Review Article

Running title: Potential Mechanisms of Action of Lithium in Bipolar Disorder

Potential Mechanisms of Action of Lithium in Bipolar Disorder

Current Understanding

Gin S. Malhi[1,2], Michelle Tanious[1,2], Pritha Das[1,2], Carissa Coulston[1,2] and Michael Berk[3-6]

[1] Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

[2] CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St. Leonards, Sydney, NSW, Australia

[3] Deakin University, School of Medicine, Barwon Health, Geelong, VIC, Australia

[4] Orygen Youth Health Research Centre, Parkville, VIC, Australia

[5] Mental Health Research Institute, University of Melbourne, Kenneth Myer Building, Parkville, VIC, Australia

[6] University of Melbourne, Department of Psychiatry, Royal Melbourne Hospital, Parkville, VIC, Australia

Correspondence: Gin S. Malhi, CADE Clinic, Level 5, Building 36, Royal North Shore Hospital, St Leonards, Sydney, NSW 2065, Australia.

Email: gin.malhi@sydney.edu.au

Fig. 1 Lithium actions. Lithium exerts its effects at multiple levels beginning with clinical changes to mood by counteracting mania and depression and diminishing suicidality. Evidence for the effects of lithium on cognition from neuropsychological and functional magnetic resonance imaging studies point overall towards cognitive compromise; however, evidence for this has been mixed. Structural imaging studies have provided evidence of neuroprotection with increased grey matter volumes in particular in the amydgala, hippocampus and prefrontal cortical regions in lithium-treated patients. Changes to neurotransmission that have clinical impact may be explained through increased inhibitory and decreased excitatory neurotransmission in lithium-treated patients. At the intracellular level, lithium influences second messenger systems, which modulate neurotransmission and facilitate cellular viability by promoting anti-oxidant defences, decreasing apoptosis and increasing neuroprotective proteins. *AC* adenyl cyclase, *bcl-2* B-cell lymphoma 2, *BDNF* brain-derived neurotrophic factor, *GSK* glycogen synthase kinase, *MARCKS* myristoylated alanine-rich c kinase substrate, *PKC* protein kinase C, ↑ indicates increased, ↓ indicates decreased

Fig. 2 The actions of lithium on pre- and post-synaptic neurotransmission. The facilitatory actions of lithium are depicted in *green*, and its inhibitory actions in *red*. Lithium inhibits excitatory neurotransmission by decreasing pre-synaptic dopamine activity and inactivating post-synaptic G-proteins. It also exerts an inhibitory effect downstream on the AC system, and via effects on cAMP, modulates further neurotransmission. Similarly, lithium promotes inhibitory neutrotransmission through its modulation of glutamatergic neurotransmission by downregulating the NMDA receptor and inhibiting the mI second messenger system, which is responsible for maintaining signalling efficiency. When activated, the mI system leads to phosphorylation of PI, which in turn initiate two second messenger pathways involving DAG and IP_3. These components of the phosphorylation cycle are responsible for modulating neurotransmission and regulating genetic transcription. Chronic modulation of this cycle through lithium exposure eventually alters gene transcription, which ultimately produces long-term changes in neurotransmission. Lithium additionally inhibits neurotransmission by facilitating the release of GABA and upregulating the $GABA_B$ receptor. *AC* adenyl cyclase, *cAMP* cyclic adenosine monophosphate, *DAG* diaglycerol, *IP₃* inositol triphosphate, *mI* myo-inositol, *PI* phosphoinositides, ↑ indicates increased, ↓ indicates decreased

Fig. 3 The effects of lithium on second messenger pathways. The inhibitory actions of lithium are depicted in *red*, and its facilitatory actions are depicted in *green*. (**a**) AC/cAMP system. Lithium modulates this system in several ways: initially, basal levels of AC and cAMP are increased. Consequently, when a cell is stimulated, large fluctuations of AC and cAMP that would normally occur

are minimized, therefore stabilizing the system. The CREB transcription factor is an important downstream target of the AC system and is activated by lithium, which facilitates the production of neuroprotective factors including BDNF and bcl-2. (**b**) The PI cycle. Lithium inhibits the PI cycle: the PI cycle is activated following stimulation of the cell surface receptor by a neurotransmitter. PLC mediates the hydrolysis of PIP_2 to the secondary messengers DAG and IP_3. These then activate downstream signalling pathways. ImPase and IPPase facilitate recycling of IP_3 back into mI, which then allows the PI cycle to continue. Lithium inhibits cellular mI by: (1) blocking the reuptake of inositol via inhibition of the SMIT and (2) via direct inhibition of IPPase and ImPase. Overall, this results in the inhibition of transmembrane signalling and triggering of autophagy. (**c**) PKC, MARCKS, GSK-3: lithium inhibits PKC, MARKS and GSK-3: PKC and MARCKS are downstream targets of DAG, and thus direct inhibition by lithium reduces pre- and post-synaptic excitatory neurotransmission. GSK-3 plays a major role in cellular structure and resilience. Direct and indirect inhibition of this kinase by lithium activates the Akt neuroprotective pathway. (**d**) Autophagy: lithium ultimately inhibits this process. Autophagy is induced by the intracellular calcium released from the mitochondria by IP_3. The mTOR protein is activated by lithium and is a negative regulator of autophagy and therefore inhibits this process. Lithium-induced depletion of IP_3 also induces autophagy; however, its inhibitory effects through the mTOR protein are more potent. *AC* adenyl cyclase, *bcl-2* B-cell lymphoma 2, *BDNF* brain-derived neurotrophic factor, *cAMP* cyclic adenosine monophosphate, *CREB* cAMP response element binding, *DAG* diaglycerol, *GSK-3* glycogen synthase kinase 3, *ImPase* inositol monophosphate 1-phosphatase, *IPPase* inositol phosphate 1-phosphatase, IP_3 inositol triphosphate, *MARCKS* myristoylated alanine-rich c kinase substrate, *mI* myoinositol, m*TOR* mammalian target of rapamycin, *PI* phosphoinositide, PIP_2 phosphoinositol 4-5-biphosphate, *PKC* protein kinase C, *PLC* phospholipase C, *SMIT* sodium myo-inositol transporter

