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Lithium's role in neural plasticity and its implications for mood disorders

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Abstract

Objective—Lithium (Li) is often an effective treatment for mood disorders, especially Bipolar Disorder (BPD), and can mitigate the effects of stress on the brain by modulating several pathways to facilitate neural plasticity. This review seeks to summarize what is known about the molecular mechanisms underlying Li's actions in the brain in response to stress, particularly how Li is able to facilitate plasticity through regulation of the glutamate system and cytoskeletal components.

Method—The authors conducted an extensive search of the published literature using several search terms, including Li, plasticity, and stress. Relevant papers were retrieved and their bibliographies consulted to expand the number of articles reviewed. The most relevant papers from both the clinical and preclinical literature were examined in detail.

Results—Chronic stress results in morphological and functional remodeling in specific brain regions where structural differences have been associated with mood disorders, such as BPD. Li has been shown to block stress-induced changes and facilitate neural plasticity. The onset of mood disorders may reflect an inability of the brain to properly respond after stress, where changes in certain regions may become “locked in” when plasticity is lost. Li can enhance plasticity through several molecular mechanisms, which have been characterized in animal models. Further, the expanding number of clinical imaging studies has provided evidence that these mechanisms may be at work in the human brain.

Conclusion—This work supports the hypothesis that Li is able to improve clinical symptoms by facilitating neural plasticity, and thereby helps to “unlock” the brain from its maladaptive state in patients with mood disorders.

Keywords

Lithium; stress; hippocampus; amygdala; bipolar disorder; glutamate; plasticity

Introduction

How the brain responds to stress in the environment remains an area of intense study. Animal models have demonstrated that throughout adulthood the brain retains the ability to undergo extensive structural and functional remodeling in certain regions, particularly the

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Declaration of interest

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hippocampus and amygdala. This neural plasticity is an essential adaptation that can provide neuroprotective benefits after an initial acute stress(1). However, these same response pathways can have negative consequences on brain structure and function after repeated exposures to stress(2). Changes in gene expression, decreased neurogenesis, changes in dendritic arborization and spine density, and diminished capacity for learning and memory have all been well documented(3). Yet, there is evidence to suggest that these negative consequences are not all permanent. Many of them can be reversed with sufficient recovery time after the stress has been discontinued, suggesting chronic stress may not cause a complete loss of neural plasticity in the normal brain(4).

Exposure to life stress can exacerbate the symptoms of many mood disorders and is associated with earlier disease onset(5, 6). However, many individuals experience stressful life events and never develop post-traumatic stress disorder (PTSD), major depressive disorder (MDD), or Bipolar disorder (BPD), indicating that mood disorders likely result from a unique confluence of genetic and environmental factors that conspire to produce a lasting maladaptive state. This inability to return to normal after a stressful event suggests an abnormal loss of plasticity, where the brain becomes “locked in” after significant stress exposure. Emerging clinical neuroimaging evidence supports a connection to the human condition, as many of the same brain regions changed in response to stress are similarly altered in patients suffering from mood disorders, particularly the hippocampus and amygdala(7, 8).

Lithium (Li) is a mood stabilizing drug that has been used effectively in the treatment of BPD, as well as other mood disorders, for over 60 years. In animal models, Li has been shown to block some of the morphological changes induced by stress in the hippocampus and amygdala (9, 10). Multiple mechanisms of action have been identified that could account for both its clinical efficacy and ability to mitigate the effects of stress on the brain. Principal among them are Li's ability to provide trophic support and facilitate neuroplasticity through activation of the Wnt/ β -catenin and brain-derived neurotrophic factor (BDNF) pathways in concert with changes in glutamate and glucocorticoid (GC) levels.

Aims of the study

This review summarizes the evidence supporting lithium's ability to counteract the effects of stress on the brain and describes the molecular mechanisms that may underlie Li's ability to facilitate neuroplasticity and thereby help to “unlock” the diseased brain. Particular focus will be given to Li's potential role in GC signaling, the glutamate system, and cytoskeletal regulation, as mechanisms facilitating neural plasticity. Finally, the relevance of this pre-clinical evidence will be discussed in the context of recent clinical imaging studies, which demonstrate Li's ability to structurally alter brain regions in patients suffering from mood disorders.

Material and methods

The authors conducted an extensive search of the published literature using PubMed, Medline and Google Scholar. Example search terms included Li, plasticity, stress, glutamate, GCs, cytoskeleton, and neuroimaging. The bibliographies from relevant articles were reviewed in order to expand the search results. Articles determined by the authors to focus on Li's impact on neural plasticity and clinical neuroimaging papers related to anatomical changes in response to Li were examined in greater depth.

