe that this targeting then effects downstream and – through feedback inhibition – upstream signaling pathways [13,132,194]. Thus, the multiple effects of lithium, and – more generally – other mood stabilizers, on biological systems may eventually be traced back to a few initial events. Lithium has been shown to have some degree of inhibition of a number of enzymes [18]. However, only a few are significantly inhibited at therapeutic concentrations (0.6–1.2 mM). Lithium inhibits a group of at least four related phosphomonoesterases [19],

the metabolic enzyme phosphoglucomutase (PGM) [20], and a crucial kinase that functions as an intermediary in numerous intracellular signaling pathways, glycogen synthase kinase-3 (GSK-3) [21] (Table 1).

The phosphomonoesterases are a group of magnesium dependent, lithium sensitive phosphatases that, in mammals, includes inositol polyphosphate 1-phosphatase (IPPase), inositol monophosphate phosphatase (IMPase), fructose 1,6-bisphosphatase 1-phosphatase (FBPase), and bisphosphate nucleotidase (BPNase). All members of the group appear to have a common core tertiary structure and contain a conserved sequence motif [19] that binds metal ions and participates in catalytic functions of the enzyme [19].

As previously discussed, IMPase is the final inositol polyphosphate phosphatase prior to conversion to inositol and IPPase removes a phosphate from inositol-1,4-bisphosphate, at a stage just prior to IMPase (Fig. 1). The finding that lithium inhibits IMPase led to the inositol depletion hypothesis [66,67], which suggests that lithium, via inhibition of IMPase, decreases the availability of myoinositol, and thus the amount of PIP₂ available for G protein mediated signaling events that rely upon this pathway [69]. Inhibition of IPPase would be expected to have similar effects. While, lithium has consistently been shown to decrease free inositol levels in brain sections, and in the brains of rodents treated chronically with lithium [71,72], studies designed to address lithium's effects on PIP₂ signaling in rodent models have resulted in inconsistent results, and those positive results that exist suggest a small effect [3,72,74]. The selective inositol-dependent reduction of PKC isozymes [85] led to the use of tamoxifen – a PKC inhibitor at high concentrations – in clinical trials; initial results are promising and have led to the initiation of a larger double-blind placebo-controlled trial [122].

Based upon function and location, it is generally thought that lithium's inhibition of FBPase, BPNase, and PGM is more relevant for the side effects of lithium than the therapeutically relevant effects [195]. Briefly, FBPase is a key enzyme in glycolysis and initial results suggesting lithium as an inhibitor have not been followed up [196,197]. BPNase removes the 3' phosphate from 3'-phosphoadenosine 5'-phosphate (PAP). The hydrolysis of PAP is involved in RNA processing metabolism, sodium homeostasis, and sulfation metabolism. Furthermore, human BPNase, similar to IPPase, hydrolyzes inositol-1,4-bisphosphate [198] and lithium prevents the hydrolysis of both substrates by BPNase [198]. The effect of lithium on PGM, an enzyme involved in glycogen metabolism, protein glycosylation, and polysaccharide biosynthesis, was originally identified in the rabbit enzyme [199,200]. This finding has recently been confirmed in humans and yeast [20].

In spite of a general lack of interest in lithium's effect on FBPase, BPNase, and PGM, it is possible that lithium's effects on these enzymes may provide a 'dampening' of neural activity (based upon a general effect on metabolism, and especially glucose metabolism), and via this mechanism perhaps may have relevance for the mood stabilizing effects of this ion.

Lithium's inhibition of GSK-3 is discussed in an earlier section of this review. This enzyme is involved in a number of neuronal functions including growth, synaptic plasticity and protection from injury [135]. Thus, the finding that GSK-3 is a direct target of lithium is of major interest and GSK-3 inhibitors are actively being developed [201].

8.2. Valproic acid

VPA, a short-chained fatty acid, had been used as an anticonvulsant in Europe for a decade before U.S. Food and Drug Administration (FDA) approval in 1978 for the treatment of epilepsy in the United States. Interest in the potential efficacy of VPA arose out of the

suggestion that facilitating the activity of an inhibitory neurotransmitter like GABA may have antimanic effects. Early reports of VPA utility in acute mania [202,203] were followed by definitive controlled studies [204–206]. VPA has proven efficacy in the acute manic phases of the illness [204,205], and may be useful as prophylaxis for future manic episodes [207,208]. It is uncertain how VPA exerts its antimanic effects. The mechanism may be via its antiepileptic effects (the GABA hypothesis) or via an entirely unrelated mechanism. Similar to carbamazepine some results suggest that VPA inhibits sodium channel activation at high frequencies [209]. VPA also inhibits the activity of some enzymes [210] (Table 1).

A leading hypothesis regarding how VPA exerts its anticonvulsant effects is by increasing the availability of GABA in GABAergic synapses [210]. GABA, an inhibitory amino acid neurotransmitter, would be expected to inhibit excessive firing of synapses, thus inhibiting epileptogenic activity. A number of studies show that VPA, at therapeutic concentrations, is an inhibitor of succinate semialdehyde dehydrogenase (SSA-DH) [210–214]. This enzyme is critical for the GABA shunt, an enzymatic series of reactions that produces both glutamate and GABA by circumventing a portion of the tricarboxylic acid (TCA) cycle. GABA transaminase (GABA-T) converts GABA to succinate semialdehyde (SSA), which is then converted to succinate by SSA-DH. VPA's effect on SSA-DH would be expected to increase levels of SSA, which has a strong inhibitory effect on GABA-T activity. Thus, GABA concentration would increase as GABA-T is inhibited by an increasing SSA concentration. Indeed, numerous studies have documented an increase in GABA concentration in rodent brain after VPA administration [210]. It is possible that VPA exerts its antimanic effects via inhibition of SSA-DH. However, since the long-term effects of VPA are only seen following long-term treatment, the effect of SSA-DH on other cellular processes (perhaps not related to GABA concentration) may be related to the long-term changes in gene expression, protein concentration, and protein phosphorylation that are postulated to be the ultimate reason for VPA's mood stabilizing effects [3]. For example, although – on average – only 8–10% of the total flux through the TCA cycle enters the GABA shunt [215], it is possible that this percentage changes in different brain regions, or in different cell types [213]. Further downstream of SSA-DH, the GABA shunt reenters the TCA cycle; thus, inhibition of the GABA shunt could lead to a lower overall activity of the TCA cycle. Indeed, a lower TCA activity – or perhaps increased GABA – may explain the decreased glucose metabolism observed during VPA treatment [210,216,217]. VPA also inhibits succinate semialdehyde reductase, the enzyme that converts succinate semialdehyde to γ -hydroxybutyrate (GHB) with a K_i of 85 μ M [210,214]. VPA also inhibits GABA transaminase, but the K_i appears to be well above therapeutic levels [210,218,219].

VPA has recently been found to be an inhibitor of histone deacetylase (HDAC) (IC_{50} = 0.4 mM) [140,220]. HDAC acetylates histones (a major epigenetic regulator of gene expression), generally deactivating gene transcription. Two classes of histones (I and II) are found in large proteinuric complexes, which together suppress gene transcription. VPA appears to have a major inhibitory effect on class I HDACs, in vitro, in cell culture, and – at least transiently – in intact animals [140,220]. Thus, VPA's effect on this enzyme could result in multiple effects on cellular signaling pathways. However, there is reason to believe that the effect of VPA on HDAC is not of major relevance for the treatment of bipolar disorder. Some studies suggest that valpromide (similar to VPA, but the carboxyl group is modified to an amide) also has antimanic properties [206]. Valpromide does not inhibit HDAC, does not result in neural tube defects in mouse embryos or the loss of anterior structures that characterizes *Xenopus* embryos following VPA injection, but does protect against chemically induced seizures in mice [140,220–224]. Furthermore while the two stereoisomers of VPA have identical antiepileptic properties, only one stereoisomer is teratogenic [224]. This stereoisomer inhibits the activity of HDAC, while the other has no effect [220]. Thus, the developmental effects of VPA are likely due, at least in part, to

inhibition of HDAC [140,220]. However, it appears less likely that HDAC is the target of VPA relevant to either the antimanic or antiepileptic effects of this drug. It is also unclear if VPA – or its metabolites – target HDAC in the intact brain.

8.3. Carbamazepine

Carbamazepine was first used in the 1960s in the treatment of trigeminal neuralgia, followed by approval in 1974 by the FDA for the treatment of epilepsy in the United States. In 1968 Dehing reported that carbamazepine decreased aggression in some chronic psychiatric patients [225]. However, carbamazepine's efficacy in complex partial seizures of the temporal lobe, its positive psychotropic profile in patients with such seizure disorders [226], the wealth of data implicating limbic dysfunction in disorders of affect, its anti-aggressive effects, and the fact that it was a CNS-penetrant agent which reduced neuronal excitability led to its use as a potential antimanic agent [23]. The clinical efficacy of carbamazepine in the treatment of acute mania was first reported by Takezaki and Hanaoka (1971) in a small open trial [227], followed by a larger open trail by Okuma and colleagues (1975) [228]. The subsequent demonstration of carbamazepine's optimal usefulness against amygdala vs. cortical-kindled seizures [229], and the development of the kindling model of recurrent affective illness by Post, led to a more systematic investigation of its efficacy in recurrent affective disorders. Ballenger and Post reported the first controlled studies of carbamazepine efficacy in acute mania [230] in 1978, after which a number of studies have replicated this finding [23].