Abstract

Lithium has been used for over half a century for the treatment of bipolar disorder as the archetypal mood stabilizer and has a wealth of empirical evidence supporting its efficacy in this role. Despite this, the specific mechanisms by which lithium exerts its mood-stabilizing effects are not well understood. Given the inherently complex nature of the pathophysiology of bipolar disorder, this paper aims to capture what is known about the actions of lithium ranging from macroscopic changes in mood, cognition and brain structure to its effects at the microscopic level on neurotransmission and intracellular and molecular pathways. A comprehensive literature search of databases including MEDLINE, EMBASE and PsychINFO was conducted using relevant keywords and the findings from the literature were then reviewed and synthesized. Numerous studies report that lithium is effective in the treatment of acute mania and for the long-term maintenance of mood and prophylaxis; in comparison, evidence for its efficacy in depression is modest. However, lithium possesses unique anti-suicidal properties that set it apart from other agents. With respect to cognition, studies suggest that lithium may reduce cognitive decline in patients; however, these findings require further investigation using both neuropsychological and functional neuroimaging probes. Interestingly, lithium appears to preserve or increase the volume of brain structures involved in emotional regulation such as the prefrontal cortex, hippocampus and amygdala possibly reflecting its neuroprotective effects. At a neuronal level, lithium reduces excitatory (dopamine and glutamate) but increases inhibitory (GABA) neurotransmission; however, these broad effects are underpinned by complex neurotransmitter systems that strive to achieve homeostasis by way of compensatory changes. For example, at an intracellular and molecular level, lithium targets second-messenger systems that further modulate neurotransmission. For instance, the effects of lithium on the adenyl cyclase and phospho-inositide pathways as well as protein kinase C may serve to dampen excessive excitatory neurotransmission. In addition to these many putative mechanisms, it has also been proposed that the neuroprotective effects of lithium are key to its therapeutic actions. In this regard, lithium has been shown to reduce the oxidative stress that occurs with multiple episodes of mania and

depression. Further, it increases protective proteins such as brain-derived neurotrophic factor and B-cell lymphoma 2 and reduces apoptotic processes through inhibition of glycogen synthase kinase 3 and autophagy. Overall, it is clear that the processes that underpin the therapeutic actions of lithium are sophisticated and most likely inter-related.

1 Introduction

Lithium, introduced 60 years ago by John Cade for the treatment of bipolar disorder, remains a first-line option because of its efficacy in long-term mood stabilization, which is supported by a wealth of empirical evidence and clinical experience[1, 2]. Lithium has also been shown to significantly reduce the risk of suicide, and this unique property sets it apart from other medications used for the treatment of bipolar disorder[3-5]. Interestingly, however, the mechanisms by which lithium exerts its putative clinical effects are largely unknown. Difficulty in defining bipolar disorder on the basis of clinical phenomenology has undoubtedly contributed to this nescience. Conversely, it could be argued that excellent lithium response is one of the best biomarkers available, and that it may be more fruitful to examine clinical features and biomarkers in this treatment-sensitive subgroup; however, this kind of approach is not consistent with the current DSM-driven zeitgeist. Further, the underlying pathophysiology of bipolar disorder is likely to be highly complex, involving many interacting neurotransmitter systems and neuronal circuits within the brain[6].

Research into the mechanism of action of lithium has been conducted at multiple levels, ranging from macroscopic changes in clinical symptoms and brain structure to alterations at the cellular and intracellular levels. In order to conceptualize these levels, Fig. 1 provides an overview of what is currently known about the effects of lithium. Macroscopically, lithium produces clinical changes in mood and cognition, and can alter brain structure. In contrast, microscopically lithium targets cellular, intracellular and molecular processes. For example, lithium modulates neuronal function, by decreasing excitatory neurotransmission through glutamate and dopamine, and increasing inhibitory neurotransmission via GABA[7]. At the intracellular and molecular levels, lithium alters the second messenger systems that operate within neurons such as inositol, diaglycerol (DAG), protein kinase C (PKC), intracellular calcium and myristoylated alanine-rich C kinase substrate (MARCKS), which ultimately alter neurotransmission

(sending and receiving signals), and promote cellular viability. Such processes are complex and involve a number of different proteins.

Fig. 1 also shows that lithium has notable protective effects that occur at multiple levels. Increasingly, bipolar disorder is being recognized as a degenerative process,[8] whereby disease-related stressors such as excitotoxicity lead to apoptosis, which produces atrophy of multiple brain regions. In this regard, lithium has been shown to increase cellular longevity by cessating or abating apoptosis, known as neuroprotection[9]. At the same time lithium has also been shown to promote the generation of new cells, referred to as neuroproliferation[8, 10, 11], and lastly, lithium is able to interrupt the cascade of neurotoxic processes that lead to tissue vulnerability and progressive brain and functional change, known as neuroprogression[12]. This paper therefore briefly elaborates upon our current understanding of the potential mechanisms through which lithium produces its broad range of actions in the context of bipolar disorder pathophysiology.

A comprehensive literature search of peer-reviewed publications, written in English but not limited by date, was conducted using MEDLINE, EMBASE and PsychINFO. Specifically, keywords that were used to identify relevant articles included 'bipolar disorder', 'lithium', 'mechanisms of action', 'therapeutic actions', 'efficacy', 'anti-suicidal', 'neuroprotection', 'neuroprogression', 'brain structure', 'functional magnetic resonance imaging', 'neuropsychology', 'neurocognition', 'cognition', 'neurotransmission', 'dopamine', 'glutamate', 'gamma-aminobutyric acid', 'NMDA', 'G-protein', 'second messenger systems', 'adenylyl cyclase', 'phosphoinositide', 'inositol', 'protein kinase C', 'myristoylated alanine-rich C kinase substrate', 'intracellular calcium', 'brain derived neurotrophic factor', 'apoptosis', 'oxidative stress', 'mitochondria', 'bcl-2', 'glycogen synthase kinase 3' and 'autophagy'. Relevant findings were then identified and synthesized in combination with additional literature known to the authors.

2 Clinical Changes to Mood

2.1 Acute Mania

Clinical trials over recent decades have consistently demonstrated that lithium is effective for the treatment of acute mania[13], with several randomized controlled trials providing robust evidence of its superiority in the treatment of acute mania when compared with mood stabilizers (valproate)[14, 15], neuroleptics (olanzapine and risperidone)[15-17] or placebo[2, 4, 15, 18, 19]. Although a recent meta-analysis has suggested that neuroleptics are superior to mood stabilizers including lithium[20], the findings have been questioned as the meta-analysis only investigated a short-term outcome (3 weeks), and it is important to consider how these results would change for long-term treatment[21].

Nevertheless, lithium monotherapy remains a first-line option for acute mania in clinical practice guidelines[4, 22-25]. When administered alone, lithium can take up to 6–10 days to relieve manic symptoms and therefore in practice it is often combined with a neuroleptic to achieve faster symptom relief[2, 4, 26].

2.2 Acute Depression

The evidence for lithium in the treatment of bipolar depression is less impressive than for acute mania, with recent clinical trials failing to demonstrate significant superiority compared with other agents or placebo[27-29]. There are several reasons for this. First, the antidepressant effect of lithium has a considerable time lag, usually 6–8 weeks, hence lithium may be perceived by patients as not being efficacious, resulting in high drop-out rates in clinical trials that can skew results[30]. Second, the psychological and social reasons for depression are often more complex than those for mania[18], hence study samples are inevitably more heterogeneous. Indeed, recent reviews on the treatment of bipolar depression using lithium have recognized the paucity of well controlled randomized trials and this limits the ability to use meta-analytical techniques to evaluate its efficacy[28, 31]. Despite this, lithium is still

recommended by current clinical practice guidelines for the treatment of bipolar depression[31-33], in particular bipolar I. This is partly because fewer studies have examined other 'subtypes' of bipolar disorder but also because lithium appears to be most effective in bipolar disorder with recognizable episodes of mania and depression where periods of illness are recurrent and separated clearly by periods of remission[18].

2.3 Maintenance and Prophylaxis

The evidence for the efficacy of lithium in the maintenance of euthymia and prophylaxis of mania, depression and suicidal behaviours has been robustly supported[4, 34, 35], and its real world effectiveness has been demonstrated in the recent BALANCE (Bipolar Affective Disorder: Lithium/Anti-Convulsant Evaluation) study[36]. Meta-analytical reviews have shown that lithium reduces the risk of a manic relapse by between 40 % and 61 % and the risk of relapse for depression by approximately 22 %[19]. Furthermore, in 60–80 % of patients, the abrupt cessation of lithium, or a rapid reduction in its plasma concentrations, precipitates relapse, underscoring its importance in maintenance therapy[23, 37-40]. Interestingly, however, there is some evidence that shows that lithium has comparable efficacy to valproate[41].

2.4 Anti-Suicidal Properties

Bipolar patients are at a tenfold increased risk of suicide or suicide attempts as compared with the general population[3], and this contributes significantly to their increased mortality rate[37]. One of the key attributes of lithium is its 'anti-suicidal' effect[3-5, 18, 42, 43]. Patients that adhere to lithium treatment show a reduction in suicidal behaviour[37] even when it has not been efficacious in achieving mood stabilization[44]. Indeed, evidence shows that the risk of suicide in lithium-treated patients is six times less than patients not taking lithium[3], and that the risk of death by suicide, as well as the risk of self-harm, is reduced by 60 % and 70 %, respectively[5, 45]. It is thought that lithium achieves these anti-suicidal effects by reducing impulsivity and aggression; however, the precise mechanism of its anti-suicidal action requires further investigation[3, 18, 34].

2.5 Summary

Lithium is a unique therapeutic agent and arguably the only true mood stabilizer in the management of bipolar disorder. It has held pole position for more than half a century and is especially effective in treating acute mania and providing long-term prophylaxis. Its profound anti-suicidal properties further justify its use in bipolar disorder.

3 Cognition
3.1 Neuropsychological Findings

Cognitive changes occur at the endpoint of the process of neuroprogression, so consequently, studying the role of lithium on cognition opens a window to understanding its neuroprotective potential. Neuropsychological effects of lithium provide additional insight into the brain regions that lithium targets, via its observed impact on cognitive functions. A recent, rigorous meta-analysis on the effects of lithium on cognition was performed by Wingo and colleagues[46] and based on 12 studies. Six of these studies were conducted on healthy volunteers, comprising 213 subjects in total, of whom 105 were exposed to lithium for a duration of 1–4 weeks. The other six studies were conducted on a total of 326 euthymic patients with affective disorders, of whom 171 were taking lithium. Analysis of the healthy subjects revealed no effects of lithium on any of the cognitive domains including immediate verbal learning and memory, attention, processing speed and executive functions. The cognitive effects of lithium among the affective disorder patients included impairments in immediate verbal learning and memory, creativity (comprising measures of verbal generativity) and more pronounced impairments on psychomotor performance. The authors concluded that these effects were a function of the duration of treatment rather than serum concentrations[46].

The findings of these neurocognitive impairments with lithium use appear to be in accordance with preliminary data from functional magnetic resonance imaging (fMRI) studies (Sect. 3.2), but are difficult

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to disentangle from the processes of the illness itself, or reconcile with its purported neuroprotective properties (Sect. 3.1 and Sect. 6.2). This further highlights that the exact mechanism and targets of lithium action are not well understood, and that lithium possibly acts on a variety of molecular targets that can produce a range of effects[46].

However, one of the main limitations of the studies that have been reviewed is that they mostly employ a cross-sectional design. In contrast to the results from the meta-analysis described above, other studies in which a longitudinal (and hence more rigorous) approach was undertaken have shown that memory is relatively unchanged with lithium therapy[47, 48]. Furthermore, hypothyroidism, a common adverse effect of lithium, may have negative effects on cognition. Interestingly, however, studies rarely measure or control for its potential effects making it difficult to determine the extent of neurocognitive impairment associated with lithium[49].

In complicating matters further, there is also evidence of improved cognition in lithium-treated patients. For example, the incidence of dementia has been shown to be decreased in bipolar disorder patients who have been taking lithium[50]. Further, a naturalistic study on cognition in bipolar disorder over 2 years reported that both at baseline and end-point lithium was associated with better psychomotor speed, although basic information processing was worse after 2 years. In this study, post hoc analysis also revealed that lithium positively predicts improvements in verbal learning, and negatively predicts deterioration in verbal memory[51]. Interestingly, another study found better executive functioning in bipolar disorder patients who were responsive to lithium as compared with lithium non-responders, suggesting that stabilization of mood may possibly be associated with preserved executive functions[52]. In aggregate, it does not appear possible to make definitive conclusions regarding the cognitive potential of lithium based on the existing evidence base.

3.2 Functional Neuroimaging Findings

There is a lack of functional neuroimaging studies that identify neural networks modulated by lithium. This is perhaps because imaging modalities such as positron emission tomography and single photon emission computed tomography require specific molecular targets within the brain[53], for which there are no known specific targets for lithium. In contrast, functional MRI studies can investigate the effects of lithium on neural networks by targeting blood flow changes within the nodes of these networks. However, most studies in bipolar disorder have primarily focused on understanding the effects of manic or depressed mood states on neural functioning, and only a few studies have examined the mood-stabilizing properties of lithium. Interestingly, studies examining the latter have been conducted by a single group. In a series of experiments looking at the effects of lithium on cognition, they found that its effect is both mood state and task dependent[54-56]. Together, these studies suggest that in the presence of pathology, lithium administration augments cognitive functioning. However, conclusions from these studies need replication and should be treated as preliminary given the small sample sizes. Of note, in keeping with these findings in humans, a recent review of the effects of lithium on cognition in rat models concluded that the benefits to cognitive functioning are only seen in the presence of neurochemical or neurodegenerative insults, suggesting that the "neuroprotective action (of lithium) is translatable to functional improvement of compromised cognitive functioning"[57].

3.3 Summary

Neuropsychological research is equivocal with regard to the effects of lithium on cognition and evidence from functional neuroimaging though emergent is at present inconclusive. One important aspect that has recently come to light is that lithium possibly preserves cognitive functioning but only in the presence of pathology.

4 Brain Structure
4.1 Neuroimaging Findings

Studies investigating brain structure have implicated both cortical and subcortical brain regions in the pathology of bipolar disorder, but these findings depend on many factors such as the population (adult/adolescents) studied, severity of illness (number of episodes) as well as the region of interest, which makes the evidence difficult to evaluate[58, 59]. Recent appraisals of the literature point toward regionally specific areas of abnormalities involving structures in the fronto-limbic network, which has implications for cognition and mood regulation[58, 60]. Among subcortical regions that have primarily been implicated in bipolar disorder in adults, because of volumetric changes, are the hippocampus[61, 62], amygdala[63, 64] and striatum[65] of which the latter two are also altered in adolescents with the disorder[66]. Furthermore, changes in the striatum appear to be related to the number of previous episodes[67].

Grey matter volume reductions have been found in the subgenual[68] and anterior cingulate cortex[69, 70]. Reductions have also been observed in the dorsomedial and left parietal prefrontal cortex in depressed bipolar disorder patients[71]. These reductions in the prefrontal cortex have been attributed to disease-related stressors such as glutamate-induced excitotoxicity and subsequent oxidative stress[72], which is reflected in the reduced neuronal densities in this area[73, 74]. Conversely, not all studies have found a difference between bipolar disorder patients and healthy controls in the subgenual[75] and anterior cingulate cortex[76]. However, it has been shown that the rate of grey matter volume reduction is more rapid in bipolar disorder patients compared with controls despite a lack of difference in grey matter volumes between the groups[77]. Together this has led researchers to conceptualize bipolar disorder as a neurodegenerative process (specific models of degeneration are discussed later in Sect. 6.2).

Total or regional changes in grey matter volume have been found to be 'prevented' by the use of lithium. Lithium-treated patients compared with non-treated patients or healthy controls, show increases in total[59, 78, 79] and regional grey matter volume. Regions that have shown improvement include the anterior

cingulate, ventral prefrontal cortex, paralimbic association cortex[78, 80], superior temporal gyri[81], left amygdala[82, 83] and hippocampus[61, 84-86]. Notably these regions are part of the fronto-limbic network. A recent longitudinal study has shown an association between an increase in prefrontal grey matter volume with lithium responsiveness[87], and in rats, the chronic administration of lithium has been shown to promote proliferation of neurons in the hippocampus[11]. These findings point to the potential neuroprotective effects of lithium[59].

4.2 Summary

The neuroprotective and neuroproliferative effects of lithium in bipolar disorder patients have been demonstrated through preservation of grey matter volume compared with patients not treated with lithium and healthy controls. The mechanisms and significance of these changes however is not fully understood.

5   Neurotransmission

The limbic system subserves emotion, sleep, arousal and sexual function and has therefore been a focus of research into the pathophysiology of bipolar disorder and the action of mood stabilizers such as lithium. Early research in this area was greatly influenced by the monamine hypothesis of depression that was proposed almost half a century ago[88]. Consequently, initial bipolar disorder studies focussed on dopaminergic[89] and serotonergic neurotransmitter systems,[90] which have been useful but not sufficient in explaining the effects of lithium. With advances in science and technology and a greater understanding of neurotransmission, researchers have focussed increasingly on additional neurotransmitters, signal transduction pathways and second messenger systems[91].

At the neuronal level, lithium acts both pre- and post-synaptically to modulate neurotransmission, and amongst the many neurotransmitters that have been investigated, it is the modulation and regulation of dopamine, glutamate and GABA that has provided useful insights (Fig. 2).

5.1 Dopamine and G-protein Coupled Receptors

Dopamine is an excitatory neurotransmitter that plays a central role in the pathophysiology of bipolar disorder. A 'cyclical dysregulation' of dopamine transmission has been hypothesized. During mania, dopamine neurotransmission is elevated and this prompts secondary homeostatic downregulation that eventuates in decreased neurotransmission and this is associated with clinical depression[92]. While there is good evidence for the role of dopamine in mania that is in keeping with this model, for example, dopamine precursors and agonists can induce mania in healthy individuals[93, 94] and levels of dopamine are elevated in both patients with mania[95] and in animal models of mania[96], its role in depression is less clear[93].

Animal studies involving lithium-treated rats have found the levels of extraneuronal dopamine to be lower and this is associated with reduced reactivity to harmful stimuli[97, 98]. However, other studies have found that the basal level of extraneuronal dopamine is unaffected by lithium treatment[99, 100].

Clinically, in patients, a lack of adherence to lithium treatment can cause therapeutic concentrations to drop and this increases the risk of relapse[101]. Hence, the effect of lithium withdrawal on dopamine levels has also been investigated albeit with conflicting results. One study in rats has shown that when dopamine re-uptake in the brain is inhibited, dopamine levels increase following lithium withdrawal and remain elevated for 3 days when compared with levels in rats that continued receiving lithium[100]. This potentially explains the recurrence of symptoms in patients following withdrawal. However, in a similar experiment, this same research group also found that rat brain dopamine levels remained lower for 3 days following lithium withdrawal as compared with rats not taking lithium, which suggests that the effects of lithium can persist for a short time[99]. While there are methodological differences between the studies, the

findings highlight the fact that the effect of lithium on dopamine neurotransmission is complex and possibly occurs at several levels.

The post-synaptic actions of dopamine are mediated via G-protein coupled receptors (Fig. 2). These protein receptors then stimulate second messenger systems such as adenyl cyclase (AC) and cyclic adenosine monophosphate (cAMP), which subsequently modulate neurotransmission (see discussion in Sect 6.1). Increased receptor and G-protein coupling has been shown in post-mortem studies of patients with bipolar disorder compared with age-matched controls. Further, particular subunits of the dopamine-associated G-protein have been reported to be higher in bipolar disorder patients, and may contribute to the pathology of bipolar disorder by altering subsequent biochemical pathways. Research has suggested that chronic lithium administration alters the functionality of these subunits, specifically the equilibrium between the active and inactive subunits, but does not change the levels of G-proteins per se[102].

5.2 Glutamate and NMDA receptors

Glutamate is a stimulatory neurotransmitter that is elevated during mania[103], and therefore glutamate neurotransmission is a reasonable target for mood stabilizers[104, 105].The NMDA glutamate receptor is structurally complex and implicated in a number of psychiatric disorders. Magnesium binds to sites on the NMDA receptor and this prevents its activation, but when glutamate and glycine bind to the receptor simultaneously, magnesium is displaced so that the receptor can be activated[106]. Lithium competes with magnesium at this binding site, and acutely stimulates the NMDA receptor, which in turn increases the availability of glutamate in the post-synaptic neuron[107]. However, with chronic lithium administration, glutamate neurotransmission stabilizes as the NMDA receptor is downregulated and this increases glutamate re-uptake, which restores glutamate transmission. This is one possible mechanism through which lithium achieves its long-term mood-stabilizing effect as well as its anti-manic properties[108-110]. Of note, the effects of lithium on glutamatergic neurotransmission appear to be specific to lithium, as other

monovalent ions such as rubidium and caesium, as well as common antidepressants have failed to show similar effects[111]. Also, the ability of lithium to modulate glutamate transmission through the inhibition of the NMDA receptor-mediated calcium influx, reduces glutamate-induced excitation and thus demonstrates its neuroprotective potential[112, 113].

Of note, however, is that NMDA receptor activation is complex and is also influenced by other neurotransmitter systems, which are altered by lithium. For instance, chronic lithium administration enhances serotonergic neurotransmission by facilitating the post-synaptic serotonin 5-HT$_{1A}$ receptor, which in turn inactivates the NMDA receptor[108]. Similarly, lithium has been shown to reduce dopamine activity (see previous discussion in Sect 5.1), and since dopamine normally increases NMDA receptor activity via dopamine D$_1$ receptors, this is also decreased by the actions of lithium on dopamine[108].

5.3 GABA and GABA receptors

GABA is an inhibitory neurotransmitter[114] that plays a crucial role in modulating both dopamine and glutamate neurotransmission[115], and hence it is also thought to play a key role in mood stabilization[108, 114-116]. Patients with mood disorders, in particular bipolar disorder, have diminished GABA-ergic neurotransmission[114-118]. Hence, some researchers have suggested that low GABA plasma levels may be used as a marker of bipolar disorder[119].

Low GABA levels result in an increase in excitatory neurotransmission that leads to excitatory toxicity and in turn causes apoptosis and cell loss[72]. In this context, lithium promotes the release of neuroprotective proteins and decreases the levels of pro-apoptotic proteins[120]. Lithium increases the level of GABA in the plasma and cerebrospinal fluid of humans as that of rats[110, 121, 122]. Interestingly, an

increase in GABA in response to lithium reduces the level of glutamate and this downregulates the NMDA receptor[108].

5.4 Summary

It is important to note that whilst specific neurotransmitter systems have been strongly implicated in the pathophysiology of bipolar disorder, these systems are highly interconnected via complex neural networks[102]. In addition, the cellular mechanisms responsible for the mediation of neurotransmission are also implicated in bipolar disorder and therefore abnormalities in any of these systems, especially those with connections to the limbic system of the brain may result in symptoms[123]. However, there are significant gaps in our current understanding of many neurotransmitter systems and because lithium has multiple interacting targets across a number of neurotransmitter and non-transmitter systems, more integrated investigations are required to unravel the complexity of the actions of lithium on neurotransmission.

6 Cellular Mechanisms
6.1 Second Messenger Systems

Second messenger systems comprise enzymes and molecules that 'translate' signals received by receptors at the cell surface following activation by neurotransmitters to an intra-cellular response. This process of information transfer is called signal transduction and results in both short-acting and long-lasting responses. For example, ion channel phosphorylation is immediate, whereas modification of gene transcription takes much longer. Further complexity arises because cells can respond differentially to the same excitatory or inhibitory stimuli[124]. Lithium affects many of the enzymes and ions within these second messenger systems (see Table 1 and Fig. 3) and therefore investigation of these downstream targets of neurotransmission is essential to understanding its therapeutic effects.

Like sodium (Na^+), lithium (Li^+) is a monovalent cation, but because it is strongly hydrated it acquires an

ionic diameter equivalent to that of magnesium (Mg^{2+}). Therefore, it primarily interferes with the binding

of this key co-factor at specific metal ion binding sites and disrupts the function of a number of essential

proteins. For example, lithium inhibits inositol monophosphatase (IMPase), glycogen synthase kinase 3

(GSK-3) and phosphoglucomutase (FGM). Its competition with Mg^{2+} also impacts AC and

phosphomonoesterases such as inositol polyphosphate-1-phosphatase and fructose 1,6-bisphosphatase

(FBPase)[9]. With the exception of the latter and FGM, which subserve glucose and glycogen metabolism,

respectively, the majority of enzymes that are lithium sensitive are pivotal to cellular signal transduction

pathways (see Table 1 and Fig. 3 for further detail).

Table 1. The actions of lithium on second messenger systems

Li^+ target	Role in cellular signalling	Change in BD	Action of Li^+
AC and cAMP	AC and cAMP are activated by monoaminergic transmission. This stimulates second messengers that consequently regulate neurotransmission[125]	Sensitivity of the system is altered resulting in modulation of excitatory neurotransmission[125]	Modulation of neurotransmission, by increasing basal levels of AC and cAMP such that large fluctuations that normally occur in response to monoaminergic stimulation are minimized[9, 126, 130]
SMIT	Responsible for regulation of inositol entry into the cell[134]	Upregulated in BD I [135]	Inhibits SMIT expression and activity, thereby limiting transport into the cell and contributes to depletion of intracellular inositol[135]
ImPase and IPPase	These are rate-limiting enzymes in the PI cycle involved in changing IP_2 to IP and IP to mI, respectively[125]	↑ in both mania and depression[102]	Direct inhibition of ImPase and IPPase. Thus, recycling to restore intracellular inositol is limited causing depletion[136]
PKC	Modulates pre- and post-synaptic transmission[132,144]	↑ in mania[144,145]	Inhibits PKC thereby reducing excitatory neurotransmission[132,

			138, 144]
MARCKS	Downstream target of PKC that is responsible for release of neurotransmitters[132]	↑ in mania[146,148]	Inhibits MARCKS directly[148] and indirectly via its action on PKC[132, 138, 147]
BDNF and Bcl-2	Neuroprotective proteins that are activated by CREB, which is a downstream target of AC and cAMP[9]	↓ in BD[181, 188]	Increases BDNF[182] and Bcl-2[187-189] levels as a consequence of CREB activation through the actions of lithium on cAMP
GSK-3	Regulation of glycogen synthesis, gene transcription, synaptic plasticity and cell structure and resilience[131, 132]	Dysregulation[192]a	Inhibits GSK directly,[193] which then activates the Akt neuroprotective pathway[195]

AC adenyl cyclase, *Bcl-2* B-cell lymphoma 2, *BD* bipolar disorder, *BD I* bipolar 1 disorder, *BDNF* brain-derived neurotrophic factor, *cAMP* cyclic adenosine monophosphate, *CREB* cAMP response element binding transcription factor, *DAG* diaglycerol, *GSK-3* glycogen synthase kinase 3, *IP* inositol phosphate, *IPPase* inositol phosphate 1-phosphatase, *IMPase* inositol monophosphate 1-phosphatase, *IP₃* inositol triphosphate, *Li⁺* lithium, *MARCKS* myristoylated alanine-rich c kinase substrate, *mI* myo-inositol, *PI* phospohinositide, *PIP₂* phosphoinositol 4-5-biphosphate, *PKC* protein kinase C, *PLC* phospholipase C, *SMIT* sodium myo-inositol transporter; ↑ indicates increased, ↓ indicates decreased

a The exact role of GSK in the pathology of BD is not well understood, but given the actions of lithium on GSK it is postulated that GSK is dysregulated in BD

6.1.1 The Adenyl Cyclase and Cyclic Adenosine Monophosphate (cAMP) System

The AC system is an important receptor-coupled second messenger system that is activated by monoaminergic neurotransmission[125]. AC is coupled to membrane-bound G-proteins that can stimulate (G_s) or inhibit (G_i) the production of cAMP [9]. The latter activates the enzyme, protein kinase A (PKA), which in turn regulates and phosphorylates ion channels, cytoskeletal structures and transcription factors such as cAMP response element binding protein (CREB). CREB is of particular interest because of its effects on brain-derived neurotrophic factor (BDNF) and B-cell lymphoma-2 (*bcl-2*) genes that are thought to play a key role in neuronal plasticity (see discussion in Sect 6.2.2 and Sect 6.2.3)[9].

At concentrations of 2 mmol/L, lithium balances AC system transduction by both enhancing basal activity while concurrently inhibiting stimulated activity. Therefore, acutely, lithium increases basal levels of AC and cAMP, partly by inhibiting the G_i protein[102, 126, 127] (see Sect. 5.1). At the same time, when cells undergo stimulation, lithium minimizes the resultant fluctuations in cAMP by reducing G_s activity and thereby conferring stability to the signalling system[110, 125-129]. These acute effects eventually give way to long-term changes that are a consequence of prolonged lithium exposure in which cAMP and AC levels are further modified through gene transcription[9, 126, 130].

6.1.2 The Phosophoinositide Cycle

Phosophoinositides (PIs) are the precursors for many signalling molecules that are important in receptor-mediated signal transduction pathways, and invoke a number of CNS responses[131-133]. Activation of a PI cycle-associated membrane receptor stimulates phospholipase C (PLC)-mediated hydrolysis of phosphoinositol-4-5-bisphosphate (PIP_2) into inositol triphosphate (IP_3) and DAG (see Fig. 3). The resulting products, IP_3 and DAG, initiate PKC activation and the release of intracellular calcium, respectively[134]. IP_3 is then successively phosphorylated via the enzymes inositol phosphate 1-phosphatase (IPPase) and ImPase[125] to replenish myo-inositol (mI), which is then used to synthesize PIs.

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Additionally, extracellular inositol can enter the cell via a high-affinity sodium mI transport (SMIT) system, which also regulates mI levels [134]. In bipolar I disorder, studies suggest that the SMIT system is upregulated[135], and that disruption of the PI cycle by lithium affects the homeostasis of intracellular calcium[133, 136, 137].

One of the most widely discussed hypotheses regarding the action of lithium is the 'mI depletion hypothesis'[116, 133]. This postulates that lithium-induced inhibition of ImPase and IPPase depletes cellular mI and that this compromises the production of PI[102, 117, 138]. In addition, lithium inhibits the expression and activity of the SMIT system, thus limiting the entry of inositol into the cell and produces further depletion[135]. Interestingly, the effects of lithium on SMIT take approximately 8 days, which is similar to the time lithium takes to exert its therapeutic effects clinically[134]. Together these changes compromise the synthesis of PI-dependent second messenger molecules[102, 117].

Studies on animals and animal models of mood disorders, as well as investigations of neural cell cultures and brain slices, have produced inconclusive evidence in relation to the mI depletion hypothesis. Clinical imaging studies using proton magnetic resonance spectroscopy (MRS) have also yielded equivocal findings. For instance, frontal lobe mI levels have been found to be increased during mania and depression, but remain comparable to healthy controls during euthymia, when mood is presumably stabilized with lithium[131, 139, 140]. Further, significant reductions in brain mI levels following acute lithium administration have been shown to correlate with an improvement in manic symptoms in children[141]. Interestingly, mI and IPPase levels are unaffected by lithium in euthymic patients supporting its role as an uncompetitive inhibitor. That is, lithium only inhibits the enzyme when it is in excess[131, 139]. However, not all studies have found evidence to support the mI depletion hypothesis, and in a number of studies changes in mI following lithium administration correlates poorly with changes in clinical state[142]. Of

note, several evaluations of the research in this field suggest that the therapeutic actions of lithium are probably not solely related to inositol but rather its downstream targets[133, 140, 142, 143].

6.1.3   Protein Kinase C and Myristoylated Alanine-Rich C Kinase Substrate (MARCKS)

PKC is an enzyme that is ubiquitous in the brain. It plays an important role in pre- and post-synaptic neurotransmission. PKC is activated by neurotransmitters through the PI cycle and phosphorylates its downstream target MARCKS, which is responsible for neuronal excitability and changes in gene expression and cell plasticity[131, 132, 138, 140, 144]. Increased platelet PKC activity has been found during periods of intense neurotransmission such as mania, further, post-mortem studies have shown increased levels of PKC in the prefrontal cortex of bipolar disorder patients compared with age-matched controls[145]. Such elevated levels of PKC may hinder neuronal functioning[144, 146].

Acute treatment with lithium has been shown to activate PKC but over longer periods of time lithium tends to downregulate the activity of this kinase[147] and its substrate MARCKS in the hippocampus[148]. It has been postulated on the basis of these studies in both animals and humans that the inhibition of PKC activity by lithium is related to its anti-manic effects[7]. For instance, elevated cystosolic and membrane-associated PKC activity in the platelets of manic patients, has been found to be significantly diminished after 2 weeks of lithium therapy at therapeutic concentrations[149]. In addition, animal models of mania have shown a reduction in PKC and MARCKS in the prefrontal cortex after 4 weeks of lithium treatment[146]. However, the precise role of PKC in the regulation of mood and the pathophysiology of bipolar disorder is not known.

6.1.4   Intracellular Calcium

Calcium is a highly diverse cation that plays multiple important roles in cellular functioning, from the regulation of neurotransmission to cellular integrity, metabolism and gene transcription[150, 151]. When the cell is stimulated via the binding of a neurotransmitter to receptors at the cell surface, calcium enters the

cell through channels on the cell membrane as well as via IP$_3$-mediated release from the endoplasmic reticulum. This results in an increase of intracellular calcium levels that then propagates the cellular signal. When stimulation is ceased, calcium levels are restored via multiple sophisticated intracellular mechanisms[150]. Maintenance of calcium homeostasis is critical for efficiency of cellular signalling as well as cellular integrity[152]. Dysregulation of intracellular calcium is extensively documented in bipolar disorder. The most consistent finding is elevation of intracellular calcium levels, encompassing both basal and receptor-regulated calcium[153, 154]. This may be a marker of illness state rather than a trait marker[155].

Lithium has documented effects on intracellular calcium signalling. Lithium blocks the uptake of calcium into cells in both individuals with bipolar disorder and controls[156]. Specifically, lithium attenuates calcium influx after activation of the NMDA receptor. Following activation of both metabotropic glutamate receptors (mGluR) 1/5, lithium attenuates calcium release, and was linked to downregulation of the plasma membrane expression of the mGluR5 receptor. Lithium decreases intracellular calcium levels and intracellular calcium stores[157]. Curiously, valproate, but not lamotrigine share the ability of lithium to attenuate the lysophosphatidic acid-stimulated calcium responses in B lymphoblast cell lines from bipolar I disorder patients[158]. Lithium blocks excitotoxic processes, at least in part via calcium. Lithium blocks the excitotoxic process induced by kainate via modulation of calcium entry and the consequent inhibition of the calpain pathway[159]. Calpain is a protease that has a role in apoptotic pathways, and is activated by intracellular calcium[160].

6.2 **Neuroprotective Pathways**

As previously mentioned, bipolar disorder is increasingly recognized as a degenerative disease for which lithium has been shown to be neuroprotective. There are several models and hypotheses that have been posited to explain how degenerative changes lead to bipolar disorder. One such theory is the 'neurosensitization model' in which manic/depressed episodes cause changes in gene expression, which

in turn permanently alter neuronal activity. This transformation renders key neuronal networks dysfunctional such that the individual becomes more susceptible to relapse and less likely to respond to medication[8]. An alternate model, the 'allostatic load hypothesis', proposes that 'wear and tear' caused by episodes of mania and depression, alters the functioning of key brain circuits that eventually lead to cognitive decline, and increase the likelihood of further illness and resistance to treatment[8]. A third hypothesis is the 'neurodevelopmental model', which simply suggests that a decrease in cell density in the bipolar brain is the product of abnormal neural development. Interestingly, this pattern of atrophy has been found not only in adults with bipolar disorder but also in paediatric patients[161], and non-symptomatic family members of bipolar disorder patients[162], suggesting that this is a process that commences early in life. More recently, the 'neuroprogression model' posits that the disorder has a progressive course, mediated by factors including inflammation, oxidative stress, neurotrophins, mitochondrial dysfunction and apoptosis[8, 12].

Lithium has demonstrated neuroprotective effects by both preventing apoptosis and promoting cellular longevity[8, 10]. When cells are exposed to an insult such as excessive glutamate excitation, certain kinases are activated through phosphorylation, specifically c-Jun N-terminal kinase and p38 mitogen-activated protein[163, 164]. Together these kinases increase binding of the DNA transcription factor, activator protein-1, and this in turn activates apoptosis. Excess glutamate therefore increases levels of pro-apoptotic proteins, such as p53 and Bax, while at the same time downregulating cytoprotective proteins such as bcl-2. Thus, cell atrophy in bipolar disorder is thought to occur not only because of the toxic consequences of recurrent affective episodes, but also the 'endogenous impairment of "cellular resiliency"'[7, 162]. Hence, chronic treatment of bipolar disorder with lithium both modulates enzymatic apoptosis pathways and increases the availability of neuroprotective factors[126, 165, 166].

6.2.1 Oxidative Metabolism

There has been growing evidence that points towards mitochondrial dysfunction playing a role in the pathophysiology of bipolar disorder. As well as being the energy centre of the cell, mitochondria play a central role in mediating apoptosis and regulating intracellular calcium, both of which have implications for neurotransmission and neuroprotection[123, 167, 168]. The underlying mechanisms involve dysfunction of endoplasmic reticulum and mitochondrial calcium homeostasis[169], and polymorphisms of the bcl-2 protein contribute to this dysregulation. Mitochondrial dysfunction is present in bipolar disorder, including decreased activity of complex 1 of the mitochondrial electron transport chain[170]. Lithium upregulates complexes I and II[171]. Glutathione plays a key role in the interaction between lithium, mitochondrial dysfunction and oxidative stress[172, 173].

Oxidative stress occurs when anti-oxidants are no longer able to remove excessive by-products of energy metabolism such as free radicals. These by-products are toxic and cause cellular damage and may induce inflammation and activate apoptosis pathways[167]. Oxidative stress is particularly pronounced during periods of mania and results in cell damage that is cumulative over time, such that with recurrent episodes the likelihood of a clinical response to treatment gradually diminishes[174, 175].

In addition to an increase in oxidative processes[176], patients with bipolar disorder have reduced levels of anti-oxidants (such as glutathione) and associated enzymes[177]. Further, N-acetyl aspartate, a marker of mitochondrial function and neuroprotection, is reduced in bipolar disorder patients[123, 178]; however, lithium is thought to stimulate mitochondrial respiratory chain complexes, in a dose-dependent manner[171], and in doing so is perhaps able to protect against oxidative stress[179]. In keeping with this, compared with patients treated with lithium during acute mania, unmedicated bipolar disorder patients have higher markers of lipid peroxidation, and levels of oxidative enzymes are increased, to possibly compensate for increased levels of stress[180].

6.2.2   Brain-Derived Neurotrophic Factor (BDNF)

BDNF is an important neuroprotective protein that has been shown to be decreased in both the manic and depressed phases of bipolar disorder[181], but increased in patients effectively treated with lithium in combination with other medications for mania.[182] This increase in BDNF expression with lithium treatment has been postulated to provide protection against glutamate-induced excitotoxicty[111]. Interestingly, BDNF levels have been shown to increase about 5 days after lithium administration in animals[111]. Clinically, lithium takes 6–10 days to achieve an anti-manic effect and some researchers have suggested that this delay is the time required for BDNF to regenerate to neuroprotective levels[183].

Interestingly, a recent study compared lithium responders with non-responders with respect to cognition and plasma BDNF levels. This study found that compared with healthy controls, lithium responders performed similarly on cognitive function tests and had no difference in BDNF levels. However, non-responders performed worse on cognitive tests and had lower levels of BDNF than both lithium responders and healthy controls. This study suggests that the neuroprotective role of lithium is related to facilitatory effects on BDNF[184]. Lithium impacts other growth factors such as epidermal growth factor and insulin growth factor, although these pathways are less well explored than BDNF[185, 186].

6.2.3   B-Cell Lymphoma 2 (Bcl-2)

Bcl-2 is a neuroprotective protein that regulates cellular apoptotic pathways and has been implicated in neurotrophy[187]. As such, a decrease in bcl-2 is thought to contribute to mania[188]. Of note, chronic lithium therapy increases both bcl-2 messenger RNA (mRNA)[166] and bcl-2 levels[187-189] and reduces apoptosis[190].

6.2.4   Glycogen Synthase Kinase 3 (GSK-3)

GSK-3 is an enzyme responsible for regulating glycogen synthesis. It has direct involvement in gene transcription, synaptic plasticity, cell structure and resilience[8, 131, 132]. Further, it is a down-stream target

of monoaminergic systems and growth factor cascades, and therefore is implicated in the regulation of mood[183]. GSK-3 is activated under conditions of chronic stress, such as prolonged exposure to dopamine during mania[191], and has been shown to cause hyperactivity in mice[192]. Lithium directly inhibits GSK-3[193] by regulating serine 9-phosphorylation 3[194] and the inhibition of GSK also activates the Akt neuroprotective pathway[165, 195].

This effect on GSK-3 may therefore be key to its therapeutic properties[131, 132, 196], and though GSK inhibition does not reliably produce an antidepressant effect in murine models of depression[197], many studies have demonstrated antidepressant-like effects[198]. Specifically, lithium has been shown to increase synaptic plasticity and decrease GSK expression that has been induced in murine models of depression[199]. These conflicting findings reflect the comparatively poorer efficacy of lithium in treating the depressive phase of bipolar disorder as compared with mania[200].

6.2.5 Autophagy

Autophagy is an important physiological process that cells use to regulate neuronal viability and function. It occurs in response to cellular stress and is responsible for degradation of intracellular proteins, and hence its main role involves the recycling of these proteins and nutrients[201, 202]. The mammalian target of rapamycin (mTOR) is a negative regulator of the autophagy process. GSK-3 inhibition activates mTOR and therefore decreases autophagy[203]. However, ImPase inhibition via lithium (see section 6.1.2), decreases IP_3 levels, which in turn induces autophagy[204]. Hence, lithium both inhibits and induces autophagy by its effects in reducing GSK-3 and ImPase, respectively[204, 205]. While its role in the inhibition of autophagy has been considered important in explaining the neuroprotective properties of lithium, it is still not well understood.

6.3 Summary

Lithium acts on a number of molecules within second messenger systems that possibly underpin its regulatory effects on neurotransmission and its neuroprotective properties. It modulates neurotransmission by moderating AC and cAMP fluctuations and by limiting mI, PKC and MARCKS. Over time these constraints modify gene transcription within the cell and yield long-lasting mood stabilization.

At the same time, lithium is able to reduce the oxidative burden caused by episodes of illness and protect against apoptosis by promoting neuroprotective pathways such as Akt and facilitating the actions of neuroprotective proteins such as BDNF and bcl-2. It also inhibits pro-apoptotic proteins such as p53 and processes such as autophagy. These neuroprotective properties are increasingly recognized as an important quality of lithium for the treatment of bipolar disorder and other neurodegenerative disorders[206].

7 Conclusion

It is clear that lithium possesses a complex set of actions involving neurotransmission and cellular signalling pathways that translate to its many clinical effects involving mood and cognition. Interestingly, its therapeutic and neuroprotective effects are most pronounced in the presence of pathology. For example, as described earlier, in studies of cognition in non-psychiatric populations the effects of lithium appear to be detrimental, but in bipolar disorder patients its long-term effects are beneficial. Similarly, when because of mania the levels of neurotransmitters such as glutamate or dopamine increase dramatically, lithium is able to counteract these changes and stabilize neurotransmission whereas in the absence of pathology it increases basal levels of these excitatory substances. This selectivity of action is also evident at a cellular level. For example, inositol is depleted by lithium in certain brain regions but only when the levels are significantly raised as found in mania or depression.

While these findings are remarkable, there remain several important considerations that limit our understanding of the mechanism of action of lithium. First, the pathophysiology of bipolar disorder is likely to be complex and will be complicated further by the effects of lithium. Therefore, the compensatory changes that accompany treatment may be difficult to disentangle from any primary dysfunction. Second, neurotransmission is in itself a highly sophisticated process that involves multiple interconnected pathways. Hence, identifying common targets across the various phases of bipolar disorder is inherently difficult and requires examination of patients in each of the various mood states. Third, a significant proportion of the findings that have contributed to our understanding of lithium derive from in vitro studies, and preclinical in vivo studies. Many of these studies use lithium concentrations that are higher than those that are used therapeutically, and while it could be speculated that different concentrations of lithium may have very different neurobiological effects that may underlie some of the different clinical effects of lithium, these studies are not easily translated for application in human studies especially as appropriate animal models of bipolar disorder have not yet been established.

It is therefore important to note that the potential mechanisms of action of lithium that have been detailed in this paper are tentative and that there are many aspects that require replication and further research. Most pressing perhaps is the need for longitudinal studies to determine whether the mood-stabilizing and neuroprotective properties of lithium share a common mechanism and how the two effects are interrelated, if at all. In addition, studies need to utilize multi-modal approaches that employ the latest advances in technology within fields such as neuroimaging and genetics alongside careful selection of patients with bipolar disorder.

By integrating basic sciences research and clinical studies it is hoped that a more complete picture of the actions of this enigmatic element will emerge and that it may also provide insights into the

pathophysiology of bipolar disorder. Indeed, it has been argued that most of the primary insights into the pathophysiology of psychiatric disorders are derived from reverse engineering the properties of effective therapies. This remains the primary road forward in bipolar disorder[207].

Acknowledgements

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Malhi

In all 3 figures, change font size to 8 pt Helvetica or Arial

Figure 1:

Change stabilisation to ==stabilization==

Change Altered Cognitive Functioning to ==Altered cognitive functioning==

Change gray to ==grey==

Change Glutamate and Dopamine to ==glutamate and dopamine==

Change Second Messenger System to ==second messenger system==

Change Inositol to ==inositol==

Change defense to ==defence==

Change Intracellular Changes to ==intracellular changes==

Close-up and spaces between ↑↓ and the first letter of a word

Figure 2:

MACRO

MICRO

Mood — ↓Mania, ↓Depression
Long-term mood stabilisation and prophylaxis
↓ Suicidality

Cognition — Altered Cognitive Functioning

Structure — Neuroprotective: ↑ Global gray matter volume
↑Amygdala, hippocampus and prefrontal cortical regions

Neurotransmission — ↑ Inhibitory neurotransmission (GABA)
↓Excitatory neurotransmission (Glutamate and Dopamine)

Cellular and Intracellular Changes — Modulation of neurotransmission
Second Messenger System modulation
(AC system, Inositol depletion, PKC and MARCKS)
↑ Anti-oxidant defense
Anti-apoptotic actions (↓GSK)
Neuroprotective factors (↑BDNF, bcl-2)