This review is divided into sections designed to highlight Li's actions at the cellular and molecular level in the brain, as well as a final section that links these basic science findings with the clinical literature demonstrating structural and functional changes in patients

undergoing Li therapy. While Li is used in a variety of mood disorders, this review is focused primarily on its use for treatment of BPD and the cellular and molecular changes that are hypothesized to underlie its clinical efficacy. Despite this focus, it is likely that the preclinical mechanisms identified have relevance to Li's treatment of other mood disorders. Further, Li treatment is likely to alter other molecular pathways beyond those described here, however, this review seeks to focus on those linked to changes hypothesized to be relevant to Li's effects on neuroplasticity.

Results

Lithium can block the effects of stress across brain regions

The stress response is characterized by activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which results in an elevation of circulating cortisol. In the brain, cortisol and other GCs are able to bind the glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) on neurons and glia to effect transcriptional regulation (11, 12). Clinically, improper regulation of the HPA-axis has been identified in mood disorders, implicating the GC signaling (13, 14). Interestingly, abnormal HPA-function is still apparent even in patients stabilized by Li (15, 16).

The most pronounced effects of GCs in the brain were initially identified in hippocampus, where elevated GCs were found to suppress neurogenesis (17) and reduced dendritic arborization and spine density (3). Both chronic elevation and chronic depletion of GCs, either by adrenalectomy (18) or by dexamethasone suppression (19), inhibit hippocampal neurogenesis, indicating there is an optimal GC level for maintaining trophic support for hippocampal neurogenesis *in vivo*. Several studies have demonstrated a trophic effect of Li on hippocampal neurogenesis *in vivo* in rats (20-22). *In vitro* studies of adult hippocampal progenitor cells have also confirmed that Li can rescue dexamethasone-induced suppression of proliferation, suggesting that Li can act independently of GC levels to promote neurogenesis (23). Li's ability to promote neurogenesis, while bypassing the GC system in the hippocampus, is one mechanism by which Li can facilitate improved neural plasticity in the mood disorders.

In addition to improving neurogenesis, Li can facilitate plasticity through regulating neuron morphology. *In vitro*, Li was initially shown to exhibit an inhibitory effect on neurite outgrowth (24), but also found to help maintain growth cone stability and facilitate spreading of growth cone filopodia (25, 26). Early *in vivo* studies demonstrating Li's effects on neuronal morphology used a pilocarpine-induced mossy fiber sprouting model system (27). Briefly, pilocarpine treatment induces mossy fiber sprouting in hippocampus (28), and post-mortem tissue from BPD patients show increased mossy fiber sprouting compared to control (29). Cadotte et al., (2003) found that Li was able to reverse the effects of increased sprouting after pilocarpine in both CA3 and dentate gyrus, but no difference in sprouting was observed in only Li treated rats. Chronic restraint stress (CRS) has long been used as a model of adult hippocampal plasticity, where CRS in rodents induces shrinkage of the dendritic arbor and decreases in spine density (3). CRS can also increase synaptic vesicle density in mossy fiber terminals in CA3 (30). Therefore, Li's effects on dendrite morphology after CRS were investigated and Li was found to block stress-induced decreases in dendritic length and branching in CA3 hippocampal neurons (9) (Fig. 1A-C). Interestingly, Li had no effect on length or branching in unstressed animals (9). This normalization of hippocampal morphology by Li has also been observed in transgenic mice prone to decreased branching of pyramidal neurons (31).

Li's ability to normalize changes in neuronal morphology *in vivo* has been observed in other brain regions. In the amygdala, chronic stress and elevated GC levels have the opposite

effect on dendritic branching and spine density as that observed in the hippocampus (32, 33). Yet, Li is also able to prevent the increased branching and length induced by stress in the amygdala (10) (Fig. 1D-E). Again, Johnson et al., (2009) observed no effect of Li on pyramidal neuron morphology in unstressed animals (Fig. 1E-F). Most recently, Li was shown to normalize spine morphology in the medial PFC of *fmr1*/KO mice, a transgenic model of Fragile X Syndrome that has increased spine number in prefrontal cortex (PFC) (34). These results demonstrate that Li can facilitate opposite outcomes on dendritic branching in response to stress in different brain regions, preventing atrophy in the hippocampus and hypertrophy in the amygdala, yet the mechanisms underlying Li's ability to mitigate stress-induced changes remains unknown. Importantly, these Li-induced changes in both branching and neurogenesis have been linked to improved cognitive performance on learning and memory tasks (35, 36).