It is widely accepted that carbamazepine exerts its antiepileptic effects by inhibiting the high-frequency firing of sodium channels (Table 1). Thus, carbamazepine, in cultured neurons [231] and in voltage-clamp experiments [232], blocks voltage dependent sodium channels; thus, inhibiting repetitive neuronal firing – a process that is thought to contribute to aggregation of neural firing (epileptogenesis). Under physiological conditions, sodium channels are thought to be in one of three conformations: a resting state, and open state, or and inactive state. Carbamazepine's specific interaction appears to be via interaction with the sodium channel only during the inactive state, thus prolonging the time of inactivation [233]. Thus, carbamazepine does not appear to affect the amplitude or duration of individual action potentials, but does reduce the ability of a neuron to produce trains of action potentials at a high frequency. While the antiepileptic function of this is intuitive, it is not clear if these physiological effects are relevant to the treatment of mania.

Another finding is that carbamazepine has both acute and long-term effects on the levels, and signaling events involving adenosine receptors when administered at therapeutic concentrations (Table 1). In addition to reports suggesting that carbamazepine effects adenosine-mediated second messenger signaling [58,234,235], the drug also appears to bind to adenosine [57,236–239]. Carbamazepine appears to act as an antagonist, with general specificity for the A₁ subtype of adenosine receptors [57] (Table 1). Carbamazepine also appears to affect protein levels of adenosine receptors. After 11 days of treatment with carbamazepine levels of adenosine receptors in rats are significantly decreased [240]. It was further shown that the changes persisted long after (up to 8 weeks) discontinuation of treatment [241]. Signaling events downstream of adenosine receptors also appears to be altered by carbamazepine. Specifically carbamazepine, via blockade of adenosine A₁ receptors, appears to modulate adenosine's potentiating effect on activation by neurotransmitters of the phosphoinositol second messenger pathway (an effect similar as has been proposed for lithium – the inositol depletion hypothesis) [57,234,242].

As discussed in an earlier section, evidence suggests that carbamazepine may have direct inhibitory effects on adenylate cyclase [61], and in a number of studies has been shown to attenuate stimulated cyclic AMP signaling [54,56–59]. This finding is especially interesting

noting that lithium also attenuates stimulated cyclic AMP signaling [13]. Reports have also found that carbamazepine regulates other additional cellular events that may be related to the drug's mood stabilizers efficacy. For example, carbamazepine attenuates stimulated AP-1 DNA binding [243], reduces CD 151 mRNA levels [244], and suppresses stimulated C-fos levels [62,245–247].

9. Future development of new agents

The development of mood stabilizers in the past was mostly due to many serendipitous discoveries. Without knowledge of how these drugs exert their therapeutic effects, it is impossible to develop new agents in a hypothesis driven manner. Based on the intracellular targets described in this review, current research is aiming to investigate modulators of these pathways in animal models and the clinical treatment of mania. Modeling drugs after the putative mechanisms of mood stabilizing agents represents a viable option of both developing more specific therapies and as 'proof of concept' of the pathways implicated in the pathophysiology and treatment of bipolar disorder. In this regard, drugs mimicking the effects of some of the available anticonvulsants (e.g. attenuation of glutamatergic function, enhancement of GABAergic functioning, blockade of sodium channels) are not currently being developed for bipolar disorder per se, but new agents with this profile (likely developed for epilepsy) will undoubtedly be investigated (albeit possibly only in initial open studies) in bipolar disorder. While there does not currently exist any predictive value when comparing antimanic efficacy to the anti-epileptic function of drugs, future studies may provide some valuable information about which systems and pathways in the brain are most responsible for mania and consequently valuable to target.

Other critical signal transduction pathways that are targets for lithium – or other mood stabilizers – are also being viewed as targets for antimanic therapy. As discussed, a converging body of preclinical data has shown that chronic lithium and VPA, at therapeutically relevant concentrations, regulates the protein kinase C signaling cascade in preclinical models, leading to the investigation of the antimanic efficacy of tamoxifen (at doses sufficient to inhibit protein kinase C), with very encouraging preliminary results [122]. Larger scale studies with tamoxifen are underway, and it is anticipated that – if successful – will lead to trials of selective CNS-penetrant PKC inhibitors.

The clinical and preclinical evidence suggesting changes in neuroplasticity and cellular resilience in bipolar disorder represent another putative target. Evidence describes possible neurotrophic effects of both lithium and valproic acid [175]. Thus, it is likely that medications under development for the treatment of classical neurodegenerative disorders will be tested for efficacy in the treatment of bipolar disorder. In this regard, the Wnt signaling pathway – and GSK-3 – have been implicated in both regulating neuroplasticity and neuroprotection [134,135,169]. These data, and the findings that both lithium and VPA regulate this pathway, suggest a therapeutic relevance [135]. GSK-3 is also a tau kinase; hence, many pharmaceutical companies are developing CNS-penetrant small molecule GSK-3 inhibitors for the treatment of Alzheimer's and other neurodegenerative diseases [201]. It is anticipated that these will also undergo trials in bipolar disorder.

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References

1. Keck, PE., Jr; Manji, HK. Current and emerging treatments for acute mania and long-term prophylaxis for bipolar disorder. In: Davis, KL.; Charney, DS.; Coyle, JT.; Nemeroff, CB., editors. *Neuropsychopharmacology: the fifth generation of progress*. Philadelphia, PA: Lippincott Williams and Wilkins; 2002. p. 1109-1118.
2. Manji HK, Bebchuk JM, Moore GJ, Glitz D, Hasanat KA, Chen G. Modulation of CNS signal transduction pathways and gene expression by mood-stabilizing agents: therapeutic implications. *J Clin Psychiatry*. 1999; 60(Suppl 2):27-39. discussion pp 40-1, 113-6. [PubMed: 10073385]
3. Gould TD, Manji HK. Signaling networks in the pathophysiology and treatment of mood disorders. *J Psychosom Res*. 2002; 53(2):687-697. [PubMed: 12169343]
4. Bowden, CL. Toward an integrated biological model of bipolar disorder. In: Young, LT.; Joffe, RT., editors. *Bipolar disorder: biological models and their clinical application*. New York: Marcel Dekker; 1997. p. 235-254.
5. Manji HK, Lenox RH. Signaling: cellular insights into the pathophysiology of bipolar disorder. *Biol Psychiatry*. 2000; 48(6):518-530. [PubMed: 11018224]
6. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. *Nat Med*. 2001; 7(5):541-547. [PubMed: 11329053]
7. Waldmeier PC. Is there a common denominator for the antimanic effect of lithium and anticonvulsants? *Pharmacopsychiatry*. 1987; 20(2):37-47. [PubMed: 3035590]
8. Chen G, Manji HK, Hawver DB, Wright CB, Potter WZ. Chronic sodium valproate selectively decreases protein kinase C alpha and epsilon in vitro. *J Neurochem*. 1994; 63(6):2361-2364. [PubMed: 7964759]
9. Lenox RH, McNamara RK, Watterson JM, Watson DG. Myristoylated alanine-rich C kinase substrate (MARCKS): a molecular target for the therapeutic action of mood stabilizers in the brain? *J Clin Psychiatry*. 1996; 57(Suppl 13-10):23-33. [PubMed: 8970502]
10. Manji HK, Chen G, Hsiao JK, Risby ED, Masana MI, Potter WZ. Regulation of signal transduction pathways by mood-stabilizing agents: implications for the delayed onset of therapeutic efficacy. *J Clin Psychiatry*. 1996; 57(13):34-48. [PubMed: 8970503]
11. Post, RM. Psychopharmacology of mood stabilizers. In: Buckley, BF.; Waddington, JL., editors. *Schizophrenia and mood disorders: the new drug therapies in clinical practice*. Oxford: Butterworth-Heinemann; 2000. p. 127-154.
12. Jope RS. Anti-bipolar therapy: mechanism of action of lithium. *Mol Psychiatry*. 1999; 4(2):117-128. [PubMed: 10208444]
13. Wang, J-F.; Young, LT.; Li, PP.; Warsh, JJ. Signal transduction abnormalities in bipolar disorder. In: Young, LT.; Joffe, RT., editors. *Bipolar disorder: biological models and their clinical application*. New York: Marcel Dekker; 1997. p. 41-79.
14. Williams RS, Cheng L, Mudge AW, Harwood AJ. A common mechanism of action for three mood-stabilizing drugs. *Nature*. 2002; 417(6886):292-295. [PubMed: 12015604]
15. Hall AC, Brennan A, Goold RG, Cleverley K, Lucas FR, Gordon-Weeks PR, et al. Valproate regulates GSK-3-mediated axonal remodeling and synapsin i clustering in developing neurons. *Mol Cell Neurosci*. 2002; 20(2):257-270. [PubMed: 12093158]
16. Amari L, Layden B, Rong Q, Gerald CF, Mota de Freitas D. Comparison of fluorescence, (31)P NMR, and (7)Li NMR spectroscopic methods for investigating Li(+)/Mg(2+) competition for biomolecules. *Anal Biochem*. 1999; 272(1):1-7. [PubMed: 10405286]
17. Ryves WJ, Harwood AJ. Lithium inhibits glycogen synthase kinase-3 by competition for magnesium. *Biochem Biophys Res Commun*. 2001; 280(3):720-725. [PubMed: 11162580]
18. Davies SP, Reddy H, Caivano M, Cohen P. Specificity and mechanism of action of some commonly used protein kinase inhibitors. *Biochem J*. 2000; 351(3 Pt 1):95-105. [PubMed: 10998351]
19. York JD, Ponder JW, Majerus PW. Definition of a metal-dependent/Li(+)-inhibited phosphomonoesterase protein family based upon a conserved three-dimensional core structure. *Proc Natl Acad Sci USA*. 1995; 92(11):5149-5153. [PubMed: 7761465]

20. Masuda CA, Xavier MA, Mattos KA, Galina A, Montero-Lomeli M. Phosphoglucomutase is an in vivo lithium target in yeast. *J Biol Chem.* 2001; 10:10.
21. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci USA.* 1996; 93(16):8455–8459. [PubMed: 8710892]
22. Li X, Ketter TA, Frye MA. Synaptic, intracellular, and neuroprotective mechanisms of anticonvulsants: are they relevant for the treatment and course of bipolar disorders? *J Affect Disord.* 2002; 69(1–3):1–14. [PubMed: 12103447]
23. Post RM, Denicoff KD, Frye MA, Dunn RT, Leverich GS, Osuch E, et al. A history of the use of anticonvulsants as mood stabilizers in the last two decades of the 20th century. *Neuropsychobiology.* 1998; 38(3):152–166. [PubMed: 9778604]
24. Spiegel, AM. G proteins, receptors, and disease. Totowa, NJ: Humana; 1998.
25. Manji HK. G proteins: implications for psychiatry. *Am J Psychiatry.* 1992; 149(6):746–760. [PubMed: 1350427]
26. Warsh, JJ.; Young, LT.; Li, PP. Bipolar medications: mechanisms of action. 1st ed.. Manji, HK.; Bowden, CL.; Belmaker, RH., editors. Washington, DC: American Psychiatric Press; 2000. p. 299–329.
27. Casebolt TL, Li XH, Jope RS. Alpha-1 adrenergic receptor binding and adrenergic-stimulated cyclic AMP production in rat cerebral cortex after chronic lithium treatment. *J Neural Transm Gen Sect.* 1990; 82(3):197–204. [PubMed: 1979002]
28. Colin SF, Chang HC, Mollner S, Pfeuffer T, Reed RR, Duman RS, et al. Chronic lithium regulates the expression of adenylate cyclase and Gi- protein alpha subunit in rat cerebral cortex. *Proc Natl Acad Sci USA.* 1991; 88(23):10634–10637. [PubMed: 1720545]
29. Jakobsen SN, Wiborg O. Selective effects of long-term lithium and carbamazepine administration on G-protein subunit expression in rat brain. *Brain Res.* 1998; 780(1):46–55. [PubMed: 9473582]
30. Li PP, Young LT, Tam YK, Sibony D, Warsh JJ. Effects of chronic lithium and carbamazepine treatment on G-protein subunit expression in rat cerebral cortex. *Biol Psychiatry.* 1993; 34(3):162–170. [PubMed: 8399809]
31. Masana MI, Bitran JA, Hsiao JK, Potter WZ. In vivo evidence that lithium inactivates Gi modulation of adenylate cyclase in brain. *J Neurochem.* 1992; 59(1):200–205. [PubMed: 1319465]
32. Ebstein RP, Oppenheim G, Ebstein BS, Amiri Z, Stessman J. The cyclic AMP second messenger system in man: the effects of heredity, hormones, drugs, aluminum, age and disease on signal amplification. *Prog Neuropsychopharmacol Biol Psychiatry.* 1986; 10(3–5):323–353. [PubMed: 3025924]
33. Newman ME, Lerer B, Lichtenberg P, Shapira B. Platelet adenylate cyclase activity in depression and after clomipramine and lithium treatment: relation to serotonergic function. *Psychopharmacology.* 1992; 109(1–2):231–234. [PubMed: 1365662]
34. Risby ED, Hsiao JK, Manji HK, Bitran J, Moses F, Zhou DF, et al. The mechanisms of action of lithium. II. Effects on adenylate cyclase activity and beta-adrenergic receptor binding in normal subjects. *Arch Gen Psychiatry.* 1991; 48(6):513–524. [PubMed: 1645514]
35. Ebstein RP, Moscovich D, Zeevi S, Amiri Z, Lerer B. Effect of lithium in vitro and after chronic treatment on human platelet adenylate cyclase activity: postreceptor modification of second messenger signal amplification. *Psychiatry Res.* 1987; 21(3):221–228. [PubMed: 2819913]
36. Hsiao JK, Manji HK, Chen GA, Bitran JA, Risby ED, Potter WZ. Lithium administration modulates platelet Gi in humans. *Life Sci.* 1992; 50(3):227–233. [PubMed: 1731175]
37. Lonati-Galligani M, Emrich HM, Raptis C, Pirke KM. Effect of in vivo lithium treatment on (–)isoproterenol-stimulated cAMP accumulation in lymphocytes of healthy subjects and patients with affective psychoses. *Pharmacopsychiatry.* 1989; 22(6):241–245. [PubMed: 2559417]
38. Wang YC, Pandey GN, Mendels J, Frazer A. Effect of lithium on prostaglandin F1-stimulated adenylate cyclase activity of human platelets. *Biochem Pharmacol.* 1974; 23(4):845–855. [PubMed: 4363215]
39. Garcia-Sevilla JA, Guimon J, Garcia-Vallejo P, Fuster MJ. Biochemical and functional evidence of supersensitive platelet alpha 2-adrenoceptors in major affective disorder. Effect of long-term lithium carbonate treatment. *Arch Gen Psychiatry.* 1986; 43(1):51–57. [PubMed: 3002293]

40. Kofman O, Li PP, Warsh JJ. Lithium, but not carbamazepine, potentiates hyperactivity induced by intra-accumbens cholera toxin. *Pharmacol Biochem Behav.* 1998; 59(1):191–200. [PubMed: 9443555]
41. Miki M, Hamamura T, Ujike H, Lee Y, Habara T, Kodama M, et al. Effects of subchronic lithium chloride treatment on G-protein subunits (Golf, Ggamma7) and adenylyl cyclase expressed specifically in the rat striatum. *Eur J Pharmacol.* 2001; 428(3):303–309. [PubMed: 11689187]
42. Herve D, Levi-Strauss M, Marey-Semper I, Verney C, Tassin JP, Glowinski J, et al. G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. *J Neurosci.* 1993; 13(5):2237–2248. [PubMed: 8478697]
43. Manji HK, Potter WZ, Lenox RH. Signal transduction pathways. Molecular targets for lithium's actions. *Arch Gen Psychiatry.* 1995; 52(7):531–543. [PubMed: 7598629]
44. Mork A, Geisler A, Hollund P. Effects of lithium on second messenger systems in the brain. *Pharmacol Toxicol.* 1992; 71(Suppl 1):4–17. [PubMed: 1336196]
45. Chen G, Masana MI, Manji HK. Lithium regulates PKC-mediated intracellular cross-talk and gene expression in the CNS in vivo. *Bipolar Disord.* 2000; 2(3 Pt 2):217–236. [PubMed: 11249800]
46. Manji HK, Chen G, Shimon H, Hsiao JK, Potter WZ, Belmaker RH. Guanine nucleotide-binding proteins in bipolar affective disorder. Effects of long-term lithium treatment. *Arch Gen Psychiatry.* 1995; 52(2):135–144. [PubMed: 7848049]
47. Li, PP.; Andreopoulos, S.; Warsh, JJ. Signal transduction abnormalities in bipolar affective disorder. In: Reith, MEA., editor. *Cerebral signal transduction: from first to fourth messengers.* Totowa, NJ: Humana; 2000. p. 283–312.
48. Jope RS. A bimodal model of the mechanism of action of lithium. *Mol Psychiatry.* 1999; 4(1):21–25. [PubMed: 10089004]
49. Wiborg O, Kruger T, Jakobsen SN. Region-selective effects of longterm lithium and carbamazepine administration on cyclic AMP levels in rat brain. *Pharmacol Toxicol.* 1999; 84(2): 88–93. [PubMed: 10068152]
50. Manji HK, Chen G. Post-receptor signaling pathways in the pathophysiology and treatment of mood disorders. *Curr Psychiatry Rep.* 2000; 2(6):479–489. [PubMed: 11122999]
51. Ram A, Guedj F, Cravchik A, Weinstein L, Cao Q, Badner JA, et al. No abnormality in the gene for the G protein stimulatory alpha subunit in patients with bipolar disorder. *Arch Gen Psychiatry.* 1997; 54(1):44–48. [PubMed: 9006399]
52. Manji, HK.; Chen, G.; Hsiao, JK.; Masana, MI.; Moore, GJ.; Potter, WZ. Regulation of signal transduction pathways by mood stabilizing agents: implications for the pathophysiology and treatment of bipolar affective disorder. In: Manji, HK.; Bowden, CL.; Belmaker, RH., editors. *Bipolar medications: mechanisms of action.* 1st ed.. Washington, DC: American Psychiatric Press; 2000. p. 129–177.
53. Ambrosio AF, Soares-Da-Silva P, Carvalho CM, Carvalho AP. Mechanisms of action of carbamazepine and its derivatives, oxcarbazepine, BIA 2-093, and BIA 2-024. *Neurochem Res.* 2002; 27(1–2):121–130. [PubMed: 11926264]
54. Palmer GC. Interactions of antiepileptic drugs on adenylate cyclase and phosphodiesterases in rat and mouse cerebrum. *Exp Neurol.* 1979; 63(2):322–335. [PubMed: 220075]
55. Palmer GC, Jones DJ, Medina MA, Stavinoha WB. Anticonvulsant drug actions on in vitro and in vivo levels of cyclic AMP in the mouse brain. *Epilepsia.* 1979; 20(2):95–104. [PubMed: 222576]
56. Elphick M, Taghavi Z, Powell T, Godfrey PP. Chronic carbamazepine down-regulates adenosine A2 receptors: studies with the putative selective adenosine antagonists PD115,199 and PD116,948. *Psychopharmacology.* 1990; 100(4):522–529. [PubMed: 2157232]
57. Van Calker D, Steber R, Klotz KN, Greil W. Carbamazepine distinguishes between adenosine receptors that mediate different second messenger responses. *Eur J Pharmacol.* 1991; 206(4):285–290. [PubMed: 1915589]
58. Lewin E, Bleck V. Cyclic AMP accumulation in cerebral cortical slices: effect of carbamazepine, phenobarbital, and phenytoin. *Epilepsia.* 1977; 18(2):237–242. [PubMed: 194771]
59. Ferrendelli JA, Kinscherf DA. Inhibitory effects of anticonvulsant drugs on cyclic nucleotide accumulation in brain. *Ann Neurol.* 1979; 5(6):533–538. [PubMed: 38736]

