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LITHIUM IN THE TREATMENT OF BIPOLAR DISORDER: PHARMACOLOGY AND PHARMACOGENETICS

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Abstract

After decades of research, the mechanism of action of lithium in preventing recurrences of bipolar disorder remains only partially understood. Lithium research is complicated by absence of suitable animal models of bipolar disorder and by having to rely on *in vitro* studies of peripheral tissues. A number of distinct hypotheses emerged over the years, but none has been conclusively supported or rejected. The common theme emerging from pharmacological and genetic studies is that lithium affects multiple steps in cellular signalling, usually enhancing basal and inhibiting stimulated activities. Some of the key nodes of these regulatory networks include GSK3, CREB, and Na^+-K^+ ATPase. Genetic and pharmacogenetic studies are starting to generate promising findings, but remain limited by small sample sizes. As full responders to lithium seem to represent a unique clinical population, there is inherent value and need for studies of lithium responders. Such studies will be an opportunity to uncover specific effects of lithium in those individuals who clearly benefit from the treatment.

Keywords

Lithium; bipolar disorder; signal transduction; glycogen synthase kinase 3; Na^+-K^+ ATPase; CREB; calcium; neuroprotection; pharmacogenetics

Introduction

Lithium occupies a unique place among psychiatric treatments. It is the third smallest atom; its physiological effects are many and yet we do not know which of them are responsible for its therapeutic effects. Lithium has been also among the oldest psychiatric treatments. Its use in the 19th century was not widespread, but already then some authors pointed to its benefits in various forms of mood disorders. It was used by Garrod for metabolic disturbances and gout (assumed to be linked to mood dysregulation), by Hammond for mania, and in Denmark specifically for recurrent mood disorders by Lange brothers Carl and Frederik.[1]

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The modern history of lithium started in 1949 with the publication of a paper by John Cade noticing its specific effect in patients with mania.[2] The history of lithium use in psychiatry has been well described and shows varying degree of acceptance in different countries as well as some controversies.[1] More widespread acceptance of lithium, especially in the US took place in the 1970s with a gradual decrease in use by the late 1980s with the advent of anticonvulsants and atypical antipsychotics.[3]

Yet, after more than 60 years lithium remains the first-line treatment for prevention of manic and depressive episodes of bipolar disorder (BD). In developed countries it is used by 1 to 3 people per 1000;[4] the savings brought by lithium between 1970 and 1991 have been estimated at $8 billion per year in the US alone.[5] A number of studies since the 1960s established lithium efficacy; these were later supported by modern trials of newer medications that used it as a comparator. Meta-analyses of these studies confirm the efficacy of lithium[6,7] and show that it reduces the risk of suicide as well as overall mortality, two outcomes known to be increased in untreated BD.[8]

Clinical effects of lithium

Lithium is used primarily for long term ("prophylactic") treatment of BD with the aim to prevent further manic and depressive recurrences. In this indication, lithium remains the first-line treatment. However, lithium has other clinical effects that may be partially independent from each other. The first modern use of lithium was for treatment of mania.[2] Lithium has also proven useful in major depression, particularly for augmentation of antidepressants;[9] for aggressive behaviour;[10,11] and it has a specific antisuicide effect.[12,13] Lithium's prophylactic and antisuicidal effects are most unique – in these indications it is the most specific treatment in psychiatry. With respect to the antisuicidal effect, lithium differs from other mood stabilizers as it reduces the risk of suicide not only through prevention of mood episodes, but also in lithium nonresponders, perhaps through a different mechanism.[12] Some of the other effects of lithium are less specific. For instance, many drugs, including anticonvulsants and antipsychotics have similar antimanic properties.[14] On the other hand, bipolar depression remains the most difficult to treat aspect of BD in spite of multiple treatment options.[15] Lithium has a limited effect in bipolar depression,[16] although it does not differ significantly from most alternatives.[14,17] As well, benefits of lithium need to be weighted against its side effects and sometimes lower acceptability by patients.[6,18]

Mechanisms

Lithium has multiple pharmacological effects on multiple signaling pathways, and other cellular processes. This presents a paradox whereby a drug with such complex effects comes closest to having the most specific clinical effects in all of psychiatry. The effects of lithium are not easy to categorize in a simple linear hierarchical fashion; it appears to modulate intricate regulatory networks via multiple key nodes. The link between individual (and often highly correlated) effects is sometimes overlooked as our field moves on to newer theories, disregarding the previous ones. Detailed reviews are available for interested readers, the recent ones heavily focused on neuroprotective mechanisms.[19–22] However, the history of lithium pharmacology is full of loose ends - observations made at various times and never

put in the context of newer discoveries. The purpose of this review is to outline possible links between the clinical effects of lithium, the known aspects of pathophysiology of BD, and pharmacology of lithium. In other words, how can clinical observations inform the search for better treatments, i.e. treatments that would retain the essential benefits of lithium without its side effects? Studies of action of lithium are also linked to those of the pathophysiology of BD; often newly discovered changes were examined with respect to the effect of lithium and conversely, lithium-mediated effects were studied as a possible basis for the neurobiology of BD. This strategy common to most psychopharmacological research is not without pitfalls, though.[23]

Box 1 summarizes some of the clinical aspect of lithium therapy that may be most relevant when discerning which actions of lithium could be responsible for its clinical effects.

Box 1

Clinical factors that could provide clues to mechanisms of action of lithium

What we know

- Lithium is effective for prevention of recurrences of BD and reduces the risk of suicide
- The response to prophylactic treatment runs in families
- Most patients need plasma levels between 0.6 and 1.0mmol/L for a full clinical effect
- Lithium works best in patients with classical (typical) features of BD
- Lithium is neuroprotective *in vitro* and likely *in vivo*

What we assume

- Various clinical effects of lithium may be independent
- Lithium may work better early in the course of illness
- Rapid discontinuation of lithium may increase the risk of relapse
- Responders to lithium differ from responders to other mood stabilizers

What we do not know

- How long does it take for lithium to exert its prophylactic effect?
- Is the mechanism of action the same for all patients?
- Is the neuroprotective essential for mood stabilization?
- Are partial responders distinct from “excellent” responders?

For instance, the knowledge of clinically effective lithium blood levels can help in interpreting animal and *in vitro* experiments and separating therapeutic from toxic effects, as some studies used much higher than therapeutic concentrations. It is also important to acknowledge that lithium is stably effective in patients with typical BD, and that the more

recent reports of reduced lithium efficacy could be attributed to expansion of the diagnostic criteria of BD in DSM-based systems.[24–27] Long term studies indicate that the distribution of response to lithium is typically bimodal, sometimes trimodal, with a smaller group of partial responders.[28] It is unclear whether partial responders are similar to responders, except that their treatment may not be optimized with respect to plasma levels or there is inadequate attention to adherence to treatment. In this respect it is useful to remember that treatment with lithium requires skill and experience best implemented in specialized clinical programs.[29,30]

Another relevant factor is time to response. This has not been investigated systematically, but it appears highly variable. In the clinic, some people respond rapidly after only few doses, while others need several months to stabilize. The general consensus is that, in the first year of treatment, morbidity on lithium may still be elevated in patients who respond fully in the long term.[31] This difference may reflect heterogeneity in mechanisms of action in fast and slow responders, but could also reflect psychological factors, compliance issues, time needed to achieve effective yet tolerable blood levels, interaction with the natural course of the illness, and other factors. As well, the time to response differs widely between antimanic or antidepressant-augmenting effects on one hand, and mood stabilizing or antisuicidal effects on the other.[31] Some of the effects described in this text follow soon after acute administration, while others develop only during chronic treatment (cf. opposite effects of short term and long term treatments on gluatamate signalling[32] or adenylate cyclase[33]).

As lithium has multiple pharmacodynamic effects, it is hard to establish which ones are responsible for its mood stabilizing properties. This might not be surprising if different mechanisms played a role in multiple discrete clinical effects or even similar effects in different patients. As outlined below, many effects are indirect, but it is not easy to disentangle what may be complex regulatory networks with multiple feedback loops, in which actions at different nodes can produce similar results.

While significantly overlapping and cross-linked, these effects (allowing for simplifications) can be grouped into those regulating cell membrane properties, cell membrane transport and ion distribution, neurotransmitter regulation, and intracellular signalling, which can be collectively characterized as linked multilevel cascades.

Additional difficulties arise from the fact that lithium may have differential effects in different tissues and/or brain regions that cannot be easily extrapolated to its effects in specific brain regions in patients with BD. Many findings are derived from laboratory animals or from studies in healthy volunteers obscuring possible differences in effects in responders, non-responders and healthy subjects. As well, pathophysiology of BD is probably dynamic, with state-dependent changes in different phases of the illness - depressive, manic, euthymic - as well as in different clinical stages of illness progression.[34,35]

Electrolytes, membrane transport, membrane potential

Some of the earliest theories of the mechanism of action of lithium derived from then active research of electrolyte balance in BD and recurrent depression. These early studies of BD pointed to increased residual sodium during episodes of depression and mania, and its normalization in the course of lithium treatment.[36] Elevated intracellular sodium has been also found in more recent investigations (see El-Mallakh for a review[37]).

As well, early studies of lithium, among others, measured the impact of lithium on neuronal (and muscle) excitability showing that lithium may reduce the resting membrane potential and reduce neuronal excitability (reviewed by Schou in 1957[38]).

In 1970s Mendels and Frazer proposed that the ratio of intra- to extra-cellular lithium concentrations was associated with the treatment response.[39] The concentration ratio was assumed to be a heritable trait underlying propensity to BD,[40,41] but these hypotheses were not confirmed by later studies. Moreover, it was subsequently discovered that lithium is not distributed in the brain (or even in neurons) evenly, questioning the relevance of the lithium ratio, especially if measured in peripheral cells.[42] Nevertheless, lithium transport is important in relation to other mechanisms. The balance of intra- and extra-cellular lithium concentrations is maintained by several processes (efflux via Li^+-Na^+ countertransport or Na^+-H^+ exchanger and influx via passive diffusion and Na^+ channels in excitable tissues). In other types of cells, such as erythrocytes, bicarbonate-sensitive transport also plays an important role.[43] The Li^+-Na^+ countertransport is inhibited during lithium treatment. Importantly, although ouabain sensitive Na^+-K^+ pump does not account for lithium transport under physiological *in vivo* conditions, it is important for the electrochemical Na^+ gradient; and the Na^+-K^+ ATPase is an important source of energy maintaining the resting membrane potential.[44] In turn, the energy needed to maintain the pump activity comes from glycolysis, but even more importantly from mitochondrial ATP.[45] Mitochondrial function in BD has been a subject of considerable interest with evidence of significant impairment.[46–48] Recent results point to the role Na^+-K^+ ATPase in signal transduction, modulation of CREB activity, apoptotic processes, and regulation of calcium homeostasis.[49,50] Thus it appears as one of several important cross-roads in cellular signaling in excitable tissues. Its dysfunction (reduced activity) has been proposed as one of pathophysiological mechanisms of BD.[37,51–53] Consistent with this are studies indicating that lithium stimulates Na^+-K^+ ATPase activity,[54] although not all studies agree.[55] Overall, lithium seems to reduce intracellular sodium (and calcium), especially in overactive neurons, via voltage-gated sodium channels.[37,56] The effect of lithium on Na^+-K^+ ATPase has been found to be coupled with another relevant finding in BD, namely with a reduction of lipid peroxidation.[57] Lithium also influences other membrane transporters, for instance choline transport, with resulting increases in intracellular availability of choline and acetylcholine.[58,59]

Monoaminergic signaling

Lithium has a prominent effect on several neurotransmitters. In animal studies it has been shown to increase serotonin transmission by multiple mechanisms including increased synthesis of serotonin, increased uptake of tryptophan, increased release of serotonin (possibly by inhibition of presynaptic $5HT_{1A}$ receptors) with activation of postsynaptic

$5HT_{1A}$ and downregulation of $5HT_2$ receptors.[60] Serotonergic effects of lithium have been suggested as responsible for its antisuicidal and antiaggressive actions, as well as contributing to antidepressant augmentation. However, a two-week study in healthy volunteers did not support a prominent effect on serotonergic function, but found small changes in noradrenergic signalling, consistent with increased norepinephrine release.[61]

Lithium administration does not seem to reduce basal dopaminergic tone, but inhibits increased dopaminergic activity possibly via action on β-arrestin complexes.[62] This has been speculated as possibly contributing to the antimanic and even antipsychotic effects[13] - although the latter one is disputed.

Other neurotransmitters

With respect to glutamatergic system, lithium shows several complementary actions. First, in acute administration it increases glutamate release, blocks glutamate reuptake, and stimulates NMDA receptors by competing with magnesium (Mg^{2+}) ion (these effects require higher than therapeutic concentrations of lithium), but after several days these effects are reversed and lithium actually reduces synaptic concentrations of glutamate by increasing and stabilizing its reuptake.[32,63]

Overall, the effect of lithium on neurotransmission is stimulation of inhibitory transmission (and inhibition of excitatory signalling).[19]

Second messenger system

Lithium has a well established effect on various components of intracellular signalling cascades. Initial studies examined G proteins and the protein kinase A (PKA) signaling pathway, including the effect of lithium on adenylate cyclase (AC). AC is under regulatory influence of G-proteins broadly categorized as stimulatory (G_s) or inhibitory (G_i). The effects of lithium complement studies of AC/PKA signalling alterations in BD. Young et al. were the first to observe an increase of $G_s\alpha$ subunit in postmortem brains from bipolar patients and an increase of second messenger cyclic adenosine monophosphate (cAMP) following forskolin stimulation.[64] Lithium has been noted to inhibit both G_i and G_s and thus reduce the amplitude of signalling.[33,65] Activation of the G protein coupled receptor signalling is terminated by β-arrestin complex through uncoupling of G proteins from receptors. AC generates cAMP that activates PKA, leading to a regulation of a number of cellular processes including transcription factors such as cAMP response element binding protein (CREB). Lithium inhibits AC[66,67] and PKA,[33] specifically their calmodulin and forskolin stimulated activities, with little or no effect on basal activity.[68] Acute effects may be mediated by competition with (and reversed by) Mg^{2+}, but not chronic effects.[33]

Activation of phospholipase B by G proteins - or phospholipase C by tyrosine kinase receptors (trk) receptors - with subsequent hydrolysis of phosphatidylinositol 4,5-bisphosphate initiates another important signal transduction cascade, namely, the phosphoinositide (PI) cycle. Lithium inhibits inositol monophosphatase (IMPase) and inositol polyphosphate-1-phosphatase (IPPase) leading to reduction in available inositol and the downstream targets of the cycle, inositol tris-phosphate (IP_3); this in turn decreases release of calcium, diacylglycerol (DAG) activation, and protein kinase C activity.[69,70] In

parallel with effects of lithium, alterations in PI signaling in BD have also been reported[71] and the inositol transporter has been found to be overexpressed in BD and down regulated by lithium.[72–74] *In vivo* studies support the hypothesis that lithium treatment reduces myo-inositol in MR spectroscopy.[75] To date the inositol depletion hypothesis remains one of the strongest candidates for lithium mechanism of action. In addition to inhibition of IMPase, lithium also affects several structurally similar enzymes that include GSK3 as well as the β-arrestin-2-Akt complex.[76] Practically all these enzymes use Mg^{2+} as co-factor.

Additionally, lithium is known to inhibit guanylate cyclase (and cyclic guanosine monophosphate (cGMP) levels[77]) as well as decrease production of nitric oxide (NO).[78] Similar to other regulatory systems, the effect of lithium on cGMP/NO pathway does not work in isolation, and it likely affects monoaminergic signalling, adding to its neuroprotective role.[79,80] In several studies the effects of lithium were discrepant (increase in NO and cGMP production under chronic treatment).[81] But the contradictory findings may be reconciled if one considers that lithium attenuates excessive activity of the pathway and increases underactive signalling.

Transcription factors

Signal transduction effects commonly lead to regulation of transcription activity via activator protein 1 (AP1, a complex of Jun and fos transcription factors) or CREB. Their regulation leads to changes in gene expression of multiple pathways. For instance CREB increases the expression of brain-derived neurotrophic factor (BDNF) and anti-apoptotic b-cell lymphoma 2 (bcl-2), and reduces expression of tumor protein p53 (p53) and bcl-2-associated X protein (BAX) both acting as pro-apoptotic factors. In turn, CREB is regulated, among other factors, by GSK3 and by PKA/cAMP. Chronic lithium administration results in decreased CREB-directed gene expression and reduced CREB phosphorylation.[82] As well, stress has been shown to increase CREB mediated transcription and this effect is also blocked by lithium.[82]

Regulation of intracellular calcium

Calcium plays multiple roles in neurons. It acts as a second messenger in cell bodies, triggers neurotransmitter release in presynpatic terminals, maintains neuronal periodicity, and plays a role in synaptogenesis, plasticity and cell death.[83] During membrane depolarization, calcium enters cells via several different mechanisms from both extracellular space and intra-cellular (endoplasmic reticulum) sites via voltage gated, ligand gated, receptor operated and store operated channels[83]. These are regulated by lithium, among others via NMDA receptors or downstream effects of IP_3. Calcium abnormalities in BD and the role of mood stabilizers in regulating calcium homeostasis have been well documented elsewhere.[84,85]

Glycogen synthase kinase

GSK3 is an important enzyme at the cross-roads of multiple signaling systems. It is inhibited by lithium in therapeutic concentrations, and this inhibition leads to multiple pharmacological effects; GSK3 has been known to regulate gene expression, embryonic development, neuronal survival, and circadian rhythms, among others.[76] Its downstream targets are manifold including: ionotropic glutamate signalling, multiple transcription

factors, and the Wingless-related integration site (Wnt)/β catenin pathway.[86] Wnt signalling plays a role in structural brain processes such as neural development, synapse formation, and neuronal plasticity.[87] Little is known about possible cross-regulation of GSK3 and another key mediator of lithium action, namely Na^+-K^+ ATPase. One proposed mechanism involves regulation of both by serum- and glucocorticoid-inducible-kinase-1 (SGK1).[88] SGK1 is likely involved in glucocorticoid-mediated reduction of neurogenesis and recent data point to its role in depression and stress response.[88,89] GSK3 activity is subject to inhibitory regulation by protein kinase B (Akt) that, itself, is activated by lithium and it is not clear if the effect of lithium on GSK is direct or indirect.[90] For instance, it has been proposed that lithium inhibits GSK3 by competing with Mg^{2+}, but such effect would require higher than therapeutic levels of Li. Thus, an indirect inhibition by enhancing phosphorylation of N-terminal serine residues of GSK3 is more likely. GSK3 function also links to CREB activity that is inhibited by GSK3 (and the inhibition is attenuated by lithium). [91] Akt activation leads to reduction of apoptotic mechanisms and this effect is mediated by β-arrestin. Furthermore, GSK3/Akt pathway is regulated by dopamine and serotonin and some of these effects are likely mediated by β-arrestin complexes.[92]

Do these effects have a common underlying mechanism?

There is a possibility that these effects have a single common denominator. One such candidate has been proposed, namely competition with Mg^{2+} ion that has a similar radius to lithium.[93,94] Lithium interferes with a number of enzymes that rely on Mg^{2+} as co-factor. Some of these are phosphodiesterases (including IMPase, IPPase and AC), G-proteins and GSK3.[87,94] Ultimately, competition with Mg^{2+}can affect a number of processes including gene expression, neuronal and synaptic plasticity, and chronobiological regulations.

In addition to Mg^{2+}, lithium can affect processes dependent on cations including sodium, potassium, and calcium. Key regulatory points in the complex networks of effects of lithium seem to be GSK3 and Na^+-K^+ ATPase. Another possibility is interaction with sodium-dependent processes, especially various sodium dependent membrane transporters.

However, it is possible that effects at multiple levels and targets are needed for lithium to be effective.[65] A combination of these molecular effects likely produces more complex changes such as neurotrophic effects or changes in chronobiological regulations.

Higher-order mechanisms

One way to conceptualize the effects of lithium is to consider neurobiological effects that might represent a composite of molecular actions and that might lie between the effects at molecular level and physiological/clinical effects. As stem cell derived neurons are becoming available these effects will represent testable hypotheses. They may serve as cellular phenotypes[95] of BD and its response to treatment.

Neuroprotection and neural plasticity

There is strong and continually accumulating evidence that lithium is neuroprotective both *in vivo* and *in vitro*. Imaging studies are typically finding that patients treated with lithium

have larger cortical and hippocampal volumes[96,97]. Similarly, magnetic resonance spectroscopy studies suggest increased levels of N-acetyl aspartate.[98,99] These findings together with reports of structural brain changes in BD, especially in patients with multiple episodes and years of illness, and also higher rates of dementia in BD patients led some to suggest that it is the neuroprotective effect of lithium that is responsible for its mood stabilizing properties.

Several molecular mechanisms may be responsible for these observations. Lithium increases the activity of CREB, a transcription factor at the point of convergence of multiple signalling pathways. Among its downstream targets are BDNF and bcl-2. A second postulated mechanism is the inhibition of GSK3 with subsequent modulation of βcatenin. Further factors include attenuation of glutamatergic activity, inhibition of several pro-apoptotic factors (Bax, p53, calpain) as well as effects on phosphoinositol turnover and increased expression of bcl-2,[20,100] but many other mechanism are likely to contribute as well. For instance, lithium has been shown to partially reverse telomere shortening in patients with BD[101] as well as increase in mitochondrial function and oxidative phosphorylation.[102]

One of the aspects of the neuroprotective (neurotrophic) effects of lithium is suppression of stress effects on the brain.[21] Lithium thus may restore brain plasticity compromised in BD. It promotes neurogenesis in the hippocampus and prevents neuronal changes induced by stress in experimental animals.[103] In support of the notion that lithium regulates downstream targets of glucocorticoids rather than acting on hypothalamo-pituitary-adrenal axis is the study by Deshauer et al. showing ongoing episodic positivity of dexamethasone suppression test in patients fully stabilized on lithium over a period of up to five years.[104]

The neuroprotective hypothesis has not been reconciled with the observations that typical lithium responders often have an episodic course of illness with good inter-episode recoveries even without treatment – and that these patients do not typically suffer from functional (and possibly structural) impairment that would need to be corrected by Li.[105] As well, in a recent study Hajek et al. reported that the positive effect of lithium on hippocampal volume was not dependent on prevention of illness episodes by Li.[106]

Chronobiology

Perhaps the most salient feature of BD is its recurrent nature, alternation between periods of depression, mania and euthymia. Patients are sensitive to effects of sleep deprivation and time shifts such as jet lag, as well as they are sensitive to effects of light. Therapy based on regulation of biological and social rhythms has been found effective.[107] Circadian rhythms are maintained by an interplay between activating and inhibitory transcription factors. Some of these factors are known to be also regulated by lithium. Lithium modifies biological rhythms, in particular it lengthens the free running cycle.[108,109] This effect is probably mediated by changes in expression of several clock genes that act as transcription factors regulating the clock oscillations. Another factor in chronobiological effects of lithium is probably the inhibition of GSK3 that phosphorylates a number of proteins involved, and stabilization of transcription factor Rev-Erb-α. As well lithium ameliorates the chronobiological dysregulation in nuclear polymerase γ1 gene (POLG1) mutant mice, one of best animal models of BD to date.[110]

Stabilization of neuronal activity

Lithium appears to act on several systems in a bimodal manner, that is inhibiting excessive (stimulated) and augmenting reduced or basal activity[65,111] This effect has been shown particularly prominent in the cAMP signaling pathway,[65,65,68] but also in other systems (cf. section on cGMP signaling). It is mostly mediated by effects on signal transduction (AC, PI, G proteins) and transcription factors.

Prediction of lithium response

Lithium presents a dilemma. Its efficacy is unsurpassed, but the benefits come at a price of side effects for a proportion of patients.[112] Thus, treatment discontinuation is not rare. Even among compliant patients only about 30% of BD patients can be considered full responders and there is evidence of bimodal distribution of the degree of response.[24,27,28,113–118] Such observations stimulated the search for factors associated with lithium response. Often these analyses relied on variables of convenience available in samples collected for other purposes. The factors can be divided into those that represent more or less stable traits (family history, pre-treatment clinical course, comorbidity) and factors that are more fluid and state-dependent (for instance the number of pre-treatment episodes). The strongest clinical predictors to date include episodic remitting pre-treatment clinical course, family history of BD, low rates of comorbidity, and typical clinical presentation.[119–122] Other variables include intermediate age at onset, mania-depression-interval pattern in biphasic episodes, absence of spontaneous rapid cycling and MM/MN blood group.[114,123–126] Among demographic and personality factors associated with the response the most prominent are high social status, social support, compliance, dominance vs. stress, high expressed emotions, neurotic personality, being employed, and low number of life events.[127] Importantly, while these predictors have a good combined power, based on the published evidence, they are not always practical from the clinical point of view. For instance, it is hard to evaluate pre-treatment course in patients with only one or two episodes (as most treatment guidelines now recommend instituting long term treatment of BD early), biphasic episodes are not frequent, and family history is less informative in small families that are more common these days. Assessment of treatment response is also complicated by variable compliance as well as comorbid substance abuse. Under such circumstances, prediction of who responds is becoming more difficult. Thus we need to study large samples evaluated systematically for treatment response, and we need to analyze different subsets of predictive variables allowing for incomplete data.

Does lithium response identify a distinct subtype of bipolar disorder?

The characteristics of patients that respond to long term lithium made some authors speculate that these represent a distinct subtype of BD. Applying the five-point criteria proposed by Robins and Guze more than 40 years ago[128] it appears that lithium responders represent a valid diagnostic category. They have a distinct clinical presentation with typical manias, melancholic depression, low rates of comorbid conditions and episodic recurrent clinical course (criterion 1). The response to lithium remains longitudinally stable in those studies that investigated compliant patients[129] (criterion 2). Family histories of lithium

responders differ from those of lithium nonresponders in higher rates of BD and lower rates of schizophrenia[124,130,131] (criteria 3 and 4). Furthermore, first degree relatives of lithium responders also tend to respond to lithium with higher probability[113,132,133] (criterion 4). At the same time there is relative paucity with respect to biological markers of the lithium responsive BD (criterion 5). Previous investigations have identified changes in membrane transport, neuroendocrine studies as well as neuroimaging[134] studies, but these have been usually small studies, and not followed by successful replications.

Pharmacogenetics of lithium

Summary of association studies

From the review so far we can see that the potential number of candidate genes to study in relation to lithium response and/or lithium responsive BD is enormous. And conversely, many positive findings can appear plausible by a *post hoc* neurobiological explanation as relevant to lithium's effect. A number of association studies examining lithium responsive BD and/or difference between responders and nonresponders have been reported in the literature. Recent reviews by Severino et al.[135] and by Geoffroy et al.[136] list analyses of 97 and 88 genes respectively. Notably, most of these studies are based on small samples (only 17 in the Geoffroy et al. review are based on samples of more than 200 subjects). In addition to low statistical power, these studies suffer from other limitations such as retrospective evaluation of treatment response, a number of separately published papers based on the same clinical samples, and analyses of only few or even a single marker per gene, especially in older studies. No positive findings have been replicated in at least two samples of 200 or more subjects. The best results in more than one study point to possible associations with nuclear receptor subfamily 1, group D, member 1 (NR1D1, also referred to as Rev-Erb-α), [137–139] GSK3,[139,140] serotonin transporter (SERT),[141,142] BDNF, [143,144] CREB,[145,146] and the transcription factor XBP1.[147,148] Notably, the reported effect sizes are such that they would be detectable by the existing GWAS – which has not been the case.

Linkage studies

Only few linkage studies examined families of probands with lithium responsive BD. Arguably, linkage studies are quite difficult in this context as only a proportion of family members may be treated with lithium for a variety of reasons. The results are not entirely consistent (reported linkage on chromosomes 18q,[149] 12q,[150] and in 3p25, 3p14 and 14q11[151]).

Genomewide association studies

In view of the limitations of the above approaches, it is not surprising that the field has turned towards genomewide association analyses. These are summarized in Table 1. Only one study found a genomewide significant result: a polymorphism in the GADL1 gene associated with lithium response with an associated OR of 82.2 in the combined discovery and replication samples.[152] The variant rs17026688 is, however, absent in Caucasians and so a direct comparison with other GWAS is not possible. Nevertheless, attempts to replicate this finding in other East Asian populations have not been successful.[153,154] A promising result albeit with small effect size comes from several GWAS of BD that identified ankyrin 3

(ANK3) as a susceptibility gene.[155,156] ANK3 has a role in assembly of voltage gated sodium channels[157] and is downregulated by lithium.[158,159]

Gene-expression studies

Attempts to gain understanding of effects of lithium by gene expression studies have been so far limited by tissues investigated (iPSC, LCLs, fibroblasts, animals, postmortem studies). Toker et al. presented a useful review of some of the methodological issues.[160] mRNA expression studies typically show effects on multiple gene and gene families without a consistent picture emerging.[161,162] So far the results of genetic studies support only weakly some of the main hypotheses (glutamate, mitochondrial, or GSK3). An intriguing finding was obtained by McCarthy et al. showing altered expression of Rev-erb-α predictive of response to lithium.[139]

Limitations of existing studies

Common to most psychiatric research are several factors that make it difficult. Some of these are summarized in Box 2.

Box 2

Limitations of existing studies

- Animal studies are limited by the lack of convincing animal models of BD
- Studies based on peripheral tissues do not model neuronal processes well
- Animal and in vitro studies sometimes based on higher-than-therapeutic lithium levels
- *In vitro* studies typically use an arbitrary treatment duration of seven days
- Healthy volunteer studies usually short-term and may not be generalizable to clinical populations
- Postmortem brain studies do not allow for testing effects of lithium; most based on lithium non-responders. Further limitations include incomplete clinical information, frequent comorbidities, many samples from suicide victims or elderly subjects
- Clinical studies often do not differentiate between responders and nonresponders to lithium; long term follow-up and systematic treatment approach are preferable to purely observational studies
- Inferring pathophysiology from pharmacological effects can be misleading

Most of current theories are based on animal studies and on studies of post-mortem brains. Yet, animal models of BD are not well developed.[163] For instance, mania is typically modeled by amphetamine administration. However, the key aspect of BD, its recurrent nature with alterations in energy and motivation is difficult to capture. Perhaps the closest is the model described by Kasahara and colleagues in mice with mutation in the POLG1 gene

and resulting mutations in mitochondrial DNA.[110] Similarly, studies of post-mortem brains are limited by sample availability, by often incomplete information as well as the fact that many such samples come from suicide victims and non-responders to treatment.

Similar to research in other psychiatric conditions, there is a tendency to infer pathophysiology from drug effects and *vice versa*. This can be problematic, especially in a situation where both sides of the equation are known very incompletely, such as in BD. One example is the neuroprotective effect of lithium discussed earlier. Demonstration that it exists does not mean that it is necessary or sufficient for lithium to be clinically effective.

Finally, some authors argue that different treatments for BD should share their mechanisms of action. If this turns out true, it will facilitate the search for true underlying effects of, for instance lithium and valproate, and can represent a useful strategy. This assumes that there is a single prophylactic mechanism in all patients. One such proposed mechanism common to lithium and other mood stabilizers is their effect on sodium channels. Yet, most of mood stabilizers are differentially effective in different patients and so searching for commonalities can prove misleading.

Conclusions

Lithium to date represents the standard of long term treatment of BD against which other medications are compared. The progress in understanding how lithium produces its clinical effect has been slow and is only partially understood. The emerging picture stresses effects in multiple nodes of regulatory networks, in which lithium may dampen excessive activity and thus contribute to stabilization of neuronal activity, stress resilience, improved neuronal/synaptic plasticity and regulation of chronobiological processes.

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Table 1

Genomewide association studies of lithium response

Study	Subjects	Assessment of lithium response	Results	Comments
STEP-BD[164]	458 discovery and 359 replication sample	Time to recurrence	Ch 10 (rs10795189) $p=5.5\times10^{-7}$ in discovery sample	<60% of subjects on lithium monotherapy; <40% treated for 1 year or more
Squassina et al.[165]	52 (26 R and 26 NR)	Retrospective scale	Ch 17 (ACCN1 gene; rs11869731 $p=7.21\times10^{-6}$	Small sample size
Chen et al.[152]	294 discovery (185 R, 109 NR) and replication (50 R, 50 NR)	Retrospective scale; inter-rater reliability reported	Ch 3 (GADL1 gene; rs17026688, rs17026651) $p=1.66\times10^{-49}$ in combined sample	The associated variant not present in Caucasians
ConLiGen[166]	1217 (374 R, 843 NR)	Retrospective scale; inter-rater reliability reported	Ch 2 (SLC4A10 gene) $p=1.95\times10^{-6}$	Preliminary results; data collection and analyses continuing
Bergen et al.[167]	940 (64% R, 28% PR, 8% NR)	Self-report	Ch 17 (GAS gene; rs12601160) $p=2.20\times10^{-6}$	Preliminary results; data collection and analyses continuing

R responders, PR partial responders, NR non-responders