Molecular mechanisms of lithium that support neuroplasticity and alter behavior

At the molecular level, Li can influence multiple pathways within the cell. Given the broad spectrum of symptoms Li is able to mitigate, a wide array of functionality seems necessary. In fact, one of the earliest hypotheses to explain its function postulated that because Li and Magnesium (Mg^{2+}) have a similar ionic size (0.076 nm for Li and 0.072 nm for Mg^{2+}), Li may substitute as a cofactor for many of the body's enzymes which require Mg^{2+} and thereby alter their functionality (37). While this may be true, the last 15 years have yielded the identification of several highly specific actions of Li within the cell.

Li's earliest identified function was as an inhibitor of glycogen synthase kinase 3 (GSK3) (38, 39). There are two GSK3 genes (α and β), both of which can be inhibited by Li directly binding and competing with Mg^{2+} (40). However, at therapeutic doses, direct competition with Li likely plays a minor inhibitory role. *In vitro* experiments suggest the primary method of inhibition of GSK3 is through phosphorylation near the N-terminus at serine-21 in GSK3 α and serine-9 in GSK3 β (41). This inhibitory serine phosphorylation can be amplified by a feedback loop involving protein phosphatase 1 (42) and increased Akt activity in response to Li treatment (43), which reduce GSK3 activity to a greater extent than is possible by direct inhibition. Further, because complete blockade of GSK3 would have severe (metabolic and other) consequences for most cells, it's believed that therapeutic doses of Li act to reduce maximal activity (44).

The β form of GSK3 has gained attention as one of the central molecules of the Wnt/ β -catenin signaling pathway. Wnt ligand binding initiates a signaling cascade that leads to the inhibition of GSK3 β and subsequent accumulation of β -catenin, which when translocated to the nucleus regulates TCF/Lef-dependent gene transcription to promote cell proliferation (45). Elegant *in vivo* work demonstrated that Wnt/ β -catenin signaling plays a role in adult hippocampal neurogenesis in the subgranular zone of the dentate gyrus (46). This finding suggested that Li inhibition of GSK3 β may facilitate cell proliferation through a β -catenin dependent mechanism. *In vitro* work has confirmed that therapeutic doses of Li promote hippocampal progenitor proliferation, shown that GSK3 β inhibition or constitutively active β -catenin mimicked the effects of Li on cell growth, and that inhibition of β -catenin can block the proliferative effects of Li (47). Chronic Li treatment *in vivo* was found to elevate β -catenin levels in the hippocampus and PFC (48-50) and overexpression of β -catenin *in vivo* replicates some of the behavioral outcomes of chronic Li treatment (51). Further, both pharmacological inhibition of GSK3 β and genetic haploinsufficiency for GSK3 in mice recapitulate the effects of Li in several behavioral assays (52, 53). Conversely, GSK3 β overexpression *in vivo* produces hyperactivity in mice (54), suggesting this pathway is relevant to the behavioral changes observed clinically with Li treatment. A SNP identified in GSK3 β (-50 T/C) in clinical populations has been linked to the age of onset of BPD (55). While initial studies found the SNP was correlated with the response of BPD patients to Li

treatment(56), subsequent work found this polymorphism was not related to the degree of Li responsiveness(57).

Li can also activate Akt, which has been implicated in multiple mechanisms of cell survival. One mechanism is through indirect inhibition of GSK3 β , by increasing its serine-9 phosphorylation (58). However, Akt activation is also associated with the inhibition of the apoptotic machinery (59). Li was found to suppress the expression of the pro-apoptotic proteins p53 and Bax, and enhance the expression of the anti-apoptotic protein Bcl-2 (60, 61). Li's ability to activate Akt and inhibit GSK3 β was found to depend on the scaffold molecule β -arrestin2 (Arr2)(62). Beaulieu et al., (2008) showed that Arr2-KO mice are insensitive to the behavioral effects of Li, and that Li disrupts the Akt: Arr2:PP2A signaling complex, both *in vitro* and *in vivo*(62). Additionally, activation of Akt in the striatum was found to be required for Li's effect on amphetamine-induced hyperlocomotion(AIH) in mice(63). However, the use of highly specific GSK3 β inhibitors appears to bypass the need for active Akt in this model(63). Therefore, much remains unknown about the interplay between these two molecules in response to Li.

Interestingly, Li's effect on AIH varies across mouse strain, with several strains appearing insensitive to Li, suggesting there are other genetic mechanisms that modulate Li responsiveness that remain to be discovered(64). The delivery of constitutively active Akt to the striatum was able to rescue the AIH effects of Li in one of the insensitive strains (DBA/2J), however, it failed to rescue their performance in the forced swim test (FST)(63). This demonstrates that region-specific activation of Akt is not sufficient to mediate every behavioral response to Li and leaves open the possibility that there may be differences in the downstream responsiveness of Akt and GSK3 β to Li across brain regions. These studies of changes in Akt and Gsk3 β activation regulating Li-induced behavior have focused on the striatum(52, 62, 63). In the PFC, multiple groups have observed increases in β -catenin levels after chronic Li treatment, whereas in the hippocampus, no difference in β -catenin levels was detected (49, 53). However, increased TCF/Lef-dependent reporter activity was evident in the dentate gyrus, suggesting this transcriptional system was activated(53). The extent to which these changes are due to cross-talk between Akt and GSK3 β remains unknown. Further, while transgenic models have demonstrated the global importance of these pathways for Li's effects, future studies that manipulate the pathway locally, in specific brain regions such as hippocampus and amygdala, will yield important insight into how Li is able to have opposing effects across brain regions. One study of the hippocampus has demonstrated changes in branching were associated with increased phospho-Ser9-GSK3 β , but not phospho-Akt at either Ser473 or Thr308 (31). However, much additional work will be necessary to parse the functions of these pathways and their relevant downstream effectors in brain regions responsive to Li. The differentially responsive mouse strains provide an excellent starting point for this type of study. A comparison of the relative activation of GSK3 β and Akt in the hippocampus and amygdala of Li-responsive and non-responsive strains could provide novel insight into their region-specific functionality. This research would begin to explain how Li facilitates distinct morphological outcomes in disparate brain regions.

In addition to Li's effects on Akt and GSK3 β , Li has been found to increase the levels of BDNF and facilitate activation of its downstream receptor, tropomyosin related kinase B (TrkB). *In vitro* studies of cortical neurons found increases in BDNF and TrkB activation after only 3-5 days of Li treatment (65). Additionally, pre-treatment with BDNF mimicked the protective effects of Li against glutamate excitotoxicity and cortical neurons derived from BDNF $^{-/-}$ mice were insensitive to Li's neuroprotective effects(65). *In vivo*, Li has been shown to increase BDNF levels in both rats and mice (66-68). In the hippocampus, studies have shown the dose and duration of Li treatment are important for its effect on BDNF,

where some groups found no difference in BDNF levels after 14 days Li treatment(69) but observed increases in BDNF after 4 weeks of Li (70). In clinical populations, changes in BDNF expression have been linked to increased risk for a variety of mood disorders, such as BPD (71, 72), MDD (73, 74), schizophrenia(75), and obsessive-compulsive disorder(76). Studies examining Li's effects on BDNF in clinical populations have been mixed, with some groups reporting increases in serum BDNF (77) and others finding no effect (78). Normal serum BDNF levels have been reported among BPD patients who are responsive to Li treatment (79), suggesting a clinical association between BDNF and Li. Finally, human SNPs in BDNF have been associated with mood disorders, particularly the valine to methionine change at positions 66 (Val66Met)(80). Several studies have now shown that certain SNPs in BDNF (including Val66Met) are associated with the effectiveness of Li in treating BPD (81, 82). Given BDNF's well-documented effects on plasticity(83, 84), further study of the interaction between Li and BDNF signaling may also yield important insight into how Li is able to facilitate neuroplasticity to "unlock" the brain.

These trophic mechanisms of Li (-catenin-dependent transcription, Akt activation, increased BDNF levels) are dependent on signaling cascades which alter gene expression at the nucleus. However, Li has been shown to have highly localized effects at the synapse as well. Early on, glutamate receptors were found to be highly permeable to Li suggesting that local accumulations of Li in dendritic spines in response to consecutive firings were capable of uncoupling local second messenger systems (85). Building on this, chronic (but not acute) Li treatment *in vitro* was found to be neuroprotective of glutamate induced excitotoxicity by reducing Ca⁺ influx (86). In the next section, the impact of Li and stress on the glutamate system is discussed in the context of how it may regulate neural plasticity. Differences in the downstream signaling from either GC or NMDA receptors may provide an underlying mechanism that could account for the distinct morphological response observed in the hippocampus and amygdala. Finally, Li can produce highly localized effects on the cytoskeleton, providing another potential mechanism by which Li could mitigate dendritic atrophy in hippocampus and hypertrophy in the amygdala in response to stress. While Li's known cytoskeletal mechanisms appear insufficient to explain these opposing effects, the *in vitro* literature will be discussed in light of recent genetic evidence from clinical populations that cytoskeletal genes are associated with mood disorders.

Modulation of glutamate signaling by lithium and glucocorticoid

Glutamate is the primary excitatory neurotransmitter and plays an important role in the neural plasticity underlying learning and memory (87). However, excess glutamate can have profound negative effects, where continuous cell firing can cause excitotoxicity and cell death (88). Therefore, maintaining an appropriate balance of glutamate is essential for normal plasticity and studying disrupted glutamate signaling in mood disorders is receiving increasing attention(89, 90). Several studies have shown that Li can modulate the glutamatergic system, and potentially intersect with GC signaling.