60. Avissar S, Schreiber G, Aulakh CS, Wozniak KM, Murphy DL. Carbamazepine and electroconvulsive shock attenuate beta-adrenoceptor and muscarinic cholinergic coupling to G proteins in rat cortex. *Eur J Pharmacol.* 1990; 189(1):99–103. [PubMed: 2171965]
61. Chen G, Pan B, Hawver DB, Wright CB, Potter WZ, Manji HK. Attenuation of cyclic AMP production by carbamazepine. *J Neurochem.* 1996; 67(5):2079–2086. [PubMed: 8863517]
62. Divish MM, Sheftel G, Boyle A, Kalasapudi VD, Papolos DF, Lachman HM. Differential effect of lithium on fos protooncogene expression mediated by receptor and postreceptor activators of protein kinase C and cyclic adenosine monophosphate: model for its antimanic action. *J Neurosci Res.* 1991; 28(1):40–48. [PubMed: 1674966]
63. Ludvig N, Mishra PK, Jobe PC. Dibutyl cyclic AMP has epileptogenic potential in the hippocampus of freely behaving rats: a combined EEG-intracerebral microdialysis study. *Neurosci Lett.* 1992; 141(2):187–191. [PubMed: 1331898]
64. Chen G, Manji HK, Wright CB, Hawver DB, Potter WZ. Effects of valproic acid on beta-adrenergic receptors, G-proteins, and adenylyl cyclase in rat C6 glioma cells. *Neuropsychopharmacology.* 1996; 15(3):271–280. [PubMed: 8873110]
65. Hudson CJ, Young LT, Li PP, Warsh JJ. CNS signal transduction in the pathophysiology and pharmacotherapy of affective disorders and schizophrenia. *Synapse.* 1993; 13(3):278–293. [PubMed: 8497811]
66. Hallcher LM, Sherman WR. The effects of lithium ion and other agents on the activity of myo-inositol-1-phosphatase from bovine brain. *J Biol Chem.* 1980; 255(22):10896–10901. [PubMed: 6253491]
67. Naccarato WF, Ray RE, Wells WW. Biosynthesis of myo-inositol in rat mammary gland. Isolation and properties of the enzymes. *Arch Biochem Biophys.* 1974; 164(1):194–201. [PubMed: 4372945]
68. Majerus PW. Inositol phosphate biochemistry. *Annu Rev Biochem.* 1992; 61:225–250. [PubMed: 1323235]
69. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. *Cell.* 1989; 59(3):411–419. [PubMed: 2553271]
70. Gani D, Downes CP, Batty I, Bramham J. Lithium and myo-inositol homeostasis. *Biochim Biophys Acta.* 1993; 1177(3):253–269. [PubMed: 8391849]
71. Allison JH, Stewart MA. Reduced brain inositol in lithium-treated rats. *Nat New Biol.* 1971; 233(43):267–268. [PubMed: 5288124]
72. Atack JR. Lithium, phosphatidylinositol signaling, and bipolar disorder. In: Manji, HK.; Bowden, CL.; Belmaker, RH., editors. *Bipolar medications: mechanism of action.* 1st ed.. Washington, DC: American Psychiatric Press; 2000.
73. Moore GJ, Bebachuk JM, Parrish JK, Faulk MW, Arfken CL, Strahl-Bevacqua J, et al. Temporal dissociation between lithium-induced changes in frontal lobe myo-inositol and clinical response in manic-depressive illness. *Am J Psychiatry.* 1999; 156(12):1902–1908. [PubMed: 10588403]
74. Chen G, Hasanat KA, Bebachuk JM, Moore GJ, Glitz D, Manji HK. Regulation of signal transduction pathways and gene expression by mood stabilizers and antidepressants. *Psychosom Med.* 1999; 61(5):599–617. [PubMed: 10511011]
75. Fauroux CM, Freeman S. Inhibitors of inositol monophosphatase. *J Enzyme Inhib.* 1999; 14(2):97–108. [PubMed: 10445037]
76. Godfrey PP, McClue SJ, White AM, Wood AJ, Grahame-Smith DG. Subacute and chronic in vivo lithium treatment inhibits agonist- and sodium fluoride-stimulated inositol phosphate production in rat cortex. *J Neurochem.* 1989; 52(2):498–506. [PubMed: 2536074]
77. Song L, Jope RS. Chronic lithium treatment impairs phosphatidylinositol hydrolysis in membranes from rat brain regions. *J Neurochem.* 1992; 58(6):2200–2206. [PubMed: 1573399]
78. Manji HK, Lenox RH. Long-term action of lithium: a role for transcriptional and posttranscriptional factors regulated by protein kinase C. *Synapse.* 1994; 16(1):11–28. [PubMed: 8134897]
79. Jope RS, Williams MB. Lithium and brain signal transduction systems. *Biochem Pharmacol.* 1994; 47(3):429–441. [PubMed: 8117309]

80. Vaden DL, Ding D, Peterson B, Greenberg ML. Lithium and valproate decrease inositol mass and increase expression of the yeast *INO1* and *INO2* genes for inositol biosynthesis. *J Biol Chem*. 2001; 276(18):15466–15471. [PubMed: 11278273]
81. Murray M, Greenberg ML. Expression of yeast *INM1* encoding inositol monophosphatase is regulated by inositol, carbon source and growth stage and is decreased by lithium and valproate. *Mol Microbiol*. 2000; 36(3):651–661. [PubMed: 10844654]
82. van Calker D, Belmaker RH. The high affinity inositol transport system – implications for the pathophysiology and treatment of bipolar disorder. *Bipolar Disord*. 2000; 2(2):102–107. [PubMed: 11252649]
83. Lubrich B, van Calker D. Inhibition of the high affinity myo-inositol transport system: a common mechanism of action of antibipolar drugs? *Neuropsychopharmacology*. 1999; 21(4):519–529. [PubMed: 10481836]
84. Coyle JT, Manji HK. Getting balance: drugs for bipolar disorder share target. *Nat Med*. 2002; 8(6):557–558. [PubMed: 12042799]
85. Manji HK, Lenox RH. Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry*. 1999; 46(10):1328–1351. [PubMed: 10578449]
86. Manji HK, Bersudsky Y, Chen G, Belmaker RH, Potter WZ. Modulation of protein kinase C isozymes and substrates by lithium: the role of myo-inositol. *Neuropsychopharmacology*. 1996; 15(4):370–381. [PubMed: 8887991]
87. Manji HK, Etcheberrigaray R, Chen G, Olds JL. Lithium decreases membrane-associated protein kinase C in hippocampus: selectivity for the alpha isozyme. *J Neurochem*. 1993; 61(6):2303–2310. [PubMed: 8245981]
88. Leli, U.; Hauser, G. Lithium modifies diacylglycerol levels and protein kinase C in neuroblastoma cells; Abstracts of the 8th international conference on second messengers and phosphoproteins; 1992. p. Z187F
89. Li X, Joje RS. Selective inhibition of the expression of signal transduction proteins by lithium in nerve growth factor-differentiated PC12 cells. *J Neurochem*. 1995; 65(6):2500–2508. [PubMed: 7595544]
90. Lenox RH, Watson DG, Patel J, Ellis J. Chronic lithium administration alters a prominent PKC substrate in rat hippocampus. *Brain Res*. 1992; 570(1–2):333–340. [PubMed: 1617424]
91. Watson DG, Lenox RH. Chronic lithium-induced down-regulation of MARCKS in immortalized hippocampal cells: potentiation by muscarinic receptor activation. *J Neurochem*. 1996; 67(2):767–777. [PubMed: 8764606]
92. Watson DG, Watterson JM, Lenox RH. Sodium valproate down-regulates the myristoylated alanine-rich C kinase substrate (MARCKS) in immortalized hippocampal cells: a property of protein kinase C-mediated mood stabilizers. *J Pharmacol Exp Ther*. 1998; 285(1):307–316. [PubMed: 9536026]
93. Einat, H.; Kofman, O.; Belmaker, RH. Animal models of bipolar disorder: from a single episode to progressive cycling models. In: Myslobodsky, M.; Weiner, I., editors. *Contemporary issues in modeling psychopathology*. London: Kluwer Academic Publishers; 2000. p. 165–179.
94. Post RM, Susan R, Weiss B. Sensitization, kindling, and carbamazepine: an update on their implications for the course of affective illness. *Pharmacopsychiatry*. 1992; 25(1):41–43. [PubMed: 1579606]
95. Lenox RH, Gould TD, Manji HK. Endophenotype in bipolar disorder. *Am J Med Genet*. 2002; 114(4):391–406. [PubMed: 11992561]
96. Steketee JD, Striplin CD, Murray TF, Kalivas PW. Possible role for G-proteins in behavioral sensitization to cocaine. *Brain Res*. 1991; 545(1–):287–291. [PubMed: 1907213]
97. Steketee JD, Kalivas PW. Sensitization to psychostimulants and stress after injection of pertussis toxin into the A10 dopamine region. *J Pharmacol Exp Ther*. 1991; 259(2):916–924. [PubMed: 1941636]
98. Steketee JD. Injection of the protein kinase inhibitor H7 into the A10 dopamine region blocks the acute responses to cocaine: behavioral and in vivo microdialysis studies. *Neuropharmacology*. 1993; 32(12):1289–1297. [PubMed: 8152520]

