

A new look at an old drug: neuroprotective effects and therapeutic potentials of lithium salts

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Abstract: Increasing evidence highlights bipolar disorder as being associated with impaired neurogenesis, cellular plasticity, and resiliency, as well as with cell atrophy or loss in specific brain regions. This has led most recent research to focus on the possible neuroprotective effects of medications, and particularly interesting findings have emerged for lithium. A growing body of evidence from preclinical in vitro and in vivo studies has in fact documented its neuroprotective effects from different insults acting on cellular signaling pathways, both preventing apoptosis and increasing neurotrophins and cell-survival molecules. Furthermore, positive effects of lithium on neurogenesis, brain remodeling, angiogenesis, mesenchymal stem cells functioning, and inflammation have been revealed, with a key role played through the inhibition of the glycogen synthase kinase-3, a serine/threonine kinase implicated in the pathogenesis of many neuropsychiatric disorders. These recent evidences suggest the potential utility of lithium in the treatment of neurodegenerative diseases, neurodevelopmental disorders, and hypoxic-ischemic/traumatic brain injury, with positive results at even lower lithium doses than those traditionally considered to be antimanic. The aim of this review is to briefly summarize the potential benefits of lithium salts on neuroprotection and neuroregeneration, emphasizing preclinical and clinical evidence suggesting new therapeutic potentials of this drug beyond its mood stabilizing properties.

Keywords: bipolar disorder, GSK-3, neurodegeneration, neurogenesis, neurodevelopmental disorders

Introduction

Lithium is still considered a first-line therapy for both the acute and long-term treatment of bipolar disorder (BD),¹ due to its well-documented antimanic,² antisuicidal,³⁻⁵ and prophylactic properties^{6,7} and the adjunctive treatment of major depression.⁸ Although all potential mechanisms underlying lithium mood-stabilizing properties have not yet been completely clarified, a growing body of evidence has recently suggested the potential benefits on neuroprotection and neuroplasticity of this drug.

There is now evidence that BD is related to progressive impairment in neurocognitive functioning, as well as to regional impairments in neuroplasticity, cellular resilience, and adult neurogenesis.⁹⁻¹⁵ Morphometric brain-imaging studies, in fact, have documented cell atrophy or loss in several brain areas, especially prefrontal regions (eg, anterior cingulate and subgenual prefrontal cortex), as well as hippocampal volume decrease and smaller amygdalar volumes, in both adult and pediatric BD patients compared with healthy control subjects.¹⁶⁻²⁰ Such regional brain abnormalities have been suggested to play a role in the pathophysiology of BD, giving rise to the debate as to whether they derive from neurodevelopmental, neurodegenerative, or combined deficits.^{10,21,22}

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Consistently, most recent research studies have progressively focused on the possible neuroprotective effects of psychotropic medications for BD, and interesting results have particularly emerged for lithium salts.

This review aims to briefly summarize the most recent evidence on lithium benefits beyond its mood-stabilizing properties, with particular attention to its potential effects on neuroprotection and neuroregeneration, in both preclinical and clinical studies, highlighting possible new therapeutic potentials of this old drug.

Methodology

MEDLINE/PubMed (1985–2015) articles published in English were identified using the following keyword combinations: lithium, bipolar disorder, neuroprotection, neurogenesis, neurodegenerative disorders, neurodevelopmental disorders, autism, and glycogen synthase kinase-3 (GSK-3).

Neuroimaging outcomes of lithium treatment in BD

Several neuroimaging studies in BD patients have shown lithium treatment to increase cortical gray matter volumes, especially in the anterior cingulate and in the paralimbic cortices that are implicated in attention, motivation, and emotional modulation, as well as the hippocampus volume.^{18,19,23–30} The association between lithium treatment and gray matter volume increase has been demonstrated regardless of the mood state, the diagnostic subtype, and presence or absence of concomitant medications.³¹

However, the nature and mechanisms of this positive association remain to be clarified in terms of whether these may depend on a direct effect of lithium on brain structures, through its action on the biochemical pathways involved in neurogenesis and apoptosis, or whether these are an epiphenomenon of the acute or prophylactic lithium efficacy. In a neuroimaging study using voxel-based morphometry, Hajek et al³² recently demonstrated that the positive association between lithium treatment and increase in hippocampal volume seems to be independent of long-term treatment response, as occurred also in those BD patients on lithium who reported episodes of illness while on treatment. Additional evidence comes from studies using quantitative proton magnetic resonance spectroscopy to measure cortex levels of N-acetyl-aspartate (NAA), a marker of neuronal viability and/or functioning, in BD patients. Chronic lithium treatment was found to increase NAA levels in both BD patients and healthy controls.^{33,34} In a study comparing two groups of BD patients with a similar illness burden but differing lithium levels of exposure with respect to healthy control subjects, prefrontal NAA levels

were found to be lower in patients without or with limited lifetime exposure to lithium compared with those under ongoing lithium treatment or controls.³⁵ Furthermore, these two latter groups of participants did not differ in terms of NAA levels; a negative correlation between prefrontal NAA and duration of illness was found only in the group of patients not exposed or with limited exposure to lithium. This lithium effect on NAA levels was suggested to be related to the expansion of neuropil content, accordingly with the evidence of lithium-induced increase in gray matter volumes.

Since the neuroprotective effects of lithium on brain structures have been shown even in healthy subjects and appear to be independent from prophylactic treatment response, Hajek and Weiner³¹ recently hypothesized that lithium treatment might help maintain brain health even in patients without BD and could possibly demonstrate disease-modifying properties in neurodegenerative disorders. In this regard, Forlenza et al³⁶ evaluated whether the neurobiological properties of lithium reflect in increased regional brain glucose metabolism with the aid of 18 fluorine-fluoro-2-deoxy-d-glucose positron emission tomography in a sample of 19 older adults with amnesic mild cognitive impairment. The exposure to subtherapeutic levels of lithium carbonate (0.25–0.5 mEq/L) for 4 years in 12 of these patients was associated with a significant reduction in the glucose uptake in several clusters of the cerebellum and in both hippocampi, in comparison with matched controls. These results do not support the hypothesis that lithium might increase regional brain metabolism as a consequence of its neurotrophic effects. However, none of the patients in the sample reported any clinically relevant signs of lithium toxicity. Future studies with appropriate methodology are needed to address the clinical implications of these findings, particularly in light of the potential use of lithium as a disease-modifying treatment approach for certain neurodegenerative disorders.

Neuroprotective effects of lithium: preclinical evidence and molecular mechanisms

A number of preclinical *in vitro* and *in vivo* studies have documented a neuroprotective effect of lithium against neuronal injury caused by various noxious insults, mainly acted by preventing apoptosis and increasing neurotrophins excretion.^{9,13,37–40} Additional neuroprotective mechanisms include the modulation of autophagy and oxidative stress and the upregulation of mitochondrial function.⁴¹ Furthermore, lithium appears to reduce proinflammatory status, by modulating inflammatory activity.^{42–46}

In particular, lithium has been shown to inhibit GSK-3 α and GSK-3 β ; upregulate neurotrophins and cell survival

molecules (eg, B-cell lymphoma 2 [Bcl-2], brain-derived neurotrophic factor [BDNF]/tropomyosin receptor kinase B [TrkB], cyclic adenosine monophosphate-responsive element-binding protein [CREB], heat shock protein 70 [Hsp70], and β -catenin); downregulate proapoptotic activities (eg, excitotoxicity, p53, Bcl-2-associated X protein, caspase, cytochrome c release, β -amyloid peptide production, and tau hyperphosphorylation); inactivate N-methyl-D-aspartate (NMDA) receptors; inhibit inositol monophosphatase (IMP); and activate the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) cell survival pathway.^{38,47–56} Such a wide range of intracellular responses involved in the neuroprotective action of lithium may be secondary to its inhibitory effect on two key targets, namely, GSK-3 β and IMP. The modification of these intracellular pathways is relevant to the understanding of the pathogenesis of certain neuropsychiatric and neurodegenerative diseases (Figure 1).⁴¹

Lithium inhibition of the GSK-3, both direct binding to the magnesium-sensitive site of the enzyme and indirect, enhancing the phosphorylation of specific N-terminal serine residues, has been demonstrated to play a major role for lithium neuroprotective functions.^{53,57} There is also evidence of lithium modulation of GSK-3 β expression at the transcriptional level in a dose-dependent manner, as a consequence of the inhibition of mRNA transcription.⁵⁸ The GSK-3 is a serine/threonine kinase that regulates several cellular processes, such as glycogen synthesis, gene transcription, synaptic plasticity, cell apoptosis, cellular structure and resilience, and the circadian cycle.⁵³ Its activation functionally inhibits CREB, β -catenin, and other survival-promoting transcription factors. Conversely, its inactivation has been suggested to promote neuronal survival and to improve cell structural stability directly influencing gene transcription.^{50,59–61} In addition, GSK-3 directly regulates several neurotransmitter systems, including serotonergic, dopaminergic, cholinergic, and glutamatergic.^{62,63} Because of changes in these neurotransmitter systems, dysregulated GSK-3 has been linked to depression, BD, and schizophrenia.

The GSK-3 is also implicated in the pathogenesis of many neuropsychiatric disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), spinocerebellar ataxia type 1 (SCA1), multiple sclerosis (MS), fragile X syndrome (FXS), Down syndrome (DS), traumatic brain injury (TBI), and ischemic stroke.^{40,64–72} It represents the predominant kinase in the brain responsible for the aberrantly hyperphosphorylation of the tau protein and also plays a major role in the amyloid deposition affecting the core pathological features of AD.^{68,73,74} Therapeutic concentrations of lithium, through the inhibition of the GSK-3, have been demonstrated to

significantly lower the levels of the tau phosphorylation in living cells and neurons, thus reducing the levels of aggregated, insoluble tau.^{75,76} Further, they have been demonstrated to block both the production of amyloid-beta peptides, by interfering with the amyloid precursor protein cleavage, and the accumulation of amyloid-beta peptides in the brain of mice that overproduce amyloid precursor protein.⁷⁶

Both the downregulation of GSK-3 β and the elevated β -catenin, two components of the canonical Wnt signaling pathway, were implicated in adult hippocampal progenitor cell proliferation triggered by lithium treatment.⁷⁷ The GSK-3 may regulate cognitive functions by influencing the components of synaptic plasticity that are long-term depression (LTD) and long-term potentiation (LTP), involved in the regulation of learning and memory.^{78,79} This kinase is a key regulator of the balance between pro- and anti-inflammatory cytokine production in both the peripheral and the central nervous system and influences T-cell proliferation, differentiation and survival, so that its inhibition determines anti-inflammatory effects.⁴² Administration of GSK-3 inhibitors in mice has been shown to control several inflammatory and immune conditions in both the periphery and the central nervous system.⁴² The inhibition of GSK-3, as well as its genetic inactivation, has also produced antidepressive-like behaviors and strong anti-manic-like effects in a wide range of animal models.^{80–87} According to this, a deficient inhibition of GSK-3 has been linked to an increased susceptibility to mood disorders.⁸⁷ The finding that transgenic mice overexpressing β -catenin demonstrate behavioral changes comparable to those observed after lithium administration gives further support to the notion that the therapeutic effects of lithium are mediated by the inhibition of GSK-3 and the consequent increase in β -catenin levels.⁸⁸

As mentioned earlier, chronic inhibition of GSK-3 may mediate the neuroprotective effects of lithium in the long term by stimulating the gene and protein expression of antiapoptotic factors (eg, CREB, nuclear factor kappa-light-chain-enhancer of activated B-cells [NF- κ B], Bcl-2, BDNF, β -catenin).^{81,89} In particular, preclinical studies in rat brains and human neurons showed chronic lithium administration to induce prominent neuroprotective and neurotrophic proteins, such as Bcl-2 and BDNF.^{48,51,90,91} The Bcl-2 not only is a major antiapoptotic protein but also stimulates axonal regeneration following injury.^{55,92} The upregulation of Bcl-2 by lithium has been postulated to account for the neuropil expansion manifesting as an increase in gray matter volume in the human brain.^{18,55} Interestingly, also the chronic administration of low lithium doses, producing plasma levels of \sim 0.35 mM, showed to robustly increase Bcl-2 levels in the frontal cortex and

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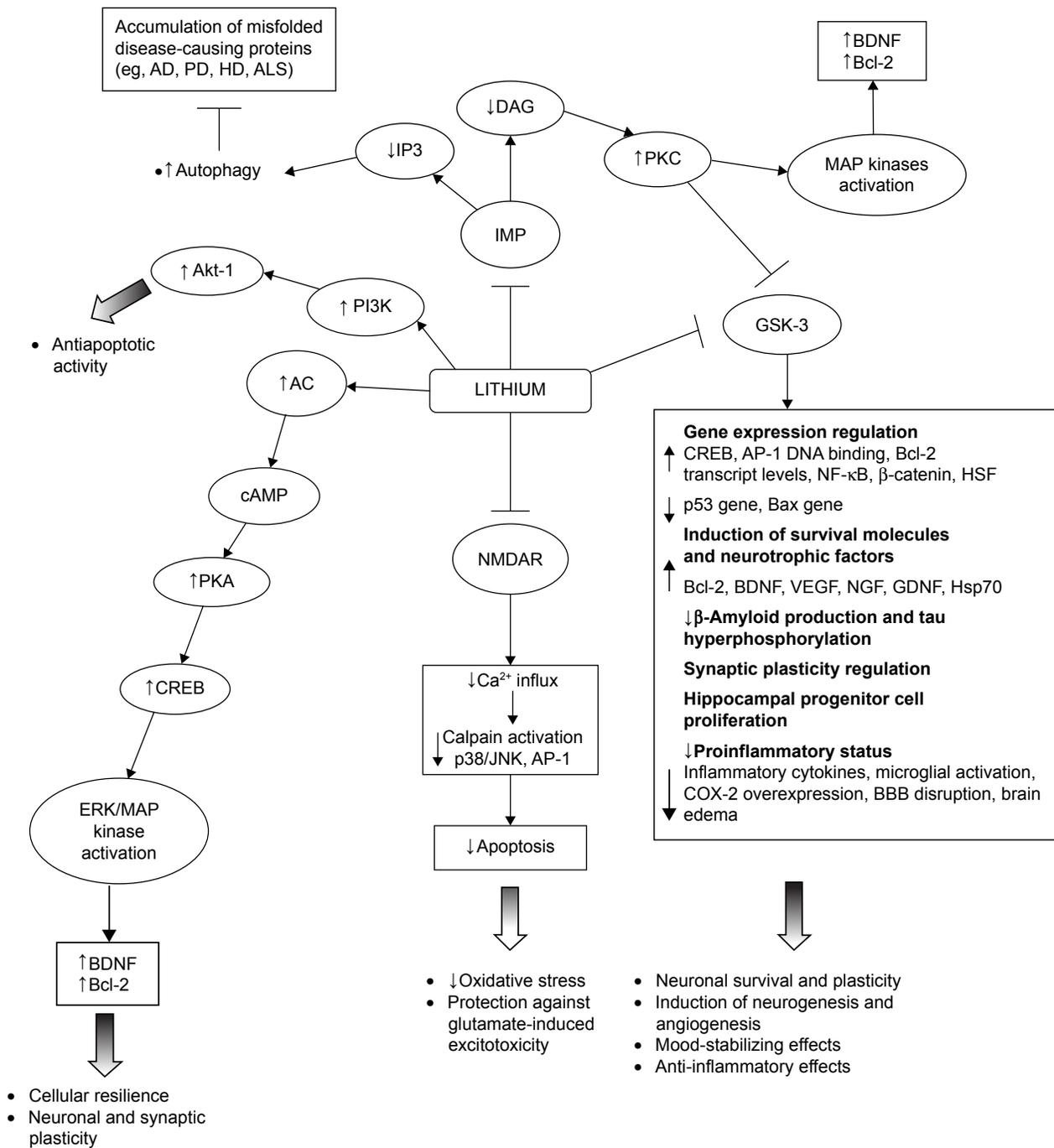


Figure 1 A schematic illustration of neurotrophic and neuroprotective mechanisms targeted by lithium.

Abbreviations: ↓, decrease; ↑, increase; AC, adenyl cyclase; AD, Alzheimer's disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; AP-1, activator protein-1; BBB, blood-brain barrier; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; COX-2, cyclooxygenase-2; CREB, cAMP-responsive element-binding protein; DAG, diacylglycerol; ERK, extracellular-regulated kinase; GDNF, glial cell line-derived neurotrophic factor; GSK-3, glycogen synthase kinase-3; HD, Huntington's disease; HSF, heat shock factor; Hsp70, heat shock protein 70; IMP, inositol monophosphate; IP3, inositol 1,4,5-triphosphate; MAP, mitogen-activated protein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; NGF, nerve growth factor; NMDAR, N-methyl-D-aspartate receptor; PD, Parkinson's disease; PI3K, phosphatidylinositol-3-kinase; PKA, protein kinase A; PKC, protein kinase C; VEGF, vascular endothelial growth factor.

hippocampus of rats.⁹³ The BDNF is a neurotrophin playing a critical role in cortical development, synaptic plasticity, neuronal differentiation, and survival.^{21,94} It has been demonstrated to be involved in the pathophysiology of mental disorders, with decreased peripheral levels being reported

during the acute manic, mixed and depressive episodes of BD,⁹⁵⁻⁹⁹ as well as in patients with chronic post-traumatic stress disorder (PTSD)¹⁰⁰ or schizophrenia.¹⁰¹ Treatment with therapeutic concentrations of lithium and valproic acid is known to selectively increase the levels of exon IV-containing

BDNF mRNA and the activity of BDNF promoter IV,⁹⁴ as well as to induce the subsequent activation of BDNF receptor (TrkB) in cultured rat cortical neurons.^{38,51} Consistently, elevated BDNF levels were reported in the hippocampus and in the frontal and temporal cortex of rat brains after chronic treatment with lithium and valproate.^{90,102–104} Clinical studies showed lithium to restore and even increase BDNF levels in patients with BD,¹⁰⁵ and a relationship between lithium prophylactic efficacy and such levels was reported in a sample of euthymic bipolar patients.¹⁰⁶ Lithium has also been shown, in *in vivo* and *in vitro* preclinical studies, to increase the expression of other neurotrophins involved in neuronal survival and plasticity, such as the nerve growth factor, the glial cell line-derived neurotrophic factor, and the vascular endothelial growth factor (VEGF).^{107–112}

Some evidence demonstrates that lithium produces neurotrophic effects affecting cyclic adenosine monophosphate-mediated signal transduction. This action is mainly exerted elevating basal adenylyl cyclase activity, but also reducing receptor-stimulated responses, as demonstrated in both preclinical and clinical studies.^{60,113,114} The physiologic effects of cyclic adenosine monophosphate are primarily mediated by the activation of protein kinase A, one of whose major targets in the central nervous system is CREB, a transcription factor that plays a major role in mediating adaptive responses at glutamatergic synapses, as well as in the neuroprotective effects of neurotrophins and in long-term neuroplasticity.⁶⁰ Indeed, the activation of the extracellular-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway via CREB initiates the transcription of BDNF and also induces Bcl-2 expression. At therapeutically relevant concentrations, both lithium and valproate have been shown to activate the ERK/MAPK cascade in human neuroblastoma SH-SY5Y cells *in vitro*,¹¹⁵ as well as in hippocampus and frontal cortex areas of the rodent brain,¹⁰³ thus producing neurotrophic effects.

Experimental studies also found chronic lithium administration to provide nearly complete protection against glutamate-induced, NMDA receptor (NMDAR)-mediated excitotoxicity in primary cerebellar, cerebral cortical, and hippocampal neuronal cultures.^{52,116,117} Excessive NMDA throughput has been, in fact, hypothesized to be involved in stress-induced hippocampal atrophy and implicated in the pathogenesis of various neurodegenerative diseases.^{38,116,118} This neuroprotective effect was obtained also with low lithium doses (0.1–0.6 mM) and was associated with the inhibition of NMDAR-mediated calcium influx.^{38,52} Additional evidence indicates that the lithium mechanism of action results from the attenuation of constitutive phosphorylation of

the N-methyl D-aspartate receptor subtype 2B (NR2B) subunit of the NMDAR, which is catalyzed by Fyn, a member of the Src tyrosine kinase family.^{52,119} Brain ischemia is known to increase Src-mediated tyrosine phosphorylation of NR2A, as well as the interaction of NR2A with Src and Fyn, which is mediated by postsynaptic density protein 95.^{120,121} Lithium was shown to reduce NR2A phosphorylation and its postsynaptic density protein 95-mediated interactions with Src and Fyn in rat hippocampus following cerebral ischemia.¹²² Furthermore, chronic lithium treatment antagonizes glutamate-induced activation of c-Jun-N-terminal kinase, p38 kinase, and activator protein-1 transcription factor binding, which has a major role in cytotoxicity, and suppresses glutamate-induced decrease of the CREB phosphorylation in cultured cerebellar granule neurons.^{38,54}

According to the inositol depletion hypothesis,¹²³ the phosphatidylinositol (PI) pathway has also been proposed as a major target through which lithium could exert its therapeutic effects. As with GSK-3, lithium directly inhibits IMP and inositol polyphosphate-1 activity by the competitive displacement of Mg²⁺ from the catalytic site of the enzyme.⁵⁶ The inhibition of IMP and inositol polyphosphate-1 prevents the reuptake of inositol, leading to depletion of intracellular levels and subsequent inhibition of the phosphoinositol cycle.⁴¹ The decrease in free-myoinositol levels and, subsequently in the production of diacylglycerol induced by the inhibition of IMP, has the downstream effect of decreasing protein kinase C levels and activity.⁶⁰ The reduction of protein kinase C levels and activity was demonstrated in cells as well as in rodents after chronic lithium treatment, with implication on neuroplastic events.¹²⁴ Moreover, the inhibition of protein kinase C has been suggested as a mechanism producing antimanic effects.^{60,125}

More recently, the ability of lithium to inhibit the activity of IMP and subsequently decrease inositol 1,4,5-triphosphate levels was identified as a novel mechanism for inducing autophagy.^{126–129} Autophagy, a physiological process for degrading cytoplasmic proteins or organelles, has been recognized as a principal response to cellular stress and an important regulator of neuronal function and survival.¹²⁹ It is believed to be particularly beneficial as a “quality control” process in neurodegenerative disorders characterized by the accumulation of misfolded disease-causing proteins (eg, AD, PD, Huntington’s disease [HD], amyotrophic lateral sclerosis [ALS]).^{130–132}

The inhibition of the two main targets of lithium, IMP, and GSK-3 β , shows opposite effects on autophagy, that is modulated in a dose-dependent manner: lithium induces inhibition of IMP at lower doses (K_i \approx 0.8 mM), enhancing autophagy,¹²⁶ while it induces inhibition of GSK-3 β at higher

doses ($K_i \approx 2$ mM), downregulating autophagy via activation of mammalian target of rapamycin (mTOR).^{118,133}

The inhibition of PI3K, a kinase involved in cell survival pathways, has been found to block the activity of the anti-apoptotic serine-threonine Akt-1 kinase causing neuronal death, and this apoptotic pathway was prevented by chronic lithium exposure increasing PI3K activity in primary cerebellar neurons.⁴⁷ Acute lithium exposure also protected cortical neurons via a PI3K-mediated increase in intracellular calcium through the phospholipase C γ pathway.¹³⁴ Furthermore, in cultured human neuroblastoma SHSY5Y cells, lithium treatment ameliorated HIV-gp120-mediated toxicity via the PI3K/Akt pathway.¹³⁵

Recent evidence suggests that lithium treatment enhances the mitochondrial respiratory rate, reduces oxidative stress, protects DNA against damage from oxidative stress, and modulates calcium influx in the mitochondria.^{60,136–139} Both lithium treatment of acute mania and clinical improvement of depressive symptoms after lithium administration were associated with a reduction of pro-oxidative stress markers.^{12,140} In addition, lithium showed to affect oxidative stress in healthy subjects increasing antioxidative and reducing pro-oxidative markers.¹⁴¹ Nitric oxide (NO) is one of the most important intracellular second messenger activated by oxidative stress status. NMDAR activation can increase the activation of NO synthase, the enzyme responsible for NO production, and lithium treatment has recently been suggested to regulate this molecular mechanism.¹⁴²

Besides promoting neuronal survival after damage, lithium has been reported to promote hippocampal neurogenesis. In mammals, new neurons continue to be produced throughout adult life in the subventricular zone and the hippocampal dentate gyrus (DG).¹⁴³ Compared with preexisting mature dentate granule cells, newborn neurons exhibit peculiar electrophysiological features (ie, increased intrinsic excitability, enhanced synaptic plasticity, reduced sensitivity to GABAergic inhibition, and lower threshold for the induction of LTP) that showed to be essential for hippocampal function in the DG, an area primarily involved in cognitive processes.^{144–147} Impaired adult neurogenesis has been observed in various models relevant to neuropsychiatric disorders (ie, BD, major depression, schizophrenia, and AD) and neurodevelopmental disorders (ie, FXS and DS).^{143,148–152} Recent data have correlated low proliferation and differentiation capacities of adult hippocampal stem cells with memory dysfunction,¹⁵² suggesting adult neurogenesis might be a promising therapeutic target for disease-associated cognitive impairment. Several preclinical studies showed lithium to stimulate the proliferation and

differentiation of neuronal progenitor cells, as well as their maturation and functioning.^{153–158}

Lithium in neurodegenerative diseases

The risk of cognitive impairment and dementia has been reported to be higher in patients with BD than in the general population, correlating with the duration of illness, as well as with the number of illness episodes, especially the depressive ones, and the degree of impairment.^{159,160} Both preclinical and clinical studies have produced new evidence of lithium benefits in terms of preventing dementia through its action on GSK-3,^{66,161} leading to its investigation also in neurodegenerative disorders.

In a case-control study that compared AD prevalence rates among elderly euthymic bipolar patients on chronic lithium therapy with respect to those of similar patients who had not been treated with lithium recently, Nunes et al¹⁶² showed lithium to be able to reduce AD prevalence to levels comparable with those of the general elderly population. Since the number of previous affective episodes was equivalent between the two patient groups, this putative neuroprotective effect was related to the intrinsic biological brain effects of lithium. Findings from two other observational studies corroborated the reduced risk of AD in BD patients on long-term lithium treatment.^{163,164} Conversely, this positive effect was not shown in patients taking anticonvulsants, antidepressants, or antipsychotics.¹⁶⁴

Evidence of benefits of lithium in preventing cognitive impairment in nonbipolar AD patients is mixed. A small, open-label study found no cognitive benefits of lithium carbonate administration for up to 1 year to 25 patients with mild to moderate AD.¹⁶⁵ In a randomized, single-blind, placebo-controlled, 10-week study of 71 patients with a mild form of AD, treatment with lithium at therapeutic levels (0.5–0.8 mmol/L) showed no significant benefits on either cognitive performance or cerebrospinal fluid concentrations of disease-related biomarkers.¹⁶⁶ On the contrary, in a subset of a greater sample recruited for a randomized, single-blind, placebo-controlled, parallel-group 10-week multicenter study, investigating the efficacy of lithium treatment in early AD patients, a significant increase of BDNF serum levels was shown.¹⁶⁷ In a 12-month, single-center, randomized, double-blind, placebo-controlled study, carried out on subjects with amnesic mild cognitive impairment,¹⁶⁸ chronic lithium administration was associated with a significant decrease in cerebrospinal fluid concentrations of P-tau and better performances on the cognitive subscale of the AD assessment

scale and in attention tasks. The reduction of the cerebrospinal fluid P-tau was found in subjects with amnesic mild cognitive impairment who did not convert to AD, suggesting that this disease-modifying effect of lithium may be a useful parameter for predicting its property to prevent, or at least to delay, the progression from pre-dementia stage to clinical dementia. Lithium was administered at subtherapeutic levels (serum levels of 0.2–0.4 mmol/L), which resulted safe and well tolerated. In contrast with previous studies that failed to find a significant effect of lithium either on cognition or on AD-related biomarkers,^{165,166} this study included individuals without a manifest form of dementia. Finally, a more recent intriguing trial found beneficial effects of a lithium micro-dose of 300 µg administered once daily to AD patients for 15 months in preventing cognitive loss.¹⁶⁹ Overall, findings from clinical samples highlight preferential benefits of lithium in dementia prevention in patients with mood disorders and mild cognitive impairment, suggesting that long-term lithium treatment may have disease-modifying properties on the core pathophysiologic features of AD, mostly if started at the earlier stages of the disease process.^{41,168,170}

Lithium inhibition of the GSK-3 has also been hypothesized to produce neuroprotective effects in other neurodegenerative disease models, such as PD, tauopathies, HD, ALS, SCA1, and MS.^{10,40,41,65,171–173} Whether these pharmacodynamic properties of lithium can be translated into neurodegenerative diseases modifying effects in human subjects is a critical question.¹⁷⁴

Several preclinical studies have suggested that lithium can prevent neurodegeneration in vitro and in vivo models of PD.^{67,175–177} Therapeutic concentrations of lithium have been shown to facilitate clearance of the mutant form of α -synuclein, one of the major components of Lewy bodies, inducing autophagic processes.^{126,177} Other preliminary data suggest that the antioxidant effects of lithium may be beneficial for PD by preventing free radical damage of dopaminergic neurons.¹⁷¹ In a mouse model of PD, mice were fed with a diet containing 1.1, 2.2, 3.3, and 4.4 g/kg lithium chloride for 4 weeks prior to the injection of the parkinsonism neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).¹⁷⁸ The 3.3 g/kg lithium diet gave serum level value very similar to what is observed in lithium therapy in man and the 4.4 g/kg diet gave serum level values well above this. Results of this study showed chronic lithium diet to prevent the decrease of dopamine levels, as well as of tyrosine hydroxylase activity and protein levels in striatum. A direct relationship was established between serum lithium concentration and the prevention of MPTP-induced depletion of striatal dopamine. MPTP-treated

mice showed significantly decreased striatal Bcl-2 levels, as opposed to increased Bcl-2-associated X protein levels, and lithium treatment was found to prevent such changes. Chen et al¹⁷⁹ demonstrated that 6-hydroxydopamine (6-OHDA), a PD mimetic, activates GSK-3 β in cultured human neuroblastoma SH-SY5Y cells, as well as in cultures of rat cerebellar granule neurons, inducing neuronal death. Lithium and other specific GSK-3 β inhibitors showed to protect SH-SY5Y cells and cerebellar granule neurons from 6-OHDA-induced apoptosis. However, other studies have presented conflicting results, showing lithium to fail in the protection of dopaminergic neurons from 6-OHDA-induced degeneration in the substantia nigra of rats.^{41,180} To date, no clinical trials have been conducted in human patients to test these findings.

HD is a progressive, autosomal dominant neurodegenerative disorder caused by an expanded CAG repeats at exon 1 of the huntingtin (Htt) gene resulting in the aggregate formation of mutant huntingtin protein (mHtt).¹⁸¹ Clinical presentation of HD includes psychiatric disturbances such as significant changes in personality or mood, cognitive decline that may gradually lead to dementia, and motor dysfunction characterized by chorea. Pathological processes and pathways involved in the development of HD include selective death/atrophy of medium-sized spiny neurons within the striatum and, to a lesser extent, loss of neurons in the cortex; dysregulation of cellular autophagy; mitochondrial dysfunction; decreased neurotrophic and growth factor levels; and transcriptional dysregulation and aberrant epigenetic modifications.¹⁸¹ Presently no cure exists to treat or halt the progression of this devastating disease. On the basis of accumulating evidence indicating the promising role of lithium for the treatment of neurodegenerative diseases, its use has been investigated in cellular and animal HD models. Pre- and posttreatment with lithium chloride (2.5–5.0 mM) protected nonneuronal and neuronal cells transfected with mutant Htt exon 1 fragment containing 74 CAG repeats, increased cell survival, and decreased aggregate formation compared with nontreated group in both the cell types.⁶⁵ In a rat model of HD induced by quinolinic acid (QA) unilateral infusion into the striatum, subcutaneous injection of lithium chloride for 16 days prior to QA infusion significantly reduced the size of the excitotoxicity-induced striatal lesion. The lithium-elicited neuroprotective action was associated with an increase in Bcl-2 protein levels.¹⁸² A subsequent study assessed the ability of lithium to reduce neurodegeneration and to stimulate cell proliferation in a rat model of HD induced by QA. LiCl (0.5–3.0 mEq/kg) was injected subcutaneously 24 hours before and 1 hour after QA infusion. Seven days

after QA injection, lithium significantly diminished the loss of neurons, prevented apoptosis by attenuating QA-induced DNA damage and caspase-3 activation, upregulated Bcl-2 levels, and promoted neuronal and astroglial progenitor cell proliferation.¹⁸³ Combined treatment with therapeutic levels of lithium (1.0 mM) and valproate (0.5 mM) was found to be more effective than treatment with either drug alone in upregulating mRNA and protein levels of BDNF, as well as other neuroprotective proteins such as Hsp70 in the striatum and cortex, in two models of transgenic HD mice. Cotreatment with lithium and valproate also more effectively alleviated spontaneous locomotor deficits and depressive-like behaviors and markedly prolonged median survival of transgenic mice, compared with monotreatment.⁶⁵ Lithium use was also investigated in clinical trials of HD. Two recent clinical studies demonstrated lithium's mood-stabilizing effects in HD patients of varying ages and duration of illness.^{184,185} The addition of lithium to tetrabenazine eliminated suicidal symptoms in all patients and improved depressive symptoms.¹⁸⁵ Moreover, it prevented the progression of chorea in three of these patients.¹⁸⁴ Despite these findings, clinical trials reported no benefits of lithium administration on improving choreiform movements.¹⁸¹ However, it is important to notice that these studies may be inconclusive due to the methodological limitations and small sample size.

Evidence of the neuroprotective effects of lithium from ALS models is inconsistent.^{186–190} In mouse models of ALS, treatment with either lithium alone or in combination with an antioxidant has been shown to improve motor function and slow down disease progression.^{189,190} The mainly hypothesized mechanism for such improvement was the stimulation of autophagy by lithium.^{186,191} Combined treatment of ALS mice with lithium and valproate produced a greater and more consistent effect in delaying the onset of disease symptoms, prolonging the lifespan, and decreasing the neurological deficit scores, in comparison with monotreatment with either drug.¹⁹¹ On the contrary, some preclinical studies reported no benefits of lithium administration in improving disease symptoms.^{187,188} In a small, 15-month pilot study on randomized ALS patients, a significant effect on disease progression and survival was reported in the lithium plus riluzole group (lithium plasma levels ranging from 0.4 to 0.8 mEq/L) compared with the riluzole only.¹⁸⁶ A subsequent randomized, double-blind, placebo-controlled trial showed no benefits of lithium (serum levels maintained between 0.4 and 0.8 mEq/L) plus riluzole combination in slowing down the progression of ALS comparing with riluzole alone.¹⁹² More recently, a multicenter, double-blind, randomized, placebo-controlled

trial (lithium carbonate in ALS trial) was designed to test the hypothesis that lithium may improve survival rates in ALS.¹⁹³ Oral doses of lithium carbonate (mean serum levels ranging from 0.4 to 0.8 mmol/L) or placebo were continuously administered for 18 months. Lithium treatment was shown to be safe, but study results did not support any evidence of lithium benefit on survival compared to placebo.^{194,195}

Results from preclinical studies also suggest that lithium may be useful for therapeutic intervention in autoimmune and inflammatory diseases, such as MS, the most common inflammatory demyelinating disease of the central nervous system. Lithium pretreatment at therapeutic doses in experimental autoimmune encephalomyelitis models not only markedly suppressed the clinical symptoms of experimental autoimmune encephalomyelitis but also greatly reduced demyelination, microglia activation, and leukocyte infiltration in the spinal cord.¹⁷²

Finally, lithium efficacy was tested in a knock-in mouse model of SCA1 (Sca1[154Q/2Q] mice) that replicates many features of the human disease, a dominantly inherited neurodegenerative disorder characterized by progressive motor and cognitive dysfunction.¹⁷³ In this study, Sca1(154Q/2Q) mice and their wild-type littermates were fed either regular chow or chow that contained 0.2% lithium carbonate. Dietary lithium carbonate supplementation resulted in the improvement of motor coordination, learning, and memory in Sca1(154Q/2Q) mice, both presymptomatically and after symptom onset. Neuropathologically, lithium treatment improved hippocampal dendritic arborization in mutant hippocampal pyramidal neurons.

Lithium in neurodevelopmental disorders

Parallel to research on neurodegenerative disorders, lithium potential neuroprotective functions have been explored in neurodevelopmental disorders, with the strongest evidence emerging in preclinical studies of FXS, the most commonly inherited form of mental retardation and autism. FXS is caused by suppressed expression of the fragile X mental retardation protein,¹⁹⁶ an RNA-binding translational regulator important for establishing and maintaining functional neuronal networks.^{197,198} An altered synaptic plasticity, with pathologically enhanced metabotropic glutamate receptor (mGluR)-dependent LTD in the hippocampal CA1 neurons and deficits in NMDAR-dependent LTP at medial perforant path synapses in the DG, has been detected in mouse models of FXS (FX mice),^{199–201} suggesting enhanced mGluR signaling to be a major cause of this syndrome.²⁰² According

to this, the inhibition of mGluR5 has been shown to reverse several behavioral and morphological phenotypes, including cognitive deficits, in both developing and adult FX mice.^{203,204} Overall, these findings established a clear link between synaptic dysfunction and learning deficits in FXS.

Furthermore, following the discovery that the GSK-3 activity and the mGluR5 signaling were coordinately elevated in the hippocampus, striatum, and cerebral cortices of FX mice, with the inhibition of mGluR5 leading to the inhibition of GSK-3, research studies investigated this kinase as a therapeutic target for the treatment of FXS.²⁰⁵ According to this, GSK-3 has been identified as a bidirectional regulator of NMDAR-dependent synaptic plasticity, as LTP induction requiring the inhibition of GSK-3 β , while GSK-3 β activity is required for LTD induction.^{206,207}

Lithium inhibition of GSK-3 was found to revert the altered phenotypes of FX mice, that is, to attenuate enhanced mGluR-mediated LTD, to ameliorate locomotor hyperactivity, audiogenic seizure hypersensitivity, increased spine density, excess protein synthesis, social behavior deficits, deficient passive avoidance learning and synaptic plasticity, and to normalize impaired hippocampus-dependent cognitive tasks.^{205,208–214} To the best of our knowledge, only one small open-label trial has been conducted in FXS patients,²¹⁵ showing lithium treatment titrated to levels of 0.8–1.2 mEq/L to improve cognitive performance modifying the disrupted regulation of group 1 metabotropic glutamate receptor (mGluR and mGluR5)-dependent translation in dendrites.

Neuropathological alterations have also been described in autism spectrum disorders (ASDs). A preclinical study on neonatal rats isolated from their mother showed apparent autistic-like symptoms, such as social deficits, excessive repetitive self-grooming behavior, and increased anxiety- and depressive-like behaviors that were accompanied by impaired adult hippocampal neurogenesis, and enhanced basal inhibitory synaptic transmission in the hippocampal CA1 pyramidal neurons.²¹⁶ Chronic lithium administration was effective in ameliorating these pathological changes, completely overcoming autistic-like behaviors, and restoring adult hippocampal neurogenesis and the balance between excitatory and inhibitory synaptic activities to physiological levels, supporting the use of lithium as a potential therapeutic agent against ASDs. Interestingly, two recent case studies described the effects of lithium treatment in two patients diagnosed with ASDs in childhood and presented regression with progressive loss of verbal and motor skills, catatonic features, aggressive and impulsive behaviors, and sleep disturbances after a stressful event during adolescence.²¹⁷ They both

presented a mutation/microdeletion of the *SHANK3* gene on chromosome 22q13.3 that encodes a scaffold protein located at the glutamatergic synapses and involved in the regulation of the structural organization of dendritic spines and binding partner of neuroligins, accounting for approximately 2% of cases of intellectual disability in ASDs patients.²¹⁸ After deletion of *SHANK3* gene, the nervous system is thought to become more susceptible to developmental problems and psychiatric disorders, less able to recover after psychiatric and somatic events and more vulnerable to degeneration in the long term.²¹⁹ Various psychotropic medications administered to the two patients (antipsychotics, benzodiazepines, antiepileptic drugs, antidepressants, and methylphenidate) failed to improve clinical symptoms and led to multiple side effects. In contrast, lithium therapy permitted reversibility of regression symptoms and catatonic features and the stabilization of behavioral disorders without significant side effects,²¹⁷ suggesting that *SHANK3* patients with ASDs may represent a more vulnerable subgroup with an atypical form of BD,²¹⁹ in agreement with previous observations.^{220,221}

Finally, lithium use has been explored in preclinical models of DS. DS is the leading genetic cause of intellectual disability and has been associated to impaired hippocampal neurogenesis. This latter plays a key role in establishing functional neuronal network and synaptic connectivity. The altered synaptic plasticity (eg, excitation/inhibition imbalance) discovered in mouse models of DS has been implicated in cognitive dysfunctions.^{143,222–224} Recent studies showed that 1-month administration of lithium in the Ts65Dn mouse, a model of DS, was able to restore adult neurogenesis in the DG and subventricular zone to physiological levels by stimulating the proliferation of neuronal precursor cells through the pharmacological activation of the Wnt/ β -catenin pathway.^{143,215} The restoration of adult neurogenesis completely rescued the synaptic plasticity of newborn neurons in the DG and led to the full recovery of behavioral performance in three distinct hippocampal-dependent cognitive tasks (contextual fear conditioning, object location, and novel object recognition).¹⁴³

Lithium in cerebral traumatic/ ischemic injury

Emerging evidence from preclinical research suggests that lithium can mitigate neurological deficits incurred from traumatic or ischemic brain injury.^{40,70}

The pathophysiology of TBI, after an initial mechanical injury that damages neurons, glia, and vascular structures, includes a cascade of secondary events that finally lead to neurodegeneration and loss of neurological functions: oxidative

stress; excitotoxicity via excess glutamate release; increased NMDAR activation; neuroinflammation via proinflammatory cytokines, NO, or prostaglandins; mitochondrial disruption; failure of the blood–brain barrier (BBB) involving cerebral edema, hypoxia, and ischemia; and cellular death via necrosis and caspase-dependent (caspase-3) and/or caspase-independent apoptosis.^{70,225,226} Neuropsychiatric sequelae such as depression, anxiety, and PTSD and behavioral and cognitive deficits accompany secondary injuries.⁷⁰ Patients afflicted by TBI show increased memory impairment, and increasing evidence suggests that TBI is a major risk factor for the development of AD.^{227–229}

Given the neuroprotective effects of lithium, recent research has investigated its putative use in preclinical studies on TBI paradigms.⁷⁰ Lithium pretreatment was found to attenuate interleukin-1 β expression, brain edema, hippocampal neurodegeneration, and loss of hemispheric tissues, improve memory and spatial learning, and alleviate depressive behaviors in mouse models of mild TBI.^{230,231} Postinjury injections with therapeutic doses of lithium also reduced lesion volume and attenuated TBI-induced neuroinflammation by inhibiting microglia activation and cyclooxygenase-2 induction, while BBB integrity was maintained through the inhibition of matrix metalloproteinase-9 expression. TBI-induced hyperlocomotor activity, anxiety-like behaviors, and impairments in motor coordination were all normalized by lithium treatment. In addition, GSK-3 β phosphorylation was found to be robustly increased after postinjury administration of lithium, with subsequent β -catenin accumulation, and reduced neuronal loss in the hippocampal CA3 region, as well as decreased hippocampal-dependent deficits in learning and memory.^{70,232,233}

Similarly, GSK-3 β has been strongly implicated in the pathogenesis of neuronal death caused by ischemic injury. While GSK-3 β , in preclinical models of transient focal cerebral ischemia, was found to be activated inducing apoptotic cell death, its inactivation shortly after permanent focal or global cerebral ischemia was found to promote survival of vulnerable neurons, thus identifying GSK-3 β inhibition as a major target for treatments.⁴⁹

Pretreatment with lithium and valproate was found to attenuate the hypoxia-induced serine dephosphorylation of GSK-3 α and GSK-3 β in mouse cerebral cortex, hippocampus, and striatum.²³⁴ Consistently, in a model of neonatal rat hypoxic–ischemic brain injury, postinsult treatment with lithium therapeutic doses reduced the ischemia-induced dephosphorylation of GSK-3 β and the extracellular signal-regulated kinase, the activation of calpain and caspase-3, the

mitochondrial release of cytochrome c and apoptosis-inducing factor, as well as autophagy.¹²⁸ Lithium inhibition of GSK-3 β is also accompanied by the upregulation of Bcl-2, increase in the DNA-binding activity of heat shock factor-1 to the heat-shock element, thus superinducing Hsp70, downregulation of p53, and decreased expression of Bcl-2-associated X protein in rat models of stroke.^{235–238} These findings highlight the prominent role of GSK-3 β inhibition in the antiapoptotic effects of lithium under ischemic conditions.

Besides the inhibition of GSK-3, lithium showed to provide neuroprotection in rat hippocampus following cerebral ischemia through the downregulation of NMDAR function, overstimulated as a consequence of the glutamate extracellular accumulation.¹²²

Long-term lithium pretreatment at therapeutically relevant doses decreased brain infarct volume and apoptotic cell death and improved neurological deficits in a permanent rat model of brain focal ischemia.^{238,239} Moreover, it prevented ischemia-induced exploratory behavioral changes and memory impairments in an animal model of global cerebral ischemia.²³⁵ These benefits were associated with an increase in the number of viable cells and a decrease in apoptotic cells in the CA1 hippocampal area of ischemic brain. Infarct volume, neurological deficits, and the number of neurons showing DNA damage in the ischemic brain were also reduced by postinsult subcutaneous injection of lithium at 0.5 mEq/kg in a rat ischemia/reperfusion model.²³⁷

Lithium has been demonstrated to inhibit neuroinflammation resulting from ischemic brain injury by preventing inflammatory disorder of the hematoencephalic barrier and neurodegeneration.²³³ Long-term lithium treatment of neonatal rats subjected to hypoxic–ischemic brain injury significantly reduced total tissue loss, at least partly by inhibiting microglia activation and attenuating proinflammatory cytokines (ie, interleukin-1 β) or chemokine levels.¹⁵⁷ Overexpression of Hsp70, leading to the inactivation of the inflammatory transcription factor NF- κ B,²⁴⁰ has been proposed as a possible mechanism by which lithium exerts its anti-inflammatory activity in experimental stroke models.

The stimulation of hippocampal neurogenesis has also been implicated in the neuroprotective effect of lithium against brain ischemia.^{157,158} In addition, lithium treatment showed to improve stroke recovery in rats by augmenting neurovascular remodeling and vascular neoformation.²⁴¹ Specifically, it was found to increase the VEGF protein levels via a mechanism involving the PI3-kinase and GSK-3 signaling pathways in cultured rat brain endothelial cells.¹⁰⁹ Since VEGF has been linked to angiogenesis, neurogenesis,

and neuroprotection,²⁴² this growth factor signaling mechanism may contribute to lithium's reported ability to promote neurovascular remodeling after ischemic stroke.

Finally, studies on mesenchymal stem cells in rat models of brain ischemia showed that incubation with lithium chloride increased their migratory ability and homing to damaged tissues, reduced infarct volume, enhanced regenerative potential and angiogenesis in the infarcted penumbra regions, and improved functional recovery.^{243,244}

Conclusion

Increasing evidence highlights BD, as well as other neuropsychiatric conditions, to be associated with morphological brain abnormalities, such as regional impairments in neuroplasticity, cellular resilience, and hippocampal neurogenesis, which highlight the role of neurodegeneration in BD. This new perspective has induced most recent research to focus on the possible neuroprotective effects of psychotropic medications, particularly those whose efficacy in the treatment of BD has been corroborated.^{9–11,13–15,20,245} Consistently, over the past few years, increasing promising results have emerged for lithium salts, a medication historically used to treat BD.

Since the GSK-3, the main target of lithium, plays a key role in the pathogenesis of many neuropsychiatric disorders, the therapeutic potentials of lithium have been investigated in various preclinical paradigms of different neurodegenerative diseases associated with cell atrophy/loss and impairment of cellular resilience, as well as, most recently, of neurodevelopmental disorders.^{49,117,246–248} There is now evidence that the neuroprotective benefits of this agent in the human brain are exerted through several complementary mechanisms leading to increased neuronal viability/function, enhanced angiogenesis and neurogenesis, BBB integrity maintenance, and anti-inflammation as well as disease-specific neuroprotective properties.¹⁰ Thus, the findings reported in the present review provide intriguing support for the neurotrophic/neuroprotective effects of chronic treatment with lithium, suggesting possible implications for its use in other neuropsychiatric conditions, including those neurodevelopmental disorders, such as ASD, recently suggested as the possible common vulnerability factor for most mental disorders.^{249,250} The encouraging results reported so far suggest the need for further studies exploring the new therapeutic potentials of this old drug in clinical samples.

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Disclosure

The authors report no conflicts of interest in this work.

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