Early work in slice cultures found that acute Li treatment actually increased glutamate in the extracellular space(91, 92). However, chronic lithium treatments *in vivo* in mice showed that Li upregulated synaptosomal reuptake of glutamate, thereby reducing the amount available in the synaptic cleft(93). Studies in rat cerebellar granular cells provided the first evidence of an underlying mechanism, where chronic Li treatment was found to protect against glutamate-induced excitotoxicity by inhibiting N-methyl-D-aspartic acid (NMDA) receptor-mediated Ca⁺ influx (86). Regulating the flow of Ca⁺ through NMDA receptors is not only important for preventing excitotoxicity, but also regulation of second messenger signaling implicated in learning and memory (94). Interestingly, Nonaka et al., (1998) did not identify any change in the expression levels of the NMDA receptor subunits, NR1, NR2A or NR2C in cerebellar granular cells *in vitro*. Subsequently, chronic Li treatment was

found to decrease phosphorylation of the NR2B subunit of the NMDA receptor at Tyr1472 (95), a site implicated in Ca^{2+} influx (96). Tyr1472 on the NR2B subunit can be phosphorylated by Src kinases, and Li was found to inhibit Src activity by decreasing its phosphorylation at Tyr416 (97). Another NMDA-dependent mechanism has been proposed through neuronal nitric oxide synthase (nNOS) signaling, which is linked to the NMDA receptor by the scaffold protein PSD-95 (98, 99). Inhibitors of nNOS were found to reduce immobility time in the mouse FST when given in combination with Li (100). Additionally, NMDA antagonists have been found to facilitate Li's antidepressant-like effects by decreasing immobility time in the mouse FST, further implicating NMDA receptor signaling in Li function (101).

Numerous studies have also examined Li's effects on AMPA receptors, which are composed of the subunits GluR1-4 and function with NMDA receptors to regulate synaptic plasticity (102). Initially, expression of GluR1 was found to be significantly reduced by Li in hippocampal synaptosomes (103). A Li-induced reduction in the AMPA/NMDA ratio of CA1 neurons was confirmed by electrophysiological studies and linked to manic behaviors through the use of AMPA specific antagonists in an amphetamine-induced hyperactivity assay (104). Similarly, the antidepressant-like effects of Li on rodent behaviors can be blocked by AMPA receptor inhibitors and Li was found to increase surface expression of AMPA receptors in hippocampus, but not PFC (105). Finally, both microarray studies and histological analysis of post-mortem tissue from mood disorder patients have identified changes in glutamate receptor subunits, suggesting the changes observed in animal models are highly relevant to the clinical condition (106, 107).

Differences in the expression, activation, and downstream signaling from NMDA & AMPA receptors in response to Li during stress may be a central mechanism through which Li can produce unique effects on different types of neurons across brain regions. Similar to the differential effects of Li on behavior, acute and chronic stress also produce highly variable behaviors across mouse strains (108-111). Mozhui et al., (2010) linked these strain differences in stress-induced behaviors to NMDA-mediated signaling in the amygdala. Microarray analysis found that stress produced the most gene expression changes in the amygdala, regardless of strain, including several genes in the glutamate receptor system (e.g. GluR1) (108). Further, the more stress-sensitive strain, DBA/2J, exhibited significantly altered NMDAR-mediated currents leading to increased neuronal excitability (108). In contrast, C57BL/6 mice, which showed minimal stress-induced behavioral changes, did not exhibit NMDA-mediated increases in neuronal excitability in the amygdala (108). This suggests that both stress and Li have highly individualized effects, which depend upon genetic background, vary across brain region, and are likely the result of localized changes in gene expression. Mozhui et al (2010) also analyzed gene expression changes in the hippocampus and PFC, where they found changes that were different from those observed in amygdala and were unique to each strain. Despite this complexity, the literature suggests that the NMDA and AMPA system are the major players coordinating these region-specific responses to stress (112). Further studies will be necessary to parse out this complexity, particularly by seeking to understand which of the downstream molecular pathways of Li and glutamate are activated during neuroplasticity.

