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REVIEW

Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders

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Abstract: In the last two decades, a growing body of evidence has shown that lithium has several neuroprotective effects. Several neurobiological mechanisms have been proposed to underlie these clinical effects. Evidence from preclinical studies suggests that neuroprotection induced by lithium is mainly related to its potent inhibition of the enzyme glycogen synthase kinase-3β (GSK-3β) and its downstream effects, ie, reduction of both tau protein phosphorylation and amyloid-β_{42} production. Additional neuroprotective effects include increased neurotrophic support, reduced proinflammatory status, and decreased oxidative stress. More recently, neuroimaging studies in humans have demonstrated that chronic use is associated with cortical thickening, higher volume of the hippocampus and amygdala, and neuronal viability in bipolar patients on lithium treatment. In line with this evidence, observational and case registry studies have shown that chronic lithium intake is associated with a reduced risk of Alzheimer's disease in subjects with bipolar disorder. Evidence from recent clinical trials in patients with mild cognitive impairment suggests that chronic lithium treatment at subtherapeutic doses can reduce cerebral spinal fluid phosphorylated tau protein. Overall, convergent lines of evidence point to the potential of lithium as an agent with disease modifying properties in Alzheimer's disease. However, additional long-term studies are necessary to confirm its efficacy and safety for these patients, particularly as chronic intake is necessary to achieve the best therapeutic results.

Keywords: lithium, Alzheimer's disease, prevention, GSK-3β, neuroprotection

Introduction

Lithium salts have been used in psychiatry since the end of the 1940s as a mood stabilizer for the treatment of affective disorders,[1] in particular bipolar disorder and as add-on therapy in treatment-resistant major depression. All major treatment guidelines recommend lithium, alone or in association, as a first-line agent for the treatment of acute mania and bipolar depression as well as for the prophylaxis of recurrent affective episodes in these patients (reviewed by Nivoli et al in 2011).[2] A growing body of evidence suggests that the benefits of lithium extend beyond mood stabilization. In particular, long-term lithium treatment has been associated with increased neuroprotection against neuronal injury not only in mood disorders but also in neurodegenerative diseases, such as Alzheimer's disease (AD).[3,4] This article aims to review the presumed mechanisms by which lithium may exert its neuroprotective effects and how such mechanisms may help to delay the progression of AD.

Lithium: pharmacological mechanisms

The specific pharmacological mechanisms of lithium are not clear, but current evidence suggests the direct involvement of classic pharmacologic targets, such as cell surface

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receptors or the direct modulation of neurotransmitters,[5] second messenger systems, and transcriptional factors. Lithium ion directly competes with magnesium (Mg^{2+}) due to its similar ionic radii (0.60 Å and 0.65 Å, respectively) and its ability to bind to similar substrates' sites. Therefore, lithium can inhibit Mg^{2+}-dependent enzymatic activity.[6,7] The competition between lithium and Mg^{2+} by substrate sites has a significant influence on the activity of several enzymes on intracellular pathways relevant to neuropsychiatric and neurodegenerative disorders, eg, glycogen synthase kinase-3β (GSK-3β), inositol monophosphatase (IMP), and Akt/β-arrestin-2.

Lithium inhibits GSK-3β activity by two distinct and interrelated mechanisms. GSK-3β is a constitutively active enzyme by the binding of Mg^{2+} to its catalytic core. By dislocating Mg^{2+} from the enzyme catalytic core, lithium directly inhibits the enzyme activity.[8,9] In addition, lithium can also inhibit GSK-3β activity by inducing the phosphorylation of the serine-9 residue, leading to conformational changes and inactivation. This indirect mechanism is due to the lithium-induced activation of intracellular kinases (eg, Akt) or by inhibiting intracellular phosphatases (eg, protein phosphatase-2).[10–12] In addition to the inhibition of GSK-3β activity, lithium can also reduce enzyme expression at the gene level.[13]

The inhibition of IMP and inositol polyphosphate 1-phosphatase activity is another putative mechanism of action of lithium. Lithium also causes a direct inhibition of IMP activity by noncompetitive dislocation of Mg^{2+} from enzyme catalytic sites.[14] An important consequence of IMP and inositol polyphosphate 1-phosphatase inhibition is the significant reduction of inositol triphosphate formation, which leads to the modulation of many intracellular pathways relevant to neuropsychiatric disorders, in particular the stimulation of autophagy (Figure 1).[15]

Another mechanism by which lithium can exert its action is by stimulating gene expression and the release of neurotrophic factors, eg, brain-derived neurotrophic factor (BDNF) and

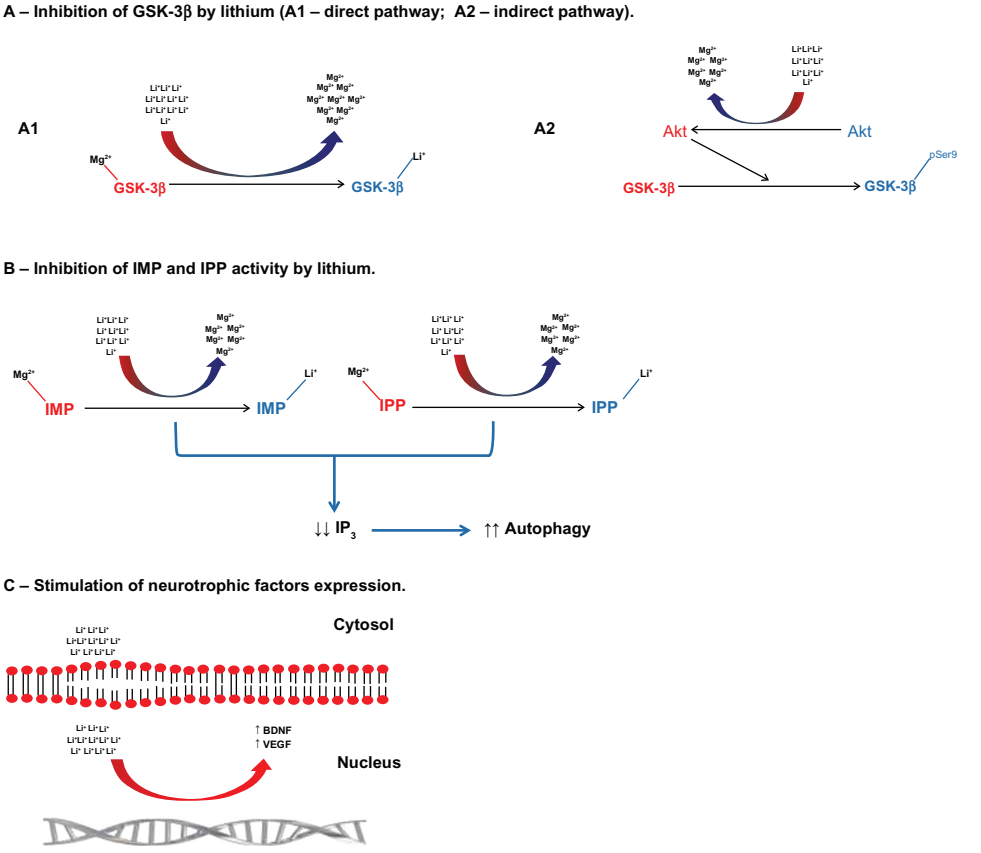

Figure 1 Putative mechanisms of action of lithium. (**A**) Lithium inhibits GSK-3β activity by dislocating magnesium ions from the catalytic core (direct pathway). Lithium can also inhibit GSK-3β activity by increasing the phosphorylation of Ser9 residue. This is secondary to the lithium-induced activation of kinases (eg, Akt) and/or inhibition of phosphatases (eg, protein phosphatase-2) (indirect pathway). (**B**) Lithium increases autophagy by inhibiting the activity of IMP and IPP and, consequently, reducing IP_3 levels. (**C**) Lithium can also directly stimulate the production of neurotrophic factors BDNF and VEGF by activation of gene expression in the nucleus.
Notes: Red color: active enzyme; blue color: inactive enzyme.
Abbreviations: BDNF, brain-derived neurotrophic factor; GSK-3β, glycogen synthase kinase-3β; IMP, inositol monophosphatase; IP_3, inositol triphosphate; IPP, inositol polyphosphate 1-phosphatase; Ser9, serine-9; VEGF, vascular endothelial growth factor.

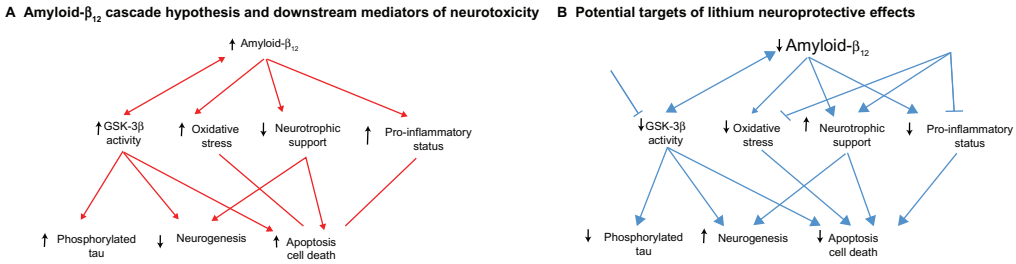

Figure 2 The mechanism and targets of lithium against Alzheimer's disease-related pathology. (**A**) The main components of the amyloid-β cascade hypothesis of Alzheimer's disease pathophysiology. (**B**) The possible targets and effects of lithium in the amyloid-β cascade.
Notes: Red arrows: activation of pathways; blue arrows: inhibition of pathways.
Abbreviation: GSK-3β, glycogen synthase kinase-3β.

vascular endothelial growth factor.[16,17] These effects are particularly interesting as (1) reduced neurotrophic factors play an important role in the physiopathology of AD and affective disorders, and (2) restoration of neurotrophic factors' levels may be a therapeutic target for these disorders.[18]

Evidence for the neuroprotective effects of lithium from preclinical studies

The neuroprotective effects of lithium are due to its modulation on several biologic cascades. In neuronal cultures, lithium significantly reduces tau phosphorylation[19,20] and amyloid-β_{42},[21,22] and protects neurons against toxic effects and cell death secondary to amyloid-β_{42} exposure.[23,24] Lithium is also able to stimulate the proliferation of progenitor cells in cultured neuronal cells[25,26] and the expression of antiapoptotic proteins, eg, B-cell lymphoma-2.[27,28] These neuroprotective effects of lithium are mediated, at least in part, by the inhibition of GSK-3β activity in neurons.[29]

Animal studies provide additional evidence for the neuroprotective effects of lithium. The most consistent effect of chronic lithium treatment is the significant reduction of tau phosphorylation either in mice bearing amyloid precursor protein (APP)-related genetic mutations or wild-type animals.[30–33] The effects of lithium on tau phosphorylation are mediated by the inhibition of GSK-3β activity. In transgenic mice bearing mutations on the APP gene, lithium reduced amyloid-β_{42} production by direct modulation of APP processing and also by inhibition of GSK-3β activity.[22,34–37] These effects of lithium on tau phosphorylation and amyloid-β_{42} are, in general, accompanied by a significant improvement in memory deficits.[36,37]

The neuroprotective effects of lithium in APP transgenic mice might be time dependent. In a recent study, lithium treatment when started earlier in 2-month-old mice had a significantly stronger effect in reducing AD-related neuropathology and memory impairment than when started later in 6-month-old mice.[38] On the other hand, lithium treatment can prevent amyloid-induced neurotoxicity, in particular tau phosphorylation and neuronal death.[37,39] Finally, the inhibition of GSK-3β activity secondary to lithium treatment can increase synaptic plasticity, facilitate long-term potentiation, and consequently improve memory performance in animals.[40–44]

Autophagic processes are important in the degradation and clearance of amyloid-β and phosphorylated tau proteins in neurons. Impairment in autophagy is observed in AD and may contribute to the accumulation of extracellular deposits of amyloid-β_{42} in neuritic plaques and intracellular deposits of hyperphosphorylated tau proteins in neurofibrillary tangles.[45–47] Lithium treatment inhibits IMP/inositol polyphosphate 1-phosphatase activity, which decreases inositol triphosphate formation and, in turn, stimulates the autophagic processes in neurons. The stimulation of autophagy by lithium leads to the more effective clearance of amyloid-β_{42} and hyperphosphorylated tau protein,[15,48,49] protecting neurons from their deleterious effects.

Another important neuroprotective effect of lithium is stimulation of the synthesis and release of neurotrophic factors, in particular BDNF and vascular endothelial growth factor. Increased availability of neurotrophic factors protects neurons against amyloid-β_{42} neurotoxic effect, stimulates hippocampal neurogenesis, and positively regulates cell survival.[50–53] These biological effects are accompanied by a significant reduction in amyloid-related pathology, memory improvement, and slow rates of age-related memory decline in animal models of AD.

Inflammation is another important component of AD physiopathology and can accelerate neurodegenerative changes in animal models of this disorder.[54] Lithium can regulate the inflammatory processes by lessening the proinflammatory response. Lithium can reduce the production of interleukin-1β and tumor

necrosis factor-α induced by lipopolysaccharide-induced inflammation in glial cells[55] and reduce microglia activation secondary to ischemic insults in mice.[56] Chronic lithium treatment can attenuate arachidonic acid production, an essential feature of unspecific inflammatory response (Figure 2).[57]

Evidence for the neuroprotective effects of lithium from clinical studies

In addition to the evidence for the neuroprotective properties of lithium in preclinical studies, a growing body of evidence corroborates its neuroprotective effects in human subjects as well. Most of the evidence derives from studies of subjects with bipolar disorder. Case registry studies found a lower risk for incident dementia, in particular of AD, in bipolar patients after long-term lithium use.[58,59] In a retrospective study, Terao et al found that patients on chronic lithium treatment showed lower rates of cognitive decline as measured by the Mini-Mental State Examination.[60] A prospective observational study showed that older bipolar patients on chronic lithium treatment had a significantly lower incidence of AD compared to those with no lithium exposure.[61] In this study, the incidence rates of AD in the group treated with lithium was comparable to those observed in the general population,[62] suggesting that chronic lithium treatment can be protective against the development of AD in high-risk populations.

The exact mechanisms by which lithium may reduce the risk of AD in bipolar subjects are unclear, but may involve the modulation of multiple cascades that are abnormal in both disorders. Lithium treatment can significantly increase GSK-3β phosphorylation and, consequently, reduce enzymatic activity in the leukocytes of patients with bipolar disorder and recurrent major depression.[63,64] The inhibition of GSK-3β in vivo can mediate the therapeutic effect of lithium as a mood stabilizer as well as its neuroprotective effect in humans.

Several studies showed that lithium treatment can significantly increase BDNF, which influences the response to treatment.[3,65] In a clinical trial with patients in acute mania, de Sousa et al reported a significant increase in plasma BDNF levels after 4 weeks of treatment. However, increased BDNF levels were not associated with treatment response.[66] In addition, maintenance treatment with lithium was associated with a persistent high level of BDNF and reduced risk of affective episode relapse.[67]

Studies have also evaluated the effect of lithium on inflammatory and oxidative stress markers. Lithium treatment of an acute mania episode was associated with a reduction in pro-oxidative stress markers, eg, thiobarbituric acid reactive substances.[68,69] In addition, lithium treatment increased anti-oxidative stress markers and reduced pro-oxidative stress markers in healthy subjects.[70] A recent study demonstrated that patients with bipolar disorder who showed a good response to lithium also had a significant reduction in plasma tumor necrosis factor-α level; in contrast, the patients who did not respond well to lithium showed a significant increase in tumor necrosis factor-α levels.[71] Lithium can restore the balance in the production of interleukin-1β and interleukin-6 in monocytes of bipolar patients in vitro; this effect is similar to that observed in vivo.[72]

Another line of evidence that demonstrates the potential for the neuroprotective effect of lithium comes from neuroimaging studies in subjects with bipolar disorder. Structural neuroimaging studies have demonstrated that short- and long-term lithium treatment was associated with increased hippocampal and amygdala volume, and cortical thickness.[73–76] In addition, lithium treatment was associated with increased N-acetylaspartate and myo-inositol levels in magnetic resonance spectroscopy.[77,78] These neuroimaging findings suggest that long-term lithium treatment may have a significant effect on synaptic density and neuronal vitality in bipolar patients.

Taken together, the findings from clinical studies, in particular with bipolar patients, support preclinical evidence that lithium can modulate several biologic cascades related to the physiopathology and progression of AD. Patients with mild cognitive impairment (MCI) and AD show higher GSK-3β activity.[79] Inhibition of this enzyme by lithium may help reduce amyloidogenesis and tau phosphorylation, core features of AD pathology. In addition, lower neurotrophic support is a common feature of AD and stimulation of the synthesis and release of neurotrophic factors can confer resilience against amyloid neurotoxicity and stimulate synaptogenesis and neurogenesis. Finally, increased proinflammatory and pro-oxidative status is common in AD and amplifies the secondary downstream damage due to amyloid-β deposition and tau hyperphosphorylation. The modulation of these cascades can help lessen amyloid and tau-induced neurotoxicity and cell death and, as a consequence, reduce the risk of progression from AD-related pathology.

Evidence of disease modification in AD

Despite the wealth of evidence from preclinical and clinical studies that lithium modulates biologic cascades related to AD and may have disease modifying properties against this

disorder, few studies have actually addressed such potential in patients with AD or MCI. A small open-label trial, including 25 patients with mild to moderate AD, found no significant effects of lithium treatment on cognitive function over a 1-year treatment period.[80] Despite the high dropout rate of this study (only eight patients completed the 1-year treatment protocol), Macdonald et al suggested that treatment with lithium was relatively safe, with most dropouts due to mild and reversible side effects at therapeutic levels. A more recent clinical trial using a microdose of lithium (300 μg daily) over 18 months demonstrated a significant improvement in cognitive performance starting after 6 months of treatment, which persisted until the trial endpoint.[81]

A single-blind clinical trial including 71 patients with mild to moderate AD found no significant benefit of a 10-week treatment of lithium at therapeutic levels (0.5–0.8 mmol/L) on cognitive performance.[82] In this study, Hampel et al also evaluated the impact of lithium on biomarkers related to AD and found no significant changes in cerebrospinal fluid concentrations of amyloid-β and phosphorylated tau and leukocyte phosphorylated GSK-3β levels. Nonetheless, the short treatment period may not have been sufficient for lