

Novel Insights into Lithium's Mechanism of Action: Neurotrophic and Neuroprotective Effects

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Abstract

The monovalent cation lithium partially exerts its effects by activating neurotrophic and neuroprotective cellular cascades. Here, we discuss the effects of lithium on oxidative stress, programmed cell death (apoptosis), inflammation, glial dysfunction, neurotrophic factor functioning, excitotoxicity, and mitochondrial stability. In particular, we review evidence demonstrating the action of lithium on cyclic adenosine monophosphate (cAMP)-mediated signal transduction, cAMP response element binding activation, increased expression of brain-derived neurotrophic factor, the phosphatidylinositol cascade, protein kinase C inhibition, glycogen synthase kinase 3 inhibition, and B-cell lymphoma 2 expression. Notably, we also review data from clinical studies demonstrating neurotrophic effects of lithium. We expect that a better understanding of the clinically relevant pathophysiological targets of lithium will lead to improved treatments for those who suffer from mood as well as neurodegenerative disorders.

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Over the past several years, significant evidence has expanded our understanding of how lithium might exert its mood-stabilizing properties in individuals suffering from bipolar disorder. As a result of novel insights into these mechanisms, recent work has demonstrated that this monovalent cation induces its cellular and molecular effects, at least partially, by activating neurotrophic and neuroprotective pathways and its associated signaling mechanisms. Although the changes that lithium exerts to produce mood-stabilizing effects have not been completely clarified, a growing body of evidence supports that neurotrophic cascades might be the common denominator underlying lithium's therapeutic efficacy. In this review, we evaluate each of the currently identified mechanisms of action, as well as the comparatively limited evidence available from human studies demonstrating the neurotrophic and neuroprotective effects of lithium.

Neurotrophic Signaling Cascades

Neurotrophins (NTs) are a family of regulatory factors. They are known to mediate the differentiation and survival of neurons, as well as the modulation of synaptic

transmission and synaptic plasticity. Members of the NT family include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, NT-4, NT-5, and NT-6. BDNF and other neurotrophic factors are necessary for the survival and function of neurons; thus, sustained reductions of these factors could affect neuronal viability.

The acute effects of BDNF on synaptic plasticity and neurotransmitter release include the release of glutamate, γ -aminobutyric acid, dopamine, and serotonin [1] although it is perhaps best known for its long-term neurotrophic and neuroprotective effects, which may be key to its putative role in the pathophysiology and treatment of mood disorders. Endogenous neurotrophic factors have traditionally been viewed as increasing cell survival by providing necessary trophic support; however, it is now clear that their survival-promoting effects are largely mediated by inhibiting cell death (apoptosis) cascades [1]. Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by activating the extracellular-regulated kinase (ERK) signaling pathway [cyclic adenosine monophosphate (cAMP) response element binding (CREB) is directly phosphorylated and activated by phospho-ERK1/2], the phospholipase C (PLC)- γ cascade, and the phosphoinositide 3-kinase (PI3K)/Akt pathway. Complementarily, phospho-CREB reductions observed after chronic stress [2] could subsequently downregulate the transcription of some neurotrophic genes such as B-cell lymphoma 2 (bcl-2) and BDNF (fig. 1).

Enhanced bcl-2 expression can offset the potentially deleterious consequences of stress-induced neuronal endangerment, suggesting that pharmacologically induced upregulation of bcl-2 may be useful in treating a variety of disorders associated with endogenous or acquired impairments of cellular resilience. In this context, it is notable that severe stress exacerbates stroke outcome by suppressing bcl-2 expression [3]; for instance, following ischemia, 70% less bcl-2 mRNA was expressed by mice exposed to aggressive social stress compared with unstressed mice. Furthermore, stress greatly exacerbated the infarct area in control mice, but this effect was not seen in transgenic mice constitutively expressing increased neuronal bcl-2. Similarly, high corticosterone concentrations were significantly correlated with larger infarcts in wild-type mice but not in transgenic mice overexpressing bcl-2. Overall, it is clear that the neurotrophic factor-ERK/mitogen-activated protein (MAP) kinase-bcl-2 signaling cascade plays a critical role in cell survival in the central nervous system (CNS), and that a fine balance is maintained between the levels and activities of cell survival and cell death factors. In parallel, dys-

regulation of the necessary coordination between ERK, CREB, and BDNF may also be a key mechanism via which prolonged stress induces atrophy of selective subpopulations of vulnerable neurons and/or distal dendrites. Conceivably, the precise kinetics of ERK and CREB activation could ultimately dictate whether the activated kinases participate in cell death- or survival-promoting pathways.