99. Steketee JD. Intra-A10 injection of H7 blocks the development of sensitization to cocaine. *Neuroreport*. 1994; 6(1):69–72. [PubMed: 7703432]
100. Giambalvo CT. Protein kinase C and dopamine transport – 2. Effects of amphetamine in vitro. *Neuropharmacology*. 1992; 31(12):1211–1222. [PubMed: 1361666]
101. Giambalvo CT. Protein kinase C and dopamine transport – 1. Effects of amphetamine in vivo. *Neuropharmacology*. 1992; 31(12):1201–1210. [PubMed: 1361665]
102. Gnegy ME, Hong P, Ferrell ST. Phosphorylation of neuromodulin in rat striatum after acute and repeated, intermittent amphetamine. *Brain Res Mol Brain Res*. 1993; 20(4):289–298. [PubMed: 8114616]
103. Iwata SI, Hewlett GH, Ferrell ST, Kantor L, Gnegy ME. Enhanced dopamine release and phosphorylation of synapsin I and neuromodulin in striatal synaptosomes after repeated amphetamine. *J Pharmacol Exp Ther*. 1997; 283(3):1445–1452. [PubMed: 9400020]
104. Iwata S, Hewlett GH, Gnegy ME. Amphetamine increases the phosphorylation of neuromodulin and synapsin I in rat striatal synaptosomes. *Synapse*. 1997; 26(3):281–291. [PubMed: 9183817]
105. Daigen A, Akiyama K, Itoh T, Kohira I, Sora I, Morimoto K, et al. Long-lasting enhancement of the membrane-associated protein kinase C activity in the hippocampal kindled rat. *Jpn J Psychiatry Neurol*. 1991; 45(2):297–301. [PubMed: 1662304]
106. Daigen A, Akiyama K, Otsuki S. Long-lasting change in the membrane-associated protein kinase C activity in the hippocampal kindled rat. *Brain Res*. 1991; 545(1–2):131–136. [PubMed: 1860039]
107. Kantor L, Gnegy ME. Protein kinase C inhibitors block amphetamine-mediated dopamine release in rat striatal slices. *J Pharmacol Exp Ther*. 1998; 284(2):592–598. [PubMed: 9454802]
108. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am*. 1998; 21(2):293–307. [PubMed: 9670227]
109. Ur E, Turner TH, Goodwin TJ, Grossman A, Besser GM. Mania in association with hydrocortisone replacement for Addison's disease. *Postgrad Med J*. 1992; 68(795):41–43. [PubMed: 1561189]
110. Haskett RF. Diagnostic categorization of psychiatric disturbance in Cushing's syndrome. *Am J Psychiatry*. 1985; 142(8):911–916. [PubMed: 2992298]
111. Dwivedi Y, Pandey GN. Administration of dexamethasone up-regulates protein kinase C activity and the expression of gamma and epsilon protein kinase C isozymes in the rat brain. *J Neurochem*. 1999; 72(1):380–387. [PubMed: 9886091]
112. Nalepa I, Vetulani J. The responsiveness of cerebral cortical adrenergic receptors after chronic administration of atypical antidepressant mianserin. *J Psychiatry Neurosci*. 1994; 19(2):120–128. [PubMed: 8204564]
113. Nalepa I, Chalecka-Franaszek E, Vetulani J. The antagonistic effect of separate and consecutive chronic treatment with imipramine and ECS on the inhibition of alpha 1-adrenoceptor activity by protein kinase C. *Pol J Pharmacol*. 1993; 45(5–6):521–532. [PubMed: 8012475]
114. Apparsundaram S, Schroeter S, Giovanetti E, Blakely RD. Acute regulation of norepinephrine transport: II. PKC-modulated surface expression of human norepinephrine transporter proteins. *J Pharmacol Exp Ther*. 1998; 287(2):744–751. [PubMed: 9808705]
115. Apparsundaram S, Galli A, De Felice LJ, Hartzell HC, Blakely RD. Acute regulation of norepinephrine transport: I. protein kinase C-linked muscarinic receptors influence transport capacity and transporter density in SK-N-SH cells. *J Pharmacol Exp Ther*. 1998; 287(2):733–743. [PubMed: 9808704]
116. Blakely RD, Ramamoorthy S, Schroeter S, Qian Y, Apparsundaram S, Galli A, et al. Regulated phosphorylation and trafficking of antidepressant-sensitive serotonin transporter proteins. *Biol Psychiatry*. 1998; 44(3):169–178. [PubMed: 9693389]
117. Zhang L, Elmer LW, Little KY. Expression and regulation of the human dopamine transporter in a neuronal cell line. *Brain Res Mol Brain Res*. 1998; 59(1):66–73. [PubMed: 9729282]
118. Goodwin, FK.; Jamison, KR. Manic-depressive illness. New York: Oxford University Press; 1990.

119. Chen SJ, Sweatt JD, Klann E. Enhanced phosphorylation of the postsynaptic protein kinase C substrate RC3/neurogranin during long-term potentiation. *Brain Res.* 1997; 749(2):181–187. [PubMed: 9138717]
120. Conn, PJ.; Sweatt, JD. Protein kinase C in the nervous system. In: Kuo, JF., editor. *Protein kinase C*. New York: Oxford University Press; 1994. p. 199-235.
121. Hahn CG, Friedman E. Abnormalities in protein kinase C signaling and the pathophysiology of bipolar disorder. *Bipolar Disord.* 1999; 1(2):81–86. [PubMed: 11252663]
122. Bebachuk JM, Arfken CL, Dolan-Manji S, Murphy J, Hasanat K, Manji HK. A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. *Arch Gen Psychiatry.* 2000; 57(1):95–97. [PubMed: 10632242]
123. Horgan K, Cooke E, Hallett MB, Mansel RE. Inhibition of protein kinase C mediated signal transduction by tamoxifen. Importance for antitumour activity. *Biochem Pharmacol.* 1986; 35(24):4463–4465. [PubMed: 3790165]
124. O'Brian CA, Housey GM, Weinstein IB. Specific and direct binding of protein kinase C to an immobilized tamoxifen analogue. *Cancer Res.* 1988; 48(13):3626–3629. [PubMed: 3378206]
125. Cohen P, Frame S. The renaissance of GSK3. *Nat Rev Mol Cell Biol.* 2001; 2(10):769–776. [PubMed: 11584304]
126. Plyte SE, Hughes K, Nikolakaki E, Pulverer BJ, Woodgett JR. Glycogen synthase kinase-3: functions in oncogenesis and development. *Biochim Biophys Acta.* 1992; 1114(2–3):147–162. [PubMed: 1333807]
127. Woodgett JR. Judging a protein by more than its name: gsk-3. *Sci STKE.* 2001; 1(200(100)):RE12. [PubMed: 11579232]
128. Haugaard ES, Mickel RA, Haugaard N. Actions of lithium ions and insulin on glucose utilization, glycogen synthesis and glycogen synthase in the isolated rat diaphragm. *Biochem Pharmacol.* 1974; 23(12):1675–1685. [PubMed: 4210202]
129. Cheng K, Creacy S, Lerner J. 'Insulin-like' effects of lithium ion on isolated rat adipocytes. II. Specific activation of glycogen synthase. *Mol Cell Biochem.* 1983; 56(2):183–189. [PubMed: 6417471]
130. Bosch F, Gomez-Foix AM, Arino J, Guinovart JJ. Effects of lithium ions on glycogen synthase and phosphorylase in rat hepatocytes. *J Biol Chem.* 1986; 261(36):16927–16931. [PubMed: 3023372]
131. Harwood AJ. Regulation of GSK-3: a cellular multiprocessor. *Cell.* 2001; 105(7):821–824. [PubMed: 11439177]
132. Grimes CA, Jope RS. The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. *Prog Neurobiol.* 2001; 65(4):391–426. [PubMed: 11527574]
133. Cadigan KM, Nusse R. Wnt signaling: a common theme in animal development. *Genes Dev.* 1997; 11(24):3286–3305. [PubMed: 9407023]
134. Salinas PC, Hall AC. Lithium and synaptic plasticity. *Bipolar Disord.* 1999; 1(2):87–90. [PubMed: 11252664]
135. Gould TD, Manji HK. The Wnt signaling pathway in bipolar disorder. *Neuroscientist.* 2002; 8(5):497–511. [PubMed: 12374432]
136. Li X, Bijur GN, Jope RS. Glycogen synthase kinase 3-beta, mood stabilizers, and neuroprotection. *Bipolar Disord.* 2002; 4:137–144. [PubMed: 12071511]
137. Manji HK, Moore GJ, Rajkowska G, Chen G. Neuroplasticity and cellular resilience in mood disorders. *Mol Psychiatry.* 2000; 5(6):578–593. [PubMed: 11126389]
138. Phiel CJ, Klein PS. Molecular targets of lithium action. *Annu Rev Pharmacol Toxicol.* 2001; 41:789–813. [PubMed: 11264477]
139. 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(3):1327–1330. [PubMed: 10037507]
140. Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem.* 2001; 276:2525–2531. [PubMed: 11264477]

141. Grimes AC, Jope RS. CREB DNA binding activity is inhibited by glycogen synthase kinase-3 β and facilitated by lithium. *J Neurochem*. 2001; 78:1–15.
142. Axelrod J, Burch RM, Jelsema CL. Receptor-mediated activation of phospholipase A2 via GTP-binding proteins: arachidonic acid and its metabolites as second messengers. *Trends Neurosci*. 1988; 11(3):117–123. [PubMed: 2465609]
143. Rapoport SI. In vivo fatty acid incorporation into brain phospholipids in relation to plasma availability, signal transduction and membrane remodeling. *J Mol Neurosci*. 2001; 16(2–3):243–261. discussion p 279–84. [PubMed: 11478380]
144. Axelrod J. Phospholipase A2 and G proteins. *Trends Neurosci*. 1995; 18(2):64–65. [PubMed: 7537411]
145. Chang MC, Contreras MA, Rosenberger TA, Rintala JJ, Bell JM, Rapoport SI. Chronic valproate treatment decreases the in vivo turnover of arachidonic acid in brain phospholipids: a possible common effect of mood stabilizers. *J Neurochem*. 2001; 77(3):796–803. [PubMed: 11331408]
146. Chang MC, Grange E, Rabin O, Bell JM, Allen DD, Rapoport SI. Lithium decreases turnover of arachidonate in several brain phospholipids. *Neurosci Lett*. 1996; 220(3):171–174. [PubMed: 8994220]
147. Rapoport SI, Bosetti F. Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder? *Arch Gen Psychiatry*. 2002; 59(7):592–596. [PubMed: 12090811]
148. Chang MC, Jones CR. Chronic lithium treatment decreases brain phospholipase A2 activity. *Neurochem Res*. 1998; 23(6):887–892. [PubMed: 9572678]
149. Rintala J, Seemann R, Chandrasekaran K, Rosenberger TA, Chang L, Contreras MA, et al. 85 kDa cytosolic phospholipase A2 is a target for chronic lithium in rat brain. *Neuroreport*. 1999; 10(18):3887–3890. [PubMed: 10716228]
150. Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci*. 2001; 2(1):24–32. [PubMed: 11253356]
151. Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. *Curr Opin Neurobiol*. 2001; 11(3):272–280. [PubMed: 11399424]
152. Riccio A, Pierchala BA, Ciarallo CL, Ginty DD. An NGF-TrkA-mediated retrograde signal to transcription factor CREB in sympathetic neurons. *Science*. 1997; 277(5329):1097–1100. [PubMed: 9262478]
153. Bonni A, Brunet A, West AE, Datta SR, Takasu MA, Greenberg ME. Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms. *Science*. 1999; 286(5443):1358–1362. [PubMed: 10558990]
154. Suzuki T, Okumura-Noji K, Nishida E. ERK2-type mitogen-activated protein kinase (MAPK) and its substrates in postsynaptic density fractions from the rat brain. *Neurosci Res*. 1995; 22(3):277–285. [PubMed: 7478291]
155. Matsubara M, Kusubata M, Ishiguro K, Uchida T, Titani K, Taniguchi H. Site-specific phosphorylation of synapsin I by mitogen-activated protein kinase and Cdk5 and its effects on physiological functions. *J Biol Chem*. 1996; 271(35):21108–21113. [PubMed: 8702879]
156. Kornhauser JM, Greenberg ME. A kinase to remember: dual roles for MAP kinase in long-term memory. *Neuron*. 1997; 18(6):839–842. [PubMed: 9208850]
157. Fukunaga K, Miyamoto E. Role of MAP kinase in neurons. *Mol Neurobiol*. 1998; 16(1):79–95. [PubMed: 9554703]
158. Robinson MJ, Stippec SA, Goldsmith E, White MA, Cobb MH. A constitutively active and nuclear form of the MAP kinase ERK2 is sufficient for neurite outgrowth and cell transformation. *Curr Biol*. 1998; 8(21):1141–1150. [PubMed: 9799732]
159. Xu Q, Fawcett TW, Gorospe M, Guyton KZ, Liu Y, Holbrook NJ. Induction of mitogen-activated protein kinase phosphatase-1 during acute hypertension. *Hypertension*. 1997; 30(1 Pt 1):106–111. [PubMed: 9231829]
160. Roberson ED, English JD, Adams JP, Selcher JC, Kondratieff C, Sweatt JD. The mitogen-activated protein kinase cascade couples PKA and PKC to cAMP response element binding protein phosphorylation in area CA1 of hippocampus. *J Neurosci*. 1999; 19(11):4337–4348. [PubMed: 10341237]

161. Roberson ED, English JD, Sweatt JD. A biochemist's view of long-term potentiation. *Learn Mem.* 1996; 3(1):1–24. [PubMed: 10456072]
162. Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, 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(2):879–882. [PubMed: 9930766]
163. Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? *Biol Psychiatry.* 1999; 46(7):929–940. [PubMed: 10509176]
164. Chen RW, Chuang DM. Long term lithium treatment suppresses p53 and Bax expression but increases Bcl-2 expression. A prominent role in neuroprotection against excitotoxicity. *J Biol Chem.* 1999; 274(10):6039–6042. [PubMed: 10037682]
165. Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharmacology (Berl).* 2001; 158(1):100–106. [PubMed: 11685390]
166. Chen G, Einat H, Yuan P, Manji HK. Evidence for the Involvement of the ERK MAP kinase signaling cascade in mood modulation. *Biol Psychiatry.* 2002; 51(8):3685.
167. 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(34):31674–31683. [PubMed: 11418608]
168. Chuang DM, Chen R, Chalecka-Franaszek E, Ren M, Hashimoto R, Senatorov V, et al. Neuroprotective effects of lithium in cultured cells and animal model of diseases. *Bipolar Disord.* 2002; 4:129–136. [PubMed: 12071510]
169. Jope RS, Bijur GN. Mood stabilizers, glycogen synthase kinase-3b and cell survival. *Mol Psychiatry.* 2002; 7:S35–S45. [PubMed: 11986994]
170. Inouye M, Yamamura H, Nakano A. Lithium delays the radiation-induced apoptotic process in external granule cells of mouse cerebellum. *J Radiat Res (Tokyo).* 1995; 36(3):203–208. [PubMed: 8558497]
171. Grignon S, Levy N, Couraud F, Bruguerolle B. Tyrosine kinase inhibitors and cycloheximide inhibit Li⁺ protection of cerebellar granule neurons switched to non-depolarizing medium. *Eur J Pharmacol.* 1996; 315(1):111–114. [PubMed: 8960871]
172. Li R, Shen Y, El-Mallakh RS. Lithium protects against ouabain-induced cell death. *Lithium.* 1994; 5(4):211–216.
173. Volonte C, Rukenstein A. Lithium chloride promotes short-term survival of PC12 cells after serum and NGF deprivation. *Lithium.* 1993; 4(3):211–219.
174. D'Mello SR, Anelli R, Calissano P. Lithium induces apoptosis in immature cerebellar granule cells but promotes survival of mature neurons. *Exp Cell Res.* 1994; 211(2):332–338. [PubMed: 8143780]
175. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry.* 2000; 48(8):740–754. [PubMed: 11063971]
176. Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry.* 2000; 48(8):766–777. [PubMed: 11063973]
177. Rajkowska G. Cell pathology in bipolar disorder. *Bipolar Disord.* 2002; 4:105–116. [PubMed: 12071508]
178. Harrison PJ. The neuropathology of primary mood disorder. *Brain.* 2002; 125(Pt 7):1428–1449. [PubMed: 12076995]
179. Miguel-Hidalgo JJ, Rajkowska G. Morphological brain changes in depression: can antidepressants reverse them? *CNS Drugs.* 2002; 16(6):361–372. [PubMed: 12027783]
180. Drevets, WC.; Gadde, K.; Krishnan, R. Neuroimaging studies of depression. In: Charney, DS.; Nester, EJ.; Bunney, BS., editors. *Neurobiology of mental illness.* New York: Oxford University Press; 1999. p. 394–418.
181. Wei H, Qin ZH, Senatorov VV, Wei W, Wang Y, Qian Y, et al. Lithium suppresses excitotoxicity-induced striatal lesions in a rat model of Huntington's disease. *Neuroscience.* 2001; 106(3):603–612. [PubMed: 11591460]

182. Nonaka S, Chuang DM. Neuroprotective effects of chronic lithium on focal cerebral ischemia in rats. *Neuroreport*. 1998; 9(9):2081–2084. [PubMed: 9674597]
183. Bruno V, Sortino MA, Scapagnini U, Nicoletti F, Canonico PL. Antidegenerative effects of Mg(2+)-valproate in cultured cerebellar neurons. *Funct Neurol*. 1995; 10(3):121–130. [PubMed: 8557213]
184. Mark RJ, Ashford JW, Goodman Y, Mattson MP. Anticonvulsants attenuate amyloid beta-peptide neurotoxicity, Ca²⁺ deregulation, and cytoskeletal pathology. *Neurobiol Aging*. 1995; 16(2):187–198. [PubMed: 7777136]
185. Mora A, Gonzalez-Polo RA, Fuentes JM, Soler G, Centeno F. Different mechanisms of protection against apoptosis by valproate and Li⁺. *Eur J Biochem*. 1999; 266(3):886–891. [PubMed: 10583382]
186. Hashimoto R, Hough C, Nakazawa T, Yamamoto T, Chuang DM. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *J Neurochem*. 2002; 80(4):589–597. [PubMed: 11841566]
187. Bijur GN, De Sarno P, Jope RS. Glycogen synthase kinase-3beta facilitates staurosporine- and heat shock-induced apoptosis. Protection by lithium. *J Biol Chem*. 2000; 275(11):7583–7590. [PubMed: 10713065]
188. Inestrosa NC, Alvarez A, Godoy J, Reyes A, De Ferrari GV. Acetylcholinesterase-amyloid-beta-peptide interaction and Wnt signaling involvement in Abeta neurotoxicity. *Acta Neurol Scand Suppl*. 2000; 176:53–59. [PubMed: 11261806]
189. Dong LP, Wang TY, Zhu J. Effects of carbamazepine on hypoxic and ischemic brain damage in mice [in Chinese]. *Zhongguo Yao Li Xue Bao*. 1994; 15(3):257–259. [PubMed: 7976382]
190. Moore GJ, Bechuk JM, Hasanat K, Chen G, Seraji-Bozorgzad N, Wilds IB, 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):1–8. [PubMed: 10913502]
191. Moore GJ, Bechuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet*. 2000; 356(9237):1241–1242. [PubMed: 11072948]
192. Soares JC. Can brain-imaging studies provide a 'mood stabilizer signature'? *Mol Psychiatry*. 2002; 71:S64–S70. [PubMed: 11986997]
193. Cade JF. Lithium salts in the treatment of psychotic excitement. *Med J Austr*. 1949; 2:349–352.
194. Lenox RH, Hahn CG. Overview of the mechanism of action of lithium in the brain: fifty-year update. *J Clin Psychiatry*. 2000; 61(Suppl 9):5–15. [PubMed: 10826655]
195. Shalubina A, Agam G, Belmaker RH. The mechanism of lithium action: state of the art, ten years later. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001; 25(4):855–866. [PubMed: 11383981]
196. Nakashima K, Tuboi S. Size-dependent allosteric effects of mono-valent cations on rabbit liver fructose-1,6-bisphosphatase. *J Biol Chem*. 1976; 251(14):4315–4321. [PubMed: 180024]
197. Nordenberg J, Kaplansky M, Beery E, Klein S, Beitner R. Effects of lithium on the activities of phosphofructo-kinase and phosphoglucomutase and on glucose-1,6-diphosphate levels in rat muscles, brain and liver. *Biochem Pharmacol*. 1982; 31(6):1025–1031. [PubMed: 6211175]
198. Yenush L, Belles JM, Lopez-Coronado JM, Gil-Masarell R, Serrano R, Rodriguez PL. A novel target of lithium therapy. *FEBS Lett*. 2000; 467(2–3):321–325. [PubMed: 10675562]
199. Rhyu GI, Ray WJ Jr, Markley JL. Enzyme-bound intermediates in the conversion of glucose 1-phosphate to glucose 6-phosphate by phosphoglucomutase. Phosphorus NMR studies. *Biochemistry*. 1984; 23(2):252–260. [PubMed: 6230103]
200. Ray WJ Jr, Szymanki ES, Ng L. The binding of lithium and of anionic metabolites to phosphoglucomutase. *Biochim Biophys Acta*. 1978; 522(2):434–442. [PubMed: 623770]
201. Martinez A, Castro A, Dorronsoro I, Alonso M. Glycogen synthase kinase 3 (GSK-3) inhibitors as new promising drugs for diabetes, neurodegeneration, cancer, and inflammation. *Med Res Rev*. 2002; 22(4):373–384. [PubMed: 12111750]
202. Emrich HM, von Zerssen D, Kissling W, Moller HJ, Windorfer A. Effect of sodium valproate on mania. The GABA-hypothesis of affective disorders. *Arch Psychiatr Nervenkr*. 1980; 229(1):1–16. [PubMed: 6778456]

203. Lambert PA, Venaud G. Use of valpromide in psychiatric therapeutics [in French]. *Encephale*. 1987; 13(6):367–373. [PubMed: 3131112]
204. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al. Efficacy of divalproex vs. lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *J Am Med Assoc*. 1994; 271(12):918–924.
205. Pope HG Jr, McElroy SL, Keck PE Jr, Hudson JI. Valproate in the treatment of acute mania. A placebo-controlled study. *Arch Gen Psychiatry*. 1991; 48(1):62–68. [PubMed: 1984763]
206. Lemperiere T. Brief history of the development of valproate in bipolar disorders [in French]. *Encephale*. 2001; 27(4):365–372. [PubMed: 11686059]
207. Lambert PA, Venaud G. Comparative study of valpromide versus lithium in the treatment of affective disorders. *Nervure*. 1992; 5:57–65.
208. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry*. 2000; 57(5):481–489. [PubMed: 10807488]
209. Macdonald RL, Kelly KM. Antiepileptic drug mechanisms of action. *Epilepsia*. 1995; 36(Suppl 2):S2–S12. [PubMed: 8784210]
210. Johannessen CU. Mechanisms of action of valproate: a commentary. *Neurochem Int*. 2000; 37(2–3):103–110. [PubMed: 10812195]
211. van der Laan JW, de Boer T, Bruinvels J. Di-n-propylacetate and GABA degradation. Preferential inhibition of succinic semialdehyde dehydrogenase and indirect inhibition of GABA-transaminase. *J Neurochem*. 1979; 32(6):1769–1780. [PubMed: 376783]
212. Anlezark GM, Horton RW, Meldrum BS, Sawaya MC, Stephenson JD. Proceedings: gamma-Aminobutyric acid metabolism and the anticonvulsant action of ethanolamine-o-sulphate and di-n-propylacetate. *Br J Pharmacol*. 1976; 56(3):383–384.
213. Sawaya MC, Horton RW, Meldrum BS. Effects of anticonvulsant drugs on the cerebral enzymes metabolizing GABA. *Epilepsia*. 1975; 16(4):649–655. [PubMed: 9890792]
214. Whittle SR, Turner AJ. Effects of the anticonvulsant sodium valproate on gamma-aminobutyrate and aldehyde metabolism in ox brain. *J Neurochem*. 1978; 31(6):1453–1459. [PubMed: 121742]
215. Balazs R, Machiyama Y, Hammond BJ, Julian T, Richter D. The operation of the gamma-aminobutyrate bypath of the tricarboxylic acid cycle in brain tissue in vitro. *Biochem J*. 1970; 116(3):445–461. [PubMed: 5435689]
216. Leiderman DB, Balish M, Bromfield EB, Theodore WH. Effect of valproate on human cerebral glucose metabolism. *Epilepsia*. 1991; 32(3):417–422. [PubMed: 2044503]
217. Gaillard WD, Zeffiro T, Fazilat S, DeCarli C, Theodore WH. Effect of valproate on cerebral metabolism and blood flow: an ¹⁸F-2-deoxyglucose and ¹⁵O water positron emission tomography study. *Epilepsia*. 1996; 37(6):515–521. [PubMed: 8641226]
218. Godin Y, Heiner L, Mark J, Mandel P. Effects of DI-n-propylacetate, and anticonvulsive compound, on GABA metabolism. *J Neurochem*. 1969; 16(3):869–873. [PubMed: 5822629]
219. Loscher W. Effects of the antiepileptic drug valproate on metabolism and function of inhibitory and excitatory amino acids in the brain. *Neurochem Res*. 1993; 18(4):485–502. [PubMed: 8097295]
220. Gottlicher M, Minucci S, Zhu P, Kramer OH, Schimpf A, Giavara S, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J*. 2001; 20(24):6969–6978. [PubMed: 11742974]
221. Loscher W, Nau H. Pharmacological evaluation of various metabolites and analogues of valproic acid. Anticonvulsant and toxic potencies in mice. *Neuropharmacology*. 1985; 24(5):427–435. [PubMed: 3927183]
222. Radatz M, Ehlers K, Yagen B, Bialer M, Nau H. Valnoctamide, valpromide and valnoctic acid are much less teratogenic in mice than valproic acid. *Epilepsy Res*. 1998; 30(1):41–48. [PubMed: 9551843]
223. Lampen A, Siehler S, Ellerbeck U, Gottlicher M, Nau H. New molecular bioassays for the estimation of the teratogenic potency of valproic acid derivatives in vitro: activation of the

- peroxisomal proliferator-activated receptor (PPARdelta). *Toxicol Appl Pharmacol.* 1999; 160(3): 238–249. [PubMed: 10544058]
224. Nau H, Hauck RS, Ehlers K. Valproic acid-induced neural tube defects in mouse and human: aspects of chirality, alternative drug development, pharmacokinetics and possible mechanisms. *Pharmacol Toxicol.* 1991; 69(5):310–321. [PubMed: 1803343]
 225. Dehing J. Studies on the psychotropic action of Tegretol. *Acta Neurol Psychiatr Belg.* 1968; 68(12):895–905. [PubMed: 4976736]
 226. Dalby MA. Antiepileptic and psychotropic effect of carbamazepine (Tegretol) in the treatment of psychomotor epilepsy. *Epilepsia.* 1971; 12(4):325–334. [PubMed: 5003567]
 227. Takezaki H, Hanaoka M. The use of carbamazepine (tegretol) in the control of manic-depressive psychosis and other manic, depressive states. *Clin Psychiatry.* 1971; 13:173–192.
 228. Okuma T, Kishimoto A, Inoue K, Matsumoto H, Ogura A. Anti-manic and prophylactic effects of carbamazepine (Tegretol) on manic depressive psychosis. A preliminary report. *Folia Psychiatr Neurol Jpn.* 1973; 27(4):283–297. [PubMed: 4801623]
 229. Albright PS, Burnham WM. Development of a new pharmacological seizure model: effects of anticonvulsants on cortical- and amygdala-kindled seizures in the rat. *Epilepsia.* 1980; 21(6): 681–689. [PubMed: 7439134]
 230. Ballenger JC, Post RM. Therapeutic effects of carbamazepine in affective illness: a preliminary report. *Commun Psychopharmacol.* 1978; 2(2):159–175. [PubMed: 352607]
 231. McLean MJ, Macdonald RL. Multiple actions of phenytoin on mouse spinal cord neurons in cell culture. *J Pharmacol Exp Ther.* 1983; 227(3):779–789. [PubMed: 6317847]
 232. Schwarz JR, Grigat G. Phenytoin and carbamazepine: potential- and frequency-dependent block of Na currents in mammalian myelinated nerve fibers. *Epilepsia.* 1989; 30(3):286–294. [PubMed: 2542011]
 233. Courtney KR, Etter EF. Modulated anticonvulsant block of sodium channels in nerve and muscle. *Eur J Pharmacol.* 1983; 88(1):1–9. [PubMed: 6303804]
 234. Van Calker, D.; Biber, K.; Walden, J.; Gebicke, P.; Berger, M. Carbamazepine and adenosine receptors. In: Manji, HK.; Bowden, CL.; Belmaker, RH., editors. *Bipolar medications: mechanisms of action.* Washington, DC: American Psychiatric Press; 2000. p. 331–345.
 235. Skerrett JH, Johnston GA, Chow SC. Interactions of the anticonvulsant carbamazepine with adenosine receptors. 2. Pharmacological studies. *Epilepsia.* 1983; 24(5):643–650. [PubMed: 6311526]
 236. Marangos PJ, Post RM, Patel J, Zander K, Parma A, Weiss S. Specific and potent interactions of carbamazepine with brain adenosine receptors. *Eur J Pharmacol.* 1983; 93(3–4):175–182. [PubMed: 6315450]
 237. Skerrett JH, Davies LP, Johnston GA. A purinergic component in the anticonvulsant action of carbamazepine? *Eur J Pharmacol.* 1982; 82(3–4):195–197. [PubMed: 7128687]
 238. Weir RL, Padgett W, Daly JW, Anderson SM. Interaction of anticonvulsant drugs with adenosine receptors in the central nervous system. *Epilepsia.* 1984; 25(4):492–498. [PubMed: 6086302]
 239. Durcan MJ, Morgan PF. Prospective role for adenosine and adenosinergic systems in psychiatric disorders. *Psychol Med.* 1990; 20(3):475–486. [PubMed: 2236358]
 240. Marangos PJ, Weiss SR, Montgomery P, Patel J, Narang PK, Cappabianca AM, et al. Chronic carbamazepine treatment increases brain adenosine receptors. *Epilepsia.* 1985; 26(5):493–498. [PubMed: 2995026]
 241. Marangos PJ, Montgomery P, Weiss SR, Patel J, Post RM. Persistent upregulation of brain adenosine receptors in response to chronic carbamazepine treatment. *Clin Neuropharmacol.* 1987; 10(5):443–448. [PubMed: 3503683]
 242. Biber K, Walden J, Gebicke-Harter P, Berger M, van Calker D. Carbamazepine inhibits the potentiation by adenosine analogues of agonist induced inositolphosphate formation in hippocampal astrocyte cultures. *Biol Psychiatry.* 1996; 40(7):563–567. [PubMed: 8886288]
 243. Pacheco MA, Jope RS. Modulation of carbachol-stimulated AP-1 DNA binding activity by therapeutic agents for bipolar disorder in human neuroblastoma SH-SY5Y cells. *Brain Res Mol Brain Res.* 1999; 72(2):138–146. [PubMed: 10529472]

244. Hua LV, Green M, Wong A, Warsh JJ, Li PP. Tetraspan protein CD151: a common target of mood stabilizing drugs? *Neuropsychopharmacology*. 2001; 25(5):729–736. [PubMed: 11682256]
245. Lee Y, Hamamura T, Ohashi K, Miki M, Fujiwara Y, Kuroda S. Carbamazepine suppresses methamphetamine-induced Fos expression in a regionally specific manner in the rat brain. Possible neural substrates responsible for antimanic effects of mood stabilizers. *Neuropsychopharmacology*. 2000; 22(5):530–537. [PubMed: 10731628]
246. Tolle TR, Castro-Lopes JM, Schadrack J, Evan G, Zieglansberger W. Anticonvulsants suppress c-Fos protein expression in spinal cord neurons following noxious thermal stimulation. *Exp Neurol*. 1995; 132(2):271–278. [PubMed: 7789465]
247. Gunn AJ, Dragunow M, Faull RL, Gluckman PD. Effects of hypoxia-ischemia and seizures on neuronal and glial-like c-fos protein levels in the infant rat. *Brain Res*. 1990; 531(1–2):105–116. [PubMed: 2126969]
248. Gurvich N, Klein PS. Lithium and valproic acid: parallels and contrasts in diverse signaling contexts. *Pharmacology and Therapeutics*. 2003; 96:45–66. [PubMed: 12441177]

Fig. 1.

G proteins, cyclic AMP and phosphoinositol mediated signaling. G proteins are composed of G protein coupled receptor α , β , and γ subunits. These three subunits form a heterotrimer when the receptor to which they are coupled is not binding a ligand. Ligand binding to a particular receptor causes the subunits to dissociate from both each other and the receptor. GTP replaces GDP, allowing the activation of second messengers such as cyclic AMP and DAG/PI3. One of the effects of cAMP is activation of protein kinase A (PKA), an enzyme that phosphorylates many substrates including the cAMP response element binding protein (CREB). After activation this protein binds to the cAMP response element (CRE), a gene sequence found in the promoter of certain genes. Activation of other G proteins induces

phospholipase C hydrolysis of phosphoinositide 4,5-bisphosphate (PIP₂) to diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP₃). DAG activates protein kinase C (PKC), an enzyme that has many effects including the activation of myristoylated alanine-rich C kinase substrate (MARCKS). IP₃ binds to the IP₃ receptor that also functions as a calcium channel in the cell. This interaction results in the release of intracellular calcium reservoirs from the endoplasmic reticulum, initiating downstream effects such as activation of calmodulins and calmodulin-dependent protein kinases. IP₃ is recycled back to PIP₂ by the enzymes inositol monophosphate phosphatase (IMP) and inositol polyphosphatase phosphatase (IPPase); both of which are targets of lithium [68].

Fig. 2.

Neurotrophins, the ERK MAP kinase signaling cascade, and GSK-3. Cell survival is dependent on neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor, and the expression of these factors can be induced by synaptic activity. The influence of neurotrophic factors on cell survival is mediated by activation of the MAP kinase cascade. Activation of neurotrophic factor receptors also referred to as Trks, results in activation of the MAP kinase cascade via several intermediate steps, including phosphorylation of the adaptor protein SHC and recruitment of the guanine nucleotide exchange factor Sos. This results in activation of the small guanosine triphosphate-binding protein Ras, which leads to activation of a cascade of serine/threonine kinases. This includes

Raf, MAP kinase kinase (MEK), and MAP kinase (also referred to as extracellular response kinase, or ERK). One target of the MAP kinase cascade is RSK, which influences cell survival in at least two ways. RSK phosphorylates and inactivates the pro-apoptotic factor BAD. RSK also phosphorylates CREB and thereby increases the expression of the anti-apoptotic factor bcl-2 and BDNF. These mechanisms underlie many of the long-term effects of neurotrophins, including neurite outgrowth, cytoskeletal remodeling, and cell survival. Recent evidence suggests that lithium and VPA activate the ERK MAP kinase pathway. Lithium and VPA also appear to target GSK-3 and the Wnt signaling pathway. The function of GSK-3 in the Wnt signaling pathway – whereby Wnt glycoproteins interact with the frizzled family of receptors to stimulate the disheveled-mediated inactivation of GSK-3 and activation of the transcription factor β -catenin – is separate from the PI₃ kinase/AKT mediated inactivation of GSK-3. Lithium is a direct inhibitor of GSK-3; both lithium and VPA increase β -catenin levels.

Fig. 3. Lithium administration to rats protects against infarct size status-post middle cerebral artery occlusion, and suppresses the quinolinic acid induced excitotoxicity-induced striatal lesions in a rat models [168]. Figures are altered with permission from Wei et al. [181] and Nonaka and Chuang [182].

Table 1

The molecular structures of mood stabilizers^a

Name	Structure	Direct target
Lithium		<p>Lithium-sensitive magnesium-dependent phosphoesterases</p> <ul style="list-style-type: none"> • Fructose 1,6-biphosphatase (fbptase) • Inositol monophosphatase (impase) • Inositol polyphosphate 1-phosphatase (1ptase) • Bisphosphate 3'-nucleotidase (Bpntase) • 3'-Phosphoadenosine 5'-phosphate (PAP) phosphatase • Signature motif: D-X_n-EE-X_n-DP(i/l)D(s/g/a)T-X_n-WD-X₁₁-GG <p>Glycogen synthase kinase 3α and β</p> <p>Phosphoglucomutase</p> <p>GABA transaminase (GABA-T)</p> <p>Succinate semialdehyde dehydrogenase (SSA-DH)</p> <p>Succinate semialdehyde reductase</p> <p>Sodium channel</p> <p>Glycogen synthase kinase 3α and β</p> <p>Histone deacetylase</p> <p>Sodium channel</p> <p>Adenosine receptor 1 (A1)</p> <p>Adenylate cyclase (AC)</p>
Valproic acid/valproate (2-propylpentanoic acid /a-propylvaleric acid)
Carbamazepine (5H-dibenz[b,f]azepine-5-carboxamide)

^aLithium, carbamazepine and valproic acid (VPA) are all effective in the treatment of mania. However, their structures are vastly different. This observation suggests that the initial mechanism of action – or target – of mood stabilizers may not be maintained among these structurally different medications. However, because of their shared efficacy in treating bipolar disorder, it is likely that the intracellular and/or physiological effects may show convergence [7]. For this reason multiple laboratories are using biochemical and cellular methods to identify common targets of mood stabilizers [8–15].

Table 2Pathways regulated by both lithium and VPA^a

Pathway	Effect
Wnt signaling	Up
ERK-MAP kinase and bcl-2	Up
Cyclic AMP	Stimulated down
Phosphoinositol/Protein kinase C (PKC)	PKC and MARCKS down
Arachidonic acid turnover	Down

^a Available treatments for mania target the absolute levels and phosphorylation of multiple proteins. Consequently the activity of signaling pathways is altered. The table shows pathways that are modulated similarly by both lithium and VPA. It is likely that future developments in the treatment of bipolar disorder will come from understanding where these pathways converge.

Table 3**Lithium and neuroprotection^a**

PC 12 cells	Primary cortical cells
Serum deprivation	β -Amyloid
NGF deprivation	Survival in culture
NGF withdrawal	
Ouabain	Intact animals (pathology and behavioral deficits)
β -Amyloid	
	Ibotenate lesions
	Focal ischemia
SH-SY5Y cells	Development (chicken embryo)
Ouabain	Cholinergic lesions
Staurosporin	Quinolinic acid
Heat shock	Promotes neurogenesis
Valinomycin	
MPP ⁺	Human effects
Thapsigargin	Increased <i>N</i> -acetyl aspartate (NAA) levels in the brains of BPD patients
Cerebellar granule cells	Increases gray matter volume in the brains of BPD patients
Radiation	
Low K ⁺	
Ceramide	BPD patients chronically treated with either lithium or valproate do not show reduced PFCx volumes
Glutamate toxicity	
Carbamazepine	
Phenytoin	
Survival in culture	
Na ⁺ depletion	
Tat	

^aLithium exerts effects consistent with neuroprotection in cell culture, animal models, and in human subjects [132,135,163,168].