GCs have also been directly implicated in the modulation of glutamate system. Early studies suggested that low doses of CORT were excitatory in the hippocampus, whereas high doses of CORT could be inhibitory (113, 114). *In vitro* studies on neonatal hippocampal neurons found that CORT prolonged the NMDA-mediated Ca^{2+} influx (115). Alternatively, slice culture experiment on adult rat hippocampus found CORT inhibited NMDA-mediated Ca^{2+} influx in CA1, but no difference was observed in the dentate gyrus (116). This discrepancy in CORT's effect on Ca^{2+} has been attributed to immature NMDA receptors in the neonatal

cultures (117). More recently, CORT's ability to reduce NMDA currents in adult hippocampal neurons was confirmed (*in vitro*) and found to be dependent on protein kinase A activity(118). CORT is also able to increase miniature excitatory post-synaptic potentials (mEPSPs) through MR-dependent signaling(119). Further, inhibition of the ERK1/2 pathway blocked the increase in mEPSPs, implicating a non-genomic mechanism of action(120). *In vitro* studies of neurons from the amygdala have found that CORT increases Ca⁺ influx through L-type channels, but no difference in NMDA subunits was observed(121). More recent studies have suggested that CORT can increase amygdala excitability by decreasing the impact of GABA_A inhibitory post-synaptic potentials (122). Increased firing in the amygdala has also been observed *in vivo* after systemic CORT injections(123).

Despite these findings, it remains unclear exactly how GCs contribute to the differential regulation of the glutamate system across brain regions, though it likely involves differences in gene transcription. Additionally, much about the mechanism underlying how Li can regulate the activity of NMDA receptors and surface expression of AMPA receptors remains unknown. While differences in Li's acute and chronic effect on extrasynaptic glutamate have been attributed to these changes in receptor expression level, a detailed understanding of how Li regulates this shift in gene expression remains unknown. Investigating the timing of these mechanisms would be of particular clinical relevance, as Li treatment can take several weeks before providing symptom relief, suggesting the need for prolonged changes in gene expression.

Lithium's and glucocorticoid's role in neural plasticity through cytoskeletal regulation

The earliest evidence that Li could impact the cytoskeleton of neurons came from *in vitro* studies showing that it inhibited neurite outgrowth (24) and increased spreading of growth cone filopodia(25). Changes in growth cone morphology were linked to the phosphorylation state of MAP1B, a target of GSK3 (25, 124). Subsequently, the effect of Li on growth cones was also found to be dependent on the levels of inositol(26). Li inhibits inositol mono- and poly-phosphatase, which decreases levels of inositol triphosphate, an important second messenger implicated in the release of intracellular Ca⁺ stores (125, 126). Therefore, inositol depletion by Li is another mechanism through which Li can impact structural plasticity, as inositol replacement in cultures blocked Li's effect on growth cones(26).

Changes in growth cone shape, similar to dendritic plasticity, require actions on both microtubule stability and filamentous actin (F-actin) polymerization. Li treatment appears to increase growth cone area by causing a redistribution of F-actin to the periphery, and induces F-actin rich protrusions while axonal microtubule stability remains intact(127). As mentioned earlier, Li can mitigate the effects of stress on dendritic branching *in vivo*, where it can block dendritic atrophy in the hippocampus (9) and the expansion of the dendritic arbor in the amygdala(10). However, Li's impact on growth cone morphology is not sufficient to explain these opposing effects in different brain regions.

Interestingly, while Li was found to block the stress-induced remodeling, Li alone had no impact on neuron morphology, suggesting Li must interact with GC signaling to regulate these changes. GC levels have been shown to regulate neuronal morphology *in vivo*, particularly dendritic spine dynamics(128). The function of GR itself has been linked to the cytoskeleton, as the movement of GR from the cytoplasm to the nucleus is dependent on stable microtubules and dynein function(129). Further, GRs can regulate the transcription of cytoskeletal components such as dynein, -actin, and LIMK1 (a LIM-domain kinase involved in actin depolymerization)(130), providing a genomic mechanism through which GCs can impact cell morphology. Therefore, the ability of Li to mitigate stress-induced changes in morphology likely relies on a combination of changes in transcriptional regulation through GRs, direct effects on microtubule stability through MAP1B, and changes in F-actin

polymerization through inositol depletion (Fig. 2). Wood et al., (2004) also observed changes in pCREB and the glutamate transporter, GLT-1, suggesting that Li's action through second messengers and the glutamate system may also have an impact. Extensive additional research will be necessary to separate the functions of each pathway. Given the time-course of response to Li and the observations of differential effects in acute vs. chronic treatments, developing an understanding of the sequence of these cellular and molecular changes would yield important insights that may open the door to more rapidly effective treatments.

In the clinical literature, several cytoskeletal components have been implicated in mood disorders. Reduced expression of neurofilament-light, a post-synaptic density protein linking NMDA receptors to the cytoskeleton, was found in post-mortem brains of schizophrenics (106). Genome-wide association studies of patients with BPD have identified mutations in two cytoskeletal proteins, myosin5B (Myo5B) (131) and Ankyrin 3 (Ank3) (132, 133). Myo5B is a member of the "motor" protein family, involved in transporting cellular components along actin filaments, and has been implicated in synaptic plasticity by functioning in AMPA receptor recycling at the membrane (134).

Ank3 is an actin scaffold protein that is required for Na⁺ channel clustering near the axon hillock and therefore normal action potential firing (135, 136). It is also required for the establishment of axo-dendritic polarity (137, 138). A clinical study examining healthy first degree relatives who carry the single nucleotide polymorphism in Ank3 that is associated with BPD were found to have mild impairment on attention tasks compared to controls without the mutation, suggesting a strong association between changes in Ank3 and abnormal cognitive function (139). In animal models, Ank3 was found to be down regulated by Li treatment in whole mouse brains by microarray analysis (140). Recent work with Ank3 deficient mice has suggested that they have decreased anxiety-like behaviors that can be attenuated by Li treatment, as well as altered stress reactivity (141). Further, data from this lab has indicated that Ank3 levels can change in response to chronic stress, suggesting that it is responsive to changes in GC levels and other stress-induced alteration, and therefore may serve an essential function in the regulation of neuroplasticity (JDG-unpublished).

Imaging studies provide evidence of lithium's effects on the brain

While its mechanisms remain incompletely understood, Li clearly facilitates neuroplasticity in animal models. Magnetic resonance imaging (MRI) studies of clinical populations, particularly of BPD patients treated with Li, are beginning to provide confirmation that perhaps these same mechanisms are at work in the human brain. One of the first studies of BPD patients found that after only 4 weeks of Li treatment, 8 out of 10 subjects showed an increase in total grey matter volume (142). Magnetic resonance spectroscopy for N-acetyl-aspartate levels (NAA, a marker of neurons localized mainly to neurites) after 4 weeks of Li treatment suggested that the increase in volume was due to an increase in the neuropil (143). Subsequent work in Li patients has produced mixed results when trying to assess Li's effect on NAA levels (144, 145). However, the most recently published multi-center study found that untreated BPD patients had decreased NAA levels in prefrontal cortex compared to controls, but Li-treated patients had NAA levels no different from healthy individuals, suggesting a neuroprotective effect (146). Li's protective effects have also been confirmed in post-mortem studies of BPD patients, where no difference in number of neurons or glia was observed in Li-treated patients, but reductions in glia number were apparent in the amygdala of untreated BPD individuals (147). Further, Li-treated patients exhibited lower pCREB levels in post-mortem amygdala when compared to mood disorder patients who had died by suicide (148), providing direct evidence that Li can alter molecular function in clinical populations.

Subsequent reports have confirmed these findings in larger samples, using improved imaging techniques and study design. Researchers comparing Li-treated BPD with untreated BPD and normal controls found that the increased cortical grey matter observed can entirely be attributed to Li treatment (149). In the hippocampus, both short-term (8 week) and long-term (2-4 years) Li treatment resulted in bilateral increases in hippocampal volume (150, 151). In longitudinal studies, the changes in hippocampal volume were coincident with improvements in verbal memory, and gray matter increases correlated with treatment response in BPD, suggesting these structural changes are correlated with functional improvements (150, 152). Comparisons of Li with other forms of treatment (either anticonvulsants or antipsychotics) found that only the Li-treated patients showed increases in gray matter volume in the brain regions previously identified (153). Recent meta-analysis combining multiple imaging studies has confirmed the protective effects of Li on hippocampal size in BPD (154). The effects of Li on the amygdala have been unclear partly because reported changes in amygdala volume in BPD have been inconsistent, with some groups reporting increases (155, 156) and others reductions (157, 158). The most recent “mega-analysis,” in which individual scans from multiple studies are pooled, found increases in both hippocampal and amygdala volume in BPD patients on Li treatment (159).

Despite early studies that found no difference in white-matter volume (142), research using diffusion tensor imaging to assess the integrity of white matter tracts has identified changes in neural connectivity in BPD. Decreases in white matter density were initially found in the frontal cortex in BPD (160). Subsequent studies have also identified decreases in the corpus callosum, anterior cingulum, as well as the right inferior and left superior longitudinal fasciculus in BPD (161-163). Recently, Li was found to be protective of some of these changes, particularly of the white matter tract connecting the amygdala with subgenual cingulate cortex (164), suggesting that Li can also impact white matter density. A study of normal controls treated with Li for 4 weeks showed increases in total white matter volume and gray matter volume in the PFC (165). Li has been shown to effect expression of the myelin gene (140), however, structural plasticity of white matter tracts in response to Li is an area of research that has remained largely unexplored in animal models.

Discussion

Changes in brain structure and function in response to stress have been extensively characterized in animal models. However, the molecular mechanisms underlying these changes remain incompletely understood. Li has been shown to block many of these changes, and a number of pathways have been hypothesized to support this neuroprotective effect. Not only can Li provide trophic support to cells, but can also modulate components of the glutamate system to regulate synaptic plasticity and cytoskeletal components to regulate neuronal morphology.

Mood disorders often develop or worsen after exposure to significant environmental stress, and clinical imaging studies have identified changes in mood disorder patients in many of the same brain regions (hippocampus & amygdala) that are most sensitive to stress. Environmental challenges, possibly compounded by a genetic susceptibility, may result in a loss of plasticity after stress. These changes leave the brain “locked-in” to the disease state. Imaging of subjects treated with Li have shown marked increases in grey matter in these regions compared to untreated subjects, suggesting many of the mechanisms underlying Li's ability to facilitate plasticity may be relevant in humans. We propose that by facilitating plasticity in these regions, Li is able to “unlock” the diseased brain and thereby provide improvement in symptoms. However, it should be noted for Li and for all drug treatments that concurrent behavioral interventions are needed to direct the renewed plasticity of the brain in a beneficial direction (166, 167).

Unfortunately, Li is not always effective for the treatment of mood disorders, therefore much more research is necessary to understand how it functions, particularly how it may interact with other neurotransmitter systems, as Li has been used for several decades to augment treatment with antidepressant drugs (168). Further, while individuals suffering from mood disorders may exhibit similar symptoms, the etiology of each individual's disease may be very different. Therefore, more work will be necessary to tease apart the biological variability of mood disorders to allow clinicians to more effectively tailor pharmacological and behavioral therapies to patients. Advances in next generation high-throughput sequencing hold the promise of making such highly-specific genotype-phenotype studies more feasible in the near future.

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Abbreviations

AIH	amphetamine-induced hyperlocomotion
Ank3	ankyrin 3
Arr2	-Arrestin 2
BDNF	Brain-derived neurotrophic factor
BPD	Bi-polar disorder
FST	forced swim test
GC	glucocorticoid
GR	glucocorticoid receptor
GSK3	glycogen synthase kinase
HPA	hypothalamic pituitary adrenal
Li	lithium
MAP1B	microtubule-associated protein 1B
MDD	major depressive disorder
mEPSP	miniature excitatory post-synaptic potentials
MR	mineralocorticoid receptor
Myo5B	myosin 5B
NAA	N-acetyl-aspartate
NMDA	N-methyl-D-aspartic acid
nNOS	neuronal nitric oxide synthase
PFC	prefrontal cortex
PTSD	post-traumatic stress disorder
TrkB	tropomyosin related kinase B

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Clinical Recommendations

- Lithium may provide therapeutic benefit by facilitating neural plasticity, and helps to “unlock” the brain from a maladaptive state in response to stress
- Studies in animal models suggest lithium's effects on neural plasticity are dependent on interactions with neurotransmitter systems and intracellular pathways that regulate the cytoskeleton.
- Imaging studies support a connection between the brain regions altered in humans with mood disorders and the molecular and histological changes observed in animal models in response to stress.

Additional Comments

- Lithium alone may not be sufficient to restore plasticity, modulation of neurotransmitters systems with other pharmacological agents and behavioral therapies may be necessary
- Imaging studies implicate the same brain regions in mood disorders as those altered by stress in animal models. However, it remains possible that distinct molecular mechanisms may underlie the human clinical conditions that are not reflected in rodent models.

Figure 1. Lithium can block stress-induced changes in neuronal morphology, by exerting opposing effects in the hippocampus and amygdala

Drawings representing pyramidal cell neurons made in CA3 of hippocampus (A) and neurons of the basolateral amygdala (D) subjected to different treatment conditions. Quantification of dendritic branch length in each treatment condition shows that rats subjected to chronic restraint stress (CRS) had shorter dendrites in the hippocampus and Li was able to reverse this effect (B). However, in the amygdala stress increased dendritic length, but no difference was observed with Li treatment (E). Quantification of dendritic branch points shows that stressed animals had simpler dendritic arbors in hippocampus (C), and Li treatment during stress blocked this effect. In contrast, stress increased dendritic

branching in the basolateral amygdala and this effect was blocked by Li (F). Con = Control, CRS = Chronic restraint stress, Li = Lithium. A-C reprinted with permission from (9). D-F reprinted with permission from (10).

Figure 2. Schematic representing the molecular mechanism underlying the effects of Li on the cytoskeleton

Li administration during stressful events may modulate the transcriptional effects of GR and CREB, which can modulate cytoskeletal components and their binding partners. Inhibition of GSK3 β by Li can directly regulate the cytoskeleton through MAP1B signaling. Changes in inositol levels due to Li treatment can alter actin stability.