Lithium Modifies cAMP-Mediated Signal Transduction

Lithium has complex effects on cAMP-mediated signaling, mainly by elevating basal adenylyl cyclase (AC) activity, but also by reducing receptor-stimulated responses in both preclinical and clinical studies (reviewed in Jope [4]). G proteins modulate intracellular cAMP levels by mediating the effect of neurotransmitters (via extracellular receptors) on AC (which catalyzes the conversion of adenosine triphosphate to cAMP). Indeed, preclinical studies conducted by several independent investigators found that the ability of the receptor-mediated signal to be propagated via AC is decreased after lithium treatment [4, 5]. These extensive cellular findings are consistent with an animal model in which the cholera toxin induced G_s and G_{olf} protein hyperactivity when injected into the nucleus accumbens of rats; furthermore, cholera toxin-induced hyperactivity was decreased after lithium administration [6], consistent with decreased G_s and/or G_{olf} activity during lithium treatment (fig. 1). However, while stimulated levels were decreased, there was evidence to suggest increased basal cAMP activity [4]. These complex and potentially regional specific effects on basal activity and stimulated AC activity may arise from the effects of lithium on G proteins and AC subtypes, as well as their relative abundance in different brain regions [4].

The physiologic effects of cAMP are primarily mediated by activation of protein kinase A (PKA), an enzyme that phosphorylates and regulates many proteins including ion channels, cytoskeletal elements, transcription factors, and other enzymes. The transcription factor CREB is one of PKA's major direct targets in the CNS (PKA phosphorylates and activates CREB), and it plays a major role in long-term neuroplasticity (although the cAMP signaling pathway does much more than simply regulate CREB activity). As mentioned above, one of the genes activated by CREB is BDNF, a protein implicated in neuronal survival and synaptic plasticity. A growing

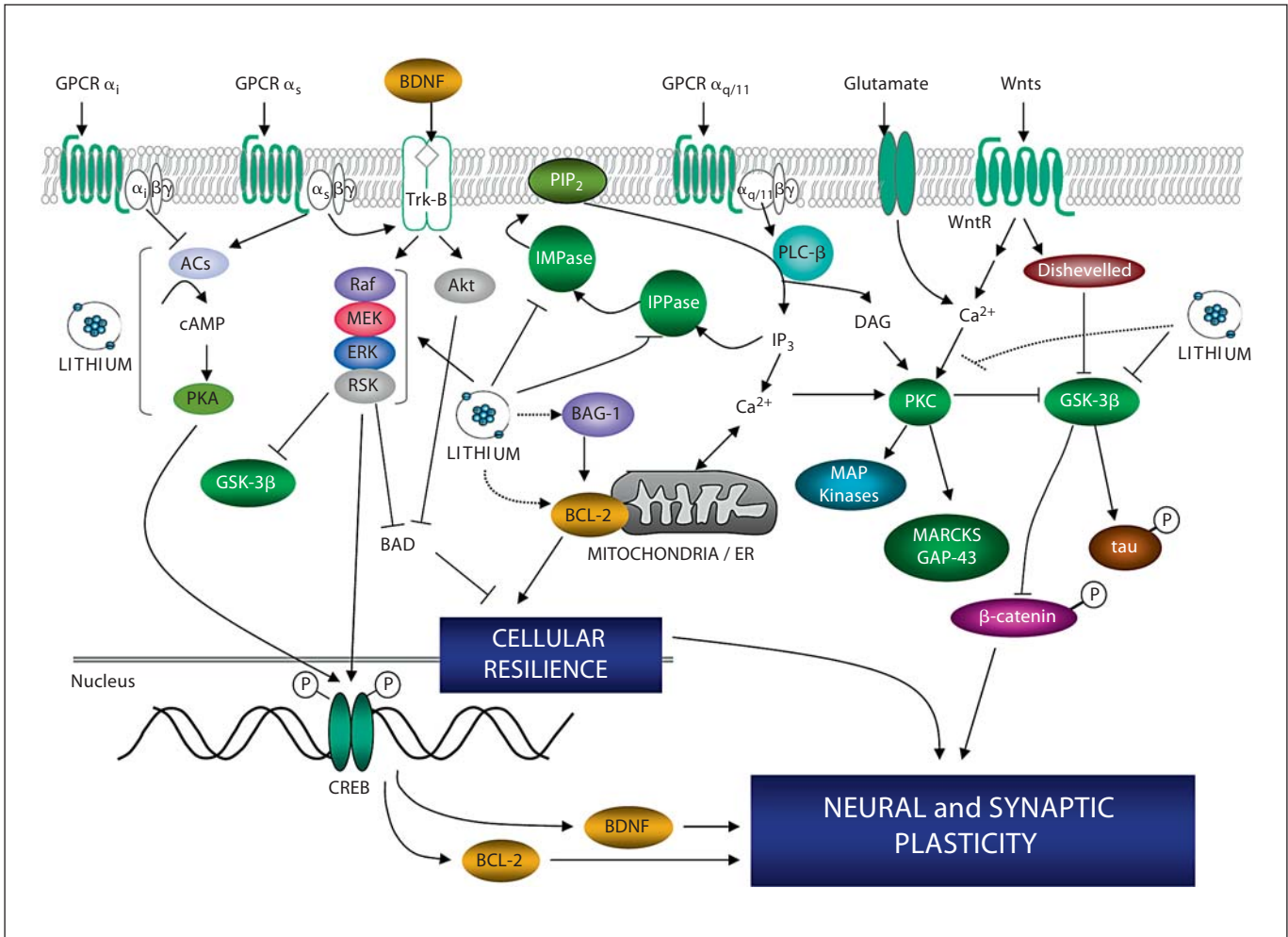


Fig. 1. Neurotrophic and neuroprotective pathways targeted by lithium. BDNF receptor (Trk-B) activation activates the ERK/ MAPK pathway, which inhibits GSK-3 β (a critical cellular target and effector for diverse proteins) and bad. This activation increases the expression of nuclear CREB, in turn facilitating the expression of neurotrophic/neuroprotective proteins such as bcl-2 and BDNF itself. Mitochondrial bcl-2 also inhibits pro-apoptotic activation of bad, as well as consequent mitochondrial increases of calcium influx and cytochrome c release. Dysregulated intracellular calcium levels, which may increase the risk of cellular apoptosis, have been associated with the pathophysiology of bipolar disorder. Lithium downregulates ER calcium release via an IP₃R-dependent mechanism, and also increases bcl-2 expression, which improves mitochondrial stability and prevents the activation of apoptotic cascades. IMPase, also directly inhibited by lithium, recycles IP₃. In addition, cellular signaling through Wnt glycoproteins and frizzled receptors inhibits GSK-3 β . Lithium's inhibition of GSK-3 β prevents β -catenin phosphorylation and stimulates its translocation to the nucleus, thus targeting the transcription of

specific genes activating neurotrophic effects and synaptogenesis. Different neurotransmitters target receptors coupled to G proteins. Among these, D₁, D₅, and β -adrenergic receptors are coupled to G α stimulatory proteins that activate AC; H₃, D₂, D₃, and D₄ receptors are coupled to G α inhibitory proteins that inhibit AC; serotonergic, α_1 -adrenergic, M₁, M₃, and M₅ receptors are coupled to G $\alpha_{q/11}$, which activates PLC. PLC, in turn, hydrolyses PIP₂ to IP₃ and DAG. DAG activates PKC, which plays a significant role in regulating pre- and postsynaptic aspects of neurotransmission and diverse cellular processes. Lithium also indirectly inhibits PKC. The text provides a complete description of these interactions. Arrows represent 'activation', perpendicular lines represent 'inhibition', and dotted lines represent 'indirect effects'. bad = bcl-2-associated death promoter; bag-1 = bcl-2-associated athanogene; GPCR = G-protein-coupled receptors; IP₃R = IP₃ receptor; MARCKS = myristoylated alanine-rich C kinase substrate; Raf, MEK, ERK, RSK = components of the ERK pathway; Trk-B = tropomyosin receptor kinase.

body of data suggests that agents that directly modulate the cAMP-PKA-CREB-BDNF signaling cascade may be of particular interest for the development of novel agents to treat depressive disorders [7]. Interestingly, lithium and valproate – both of which are mood stabilizers used in the treatment of bipolar disorder – are known to increase BDNF levels in the brains of rats treated chronically with these drugs [8–10].

Lithium Activates CREB and Increases BDNF Expression

At therapeutically relevant concentrations, both lithium and valproate activated the ERK/MAP kinase cascade in human neuroblastoma SH-SY5Y cells *in vitro* [11]; *in vivo*, these agents activated the same cascade in the hippocampus and frontal cortex areas of the rodent brain [8]. Lithium also activated ERK1/2 after ischemia, and significantly increased cell proliferation in the hippocampal dentate gyrus [12]. Via CREB, the activation of the ERK/MAP kinase pathway initiates the transcription of BDNF, and also induces bcl-2 gene expression. Consistent with the activation of neurotrophic signaling cascades, chronic treatment of rats with therapeutically equivalent lithium or valproate concentrations increased the activation of ribosomal S6 kinase (a member of the MAPK signaling pathway) and CREB, and eventually doubled bcl-2 levels in the frontal cortex, as evidenced by an increased number of bcl-2 immunoreactive cells in layers II and III of the frontal cortex [13–16].

Several preclinical studies have also investigated the effects of lithium on CREB phosphorylation and activity with mixed overall results [8, 17, 18]. For instance, administration of lithium or valproate increased expression of BDNF in the rodent brain [8, 9], particularly in the hippocampus [19] and frontal cortex [20]. Therapeutic concentrations of lithium selectively increased levels of exon IV-containing BDNF mRNA, and the activity of BDNF promoter IV [21]. While studies have obtained both positive and negative results after lithium exposure [22, 23], most recent evidence suggests that the neurotrophic effect of lithium in cortical neurons requires BDNF expression [24]. In humans, recent data suggested that the Val66Met BDNF gene polymorphism may be associated with the degree of prophylactic response to lithium; there was a trend for the Met allele genotype to be associated with a higher incidence in positive responders to lithium compared to nonresponders [25]. On the other hand, postmortem studies have noted that individuals with bi-

polar disorder treated with lithium had reduced CREB phosphorylation [26, 27], although the postmortem instability of phosphorylated proteins is a well-known concern in interpreting such reports.

Finally, the modification of other neurotrophic factors has also been associated with chronic lithium treatment. Changes in NGF and glial cell line-derived neurotrophic factor were observed in a rat model of depression [10], including significant increases of NGF concentrations in the frontal cortex, limbic forebrain, hippocampus, and amygdala of adult rats [28]. Lithium also increased serum and hippocampal NT-3 levels in an animal model of mania [29], and upregulated vascular endothelial growth factor in brain endothelial cells and astrocytes [30]. Interestingly, vascular endothelial growth factor has been implicated in neuronal survival, neurotrophic effects, regeneration, growth, and differentiation. Consistent with these effects on neurotrophic signaling cascades, lithium was found to be neuroprotective in other animal and cell models of neuronal insult and disease [31, 32], to promote neurogenesis in the hippocampus of rats, and to increase the regeneration of CNS axons [33].

Lithium Modifies the PI Cascade and Inhibits Protein Kinase C

Inositol phospholipids play a key role in receptor-mediated signal transduction pathways, and are implicated in a variety of responses including cell division, secretion, neuronal excitability, and responsiveness. The PI pathway is initiated by the activation of G-protein-coupled receptors, which pair neurotransmitter receptors to multiple types of intracellular effector proteins. M1, M2, M3, α_1 , and serotonin receptors coupled to $G\alpha_{q/11}$ induce PLC, which hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP₂) to yield 2 second messengers: inositol-1,4,5-triphosphate (IP₃) and diacylglycerol (DAG). IP₃ and DAG subsequently modulate the activity of many intracellular events. IP₃ binds to the IP₃ receptor [facilitating the release of calcium from intracellular stores, particularly in the endoplasmic reticulum (ER)] [34, 35], and DAG activates protein kinase C (PKC) (fig. 1).

The direct effect of lithium on inositol monophosphatase (IMPase) [36, 37] and, secondarily, on inositol polyphosphate 1-phosphatase [38, 39] led to the inositol depletion hypothesis of lithium action [40, 41]. This hypothesis suggests that lithium exerts its mood-stabilizing effects by inhibiting IMPase, thereby decreasing inositol concentrations and the amount of PIP₂ available for signal-

ing cascades that rely upon this pathway; this includes, but is not limited to, the neurotrophin signaling pathways, the receptor tyrosine kinase pathways, and the G-protein-mediated signaling, all of which rely on PI availability [40]. The brain is believed to be particularly sensitive to lithium, due to the relatively poor penetration of inositol across the blood-brain barrier [40] or to a reduced ability of specific neuronal populations to transport inositol across their cell membranes [42]. In fact, it has been shown that lithium, carbamazepine, and valproate inhibit sodium myo-inositol transporter 1 (SMIT1) on astrocyte-like cells at therapeutically relevant concentrations [43]. More recently, homozygote knockout mice for the SMIT1 gene (receiving inositol supplementation) appeared to behave similarly to lithium-treated animals in seizure and depression models [44]. However, it has also been reported that reduced intracellular inositol in the brains of SMIT1 knockout mice had no effect on PI levels [45], suggesting that inositol depletion may not have major effects on PI-mediated signaling in this paradigm. Importantly, it has also been reported that the content of SMIT1 mRNA in neutrophils of untreated patients with bipolar I disorder is higher than in a control population while the levels are reduced in treated versus control and untreated bipolar subjects [46]. Although there are some limitations associated with the peripheral nature of the cells studied (that may not reflect brain pathophysiology) and the post hoc origin of the analysis, this hypothesis generating research confirms the need to better understand the role that PI pathways play in bipolar disorder.

As mentioned above, lithium interacts with the PI/PKC pathway by inhibiting IMPase, resulting in decreased free myo-inositol and the subsequent production of DAG, with the downstream effect of also decreasing PKC levels and activity (in some cell culture models, there is evidence of a biphasic action showing initial PKC activation followed by downregulation). PKC is an omnipresent enzyme, and highly enriched in the brain, where it regulates both pre- and postsynaptic aspects of neurotransmission [47], as well as several cellular processes. These include the stimulation of transmembrane glucose transport, secretion, exocytosis, smooth muscle contraction, gene expression, modulation of ion conductance, cell proliferation, and desensitization of extracellular receptors [47]. Interestingly, certain PKC isoforms phosphorylate and inactivate glycogen synthase kinase 3 (GSK-3) *in vitro* [48] (see below).

PKC isoforms differ in their structure, subcellular localization, tissue specificity, mode of activation, and sub-

strate specificity. It is important to note that chronic lithium treatment decreases the level of PKC isozymes α and ϵ [49–51] in cells as well as in treated rodents (in part due to the ability of lithium to inhibit IMPase [32, 49]). Following chronic treatment in rats, lithium also decreases the levels and phosphorylation of myristoylated alanine-rich C kinase substrate, a major PKC substrate that has been implicated in signaling and neuroplastic events associated with cytoskeletal architecture [52, 53].

Taken together with the abundant preclinical biochemical and behavioral data supporting the notion that PKC activity may mediate manic-like behaviors, the inhibition of PKC by lithium led to a series of hypothesis-driven clinical studies investigating this relationship. The first study of a fairly selective PKC inhibitor in humans was a small, open-label trial of tamoxifen, which was found to produce a greater than 50% decrease in manic symptoms in 5 of 7 subjects [54]. Furthermore, this effect was very recently confirmed in 2 double-blind, placebo-controlled studies of acutely manic patients by the original researchers [55], and by an independent group of investigators [56].

Action of Lithium on the Arachidonic Acid Signaling Cascade

Lithium also plays an important role in the arachidonic acid (AA) cascade. AA is an important mediator of second messenger pathways in the brain [57, 58], and is released from membrane phospholipids via the activation of receptor/G-protein-initiated phospholipase A2 (PLA2) [59]. This results in AA release from the cellular membrane, and cyclooxygenase-mediated production of eicosanoid metabolites such as prostaglandins and thromboxanes. Due to their lipid-permeable nature, these metabolites mediate numerous subsequent intracellular responses as well as transynaptic responses. In rats, treatment with lithium or valproate resulted in selective reductions in the turnover rate in the brain phospholipids of AA [60–62]. In the case of lithium, an 80% reduction of AA turnover was observed. In addition, lithium decreased the gene expression and protein levels of an AA-specific PLA2 (specifically, cytosolic PLA2) [63, 64], as well as cyclooxygenase 2 protein levels [65]. These findings suggest that the effects of mood stabilizers on cell membranes – and specifically on AA turnover – might be relevant to the pharmacological action of mood stabilizers [58, 62].

Competition of Lithium with Magnesium

Lithium also inhibits some enzymes through direct competition with magnesium, an often-required cofactor [5, 66, 67]. At least 4 related phosphomonoesterases are significantly inhibited at therapeutic serum lithium concentrations [68] (0.6–1.2 mM); in mammals, this group of magnesium-dependent, lithium-sensitive phosphatases includes inositol polyphosphate 1-phosphatase and IMPase (discussed above), fructose 1,6-bisphosphatase, bisphosphate nucleotidase [69], and phosphoglucomutase [70–73]. A significant amount of research has focused on IMPase as a possible therapeutically relevant target of lithium inhibition, predominantly due to the role this enzyme plays in CNS functions [74].

GSK-3 Inhibition by Lithium

GSK-3 is a serine/threonine kinase that regulates diverse cellular processes and directly regulates cell apoptosis. It is key to glycogen synthesis, gene transcription, synaptic plasticity, apoptosis (cell death), cellular structure and resilience, and the circadian cycle [75], all of which are significantly implicated in the pathophysiology of severe recurrent mood disorders. In 1996, GSK-3 was identified as the lithium target responsible for developmental effects in *Xenopus* embryos [76], but more recently, further evidence substantially supports the claim that GSK-3 is one of the *therapeutic* targets of lithium.

GSK-3 β activation functionally inhibits CREB, β -catenin (an important component of memory consolidation), and other survival-promoting transcription factors. GSK-3 is also directly regulated by signals originating from a number of different signaling pathways including the Wnt pathway, the PI3K pathway, PKA, and PKC. Its other targets include transcription factors like c-Jun, proteins bound to microtubules (Tau, microtubule-associated protein 1B, kinesin light chain), cell cycle mediators (cyclin D), and metabolic regulators (glycogen synthase, pyruvate dehydrogenase) [77]. GSK-3 also directly regulates the dopaminergic, glutamatergic, and serotonergic neurotransmitter systems (reviewed in Beaulieu et al. [78] and Jope and Roh [79]). It is interesting to note that increases in phosphorylated GSK-3 levels have also been observed by 5-HT1A receptor activation, 5-HT2 receptor blockage [80], and by atypical antipsychotic administration (with D₂ but also 5-HT2A blocking activity) in experiments with mice [81].

Early studies suggested that peripheral administration of lithium inhibited GSK-3 in the brains of 7-day-old rats [82], as well as during long-term treatment at therapeutic concentrations. Investigators also found that 9 days of lithium treatment in rats (at a mean serum concentration of 0.8 mM) increased cytosolic protein levels of β -catenin, a transcription factor directly regulated by GSK-3 [83]. Small but significant decreases in β -catenin mRNA levels (reflecting cellular compensation) accompanied this increase, further suggesting that lithium exerted its actions post-translationally by inhibiting GSK-3 [83]. Similar findings have noted that chronic lithium does indeed activate β -catenin-dependent transcription in the mouse brain [84] (fig. 1).

Because GSK-3 inhibition is commonly associated with the neurotrophic effects of different survival factors, this kinase may mediate the neuroprotective effects of lithium. In fact, GSK-3 inhibition directly influences gene transcription, leading to anti-apoptotic effects and improved cell structural stability [85]. Notably, diverse studies have noted that GSK-3 is downregulated by lithium, thereby inducing direct neuronal protection against different injuries [86], and providing new insights into the neurotrophic effects of lithium (reviewed in Jope [4]). Furthermore, recent evidence suggests that the behavioral effects of lithium, at least in rodent models, may also be due to GSK-3 inhibition. For instance, the administration of GSK-3 inhibitors resulted in antidepressant-like effects in the forced swim test paradigm following either peripheral lithium administration in rats [71], or lithium administration in mice [84], including intracerebral ventricle injections in mice [87]. While initial reports suggested that knocking out a single copy of the GSK-3 β gene in mice resulted in antidepressant-like effects analogous to lithium administration [84], these findings were subsequently not confirmed in mice of a different genetic background [88].

More recently, transgenic mice overexpressing β -catenin demonstrated changes comparable to those observed following lithium administration. These changes included decreased immobility time in the forced swim test and the inhibition of D-amphetamine-induced hyperlocomotion. Such findings are consistent with the notion that the behavioral effects of lithium are mediated via direct inhibition of GSK-3 and the consequent increase in β -catenin [89].

Effect of Lithium on bcl-2 and Mitochondrial Function

The regulatory effects of lithium on apoptosis-controlling proteins appear to occur in both the mitochondria [35] and the ER [90–92]. Relatedly, altered calcium dynamics are the most reproducible biological measure in the pathophysiology of bipolar disorder (reviewed in Quiroz et al. [35] and Warsh et al. [93]). A large movement of calcium into the mitochondria will exceed the mitochondrial capacity to export protons, potentially interrupting adenosine triphosphate synthesis and the activation of the permeability transition pore with release of cytochrome c, thus initiating cellular apoptosis [35]. In addition, excessive production of reactive oxygen species (or free radicals) triggered by mitochondrial dysfunction may lead to oxidative stress, regardless of whether or not this is related to lower antioxidant capacity.

Mitochondria are well known for their critical role in regulating energy production via oxidative phosphorylation, regulation of intracellular calcium, and as critical mediators of cellular apoptosis. Increasing evidence suggests that they may also be integrally involved in general processes of synaptic plasticity [35]. As noted previously, the bcl-2 family of proteins includes both pro- and anti-apoptotic proteins embedded in the inner mitochondrial membrane, although they may also be present in nuclear membranes and in the ER. Therefore, expression and/or activation of pro-apoptotic bcl-2 family members (e.g. bad and bax) may increase mitochondrial membrane permeability, while anti-apoptotic members (e.g. bcl-2 and bcl-xl) have the opposite effect [35]. Interestingly, lithium also increases the expression of bcl-2-associated athanogene (bag-1), which is known to attenuate glucocorticoid receptor nuclear translocation, to activate the ERK/MAP kinases, and to potentiate the anti-apoptotic functions of bcl-2 [94] (fig. 1).

Several biochemical changes have been hypothesized to account for the neurotrophic properties of lithium against oxidative stress and apoptosis, including its ability to regulate bcl-2. bcl-2 levels were found to be robustly increased in the frontal cortex after lithium treatment, particularly in layers II and III [13]. Also, long-term lithium treatment of cultured cerebellar granule cells induced concentration-dependent decreases in p53 mRNA levels as well as bax protein levels (both of which are pro-apoptotic), while acute treatment had no effect. Conversely, bcl-2 mRNA and protein levels increased considerably with long-term lithium treatment, and the bcl-2/bax protein level ratio increased approximately 5-fold af-

ter lithium treatment for 5–7 days [16]. Furthermore, chronic treatment with lithium in drinking water prevented the aluminum-induced translocation of cytochrome c, upregulating bcl-2 and bcl-xl, and thus reducing DNA damage. As noted previously, animal models have also noted a relationship between stress and bcl-2 expression.

Human Studies Demonstrating the Neurotrophic Effects of Lithium

While the preclinical data demonstrating that lithium has neurotrophic and neuroprotective effects are striking, considerable caution must be exercised in extrapolating these data to human clinical situations, where the data regarding the neurotrophic effects of lithium are considerably more limited.

The most replicated finding from structural neuroimaging studies is the association between lithium treatment and increased gray matter (GM) volume in brain areas implicated in emotional processing and cognitive control, including the anterior cingulate gyrus, amygdala, and hippocampus [95, 96]. In structural studies, re-analyzed data demonstrated approximately 40% reductions in subgenual prefrontal cortex volumes in individuals with familial mood disorders [97]. These investigators also studied glial cell densities in a small number of individuals with major depressive disorder and found that they exhibited reduced glial cell densities; in contrast, in individuals with bipolar disorder, only those who had discontinued chronic treatment with lithium or valproate exhibited similar reductions [98], suggesting that these mood stabilizers conferred neuroprotective properties.

More recently, a longitudinal high-resolution volumetric MRI study of well-characterized, medication-free individuals with bipolar depression compared total brain GM, prefrontal GM, and left subgenual GM at baseline and after 4 weeks of blinded lithium treatment [93]. Significant increases in total brain GM were observed after chronic lithium administration. Furthermore, region-specific analyses revealed significant differences between lithium responders (>50% decrease in Hamilton Depression Rating Scale scores) and nonresponders; only the lithium responders had significant increases in GM volume in the prefrontal cortex and a trend level increase in the left subgenual prefrontal cortex volume [99]. Another study found that individuals with bipolar disorder not treated with lithium had significantly reduced left ante-

rior cingulate volumes compared to healthy volunteers and lithium-treated patients [100]. Additional MRI studies compared GM and white matter volumes in untreated and lithium-treated patients with bipolar disorder and healthy controls, and found that total GM volume was significantly higher in individuals treated with lithium than in untreated patients and healthy controls [101]. GM density was also found to be significantly greater in diffuse cortical regions in individuals with bipolar disorder who were treated with lithium relative to healthy controls [102]. Interestingly, total hippocampal volume was also significantly greater in lithium-treated patients with bipolar disorder compared with healthy controls or unmedicated patients (by 10 and 14%, respectively) [103], also shown in both short-term (1–8 weeks) and long-term lithium treatment in drug-naïve bipolar subjects [104, 105].

Future Directions: The Neurotrophic Effects of Lithium Might Be Relevant in the Treatment of Other Neuropsychiatric Disorders

As the evidence reviewed above makes clear, lithium has garnered considerable interest as a neuroprotective drug. Data from many *in vitro* models have evaluated the properties of lithium against excitotoxicity or apoptosis, including glutamate-induced excitotoxicity, C₂-ceramide-induced apoptosis, oxygen and glucose deprivation, aluminum, low potassium medium, ouabain-induced LDH, b-bungarotoxin, and pilocarpine-induced mossy fiber sprouting (reviewed in Bowley et al. [98]). This evidence has prompted a considerable amount of research in an effort to clarify the pathophysiological role of the neuroprotective properties of lithium in animal models of several human diseases. These include models of brain ischemia, injury (especially spinal cord and optic

nerve injury), infection, irradiation, neurodegeneration and neuroinflammation, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, HIV-associated cognitive impairments, spinocerebellar ataxia, and cranial irradiation (reviewed in Machado-Vieira et al. [106]). Interestingly, lithium also appears to stimulate the biogenesis of mitochondria in the CNS and spinal cord, thus inducing neurogenesis and neuronal differentiation also in subjects with amyotrophic lateral sclerosis [107]. Promising preliminary results were obtained from these preclinical studies, leading to current epidemiological and clinical studies addressing the putative use of lithium in human populations. While the results are still to come, these are expected to significantly improve our understanding of these devastating diseases.

Conclusions

Recent studies investigating the robust neurotrophic and neuroprotective effects of lithium have identified novel, exciting, and promising targets. Due to the accumulating data linking lithium mechanisms of action with the enhancement of neurotrophic cascades and pathways, we are optimistic that this evidence will ultimately lead to a better understanding of clinically relevant pathophysiological targets, and the consequent development of improved treatments for those who suffer from these devastating psychiatric and neurodegenerative disorders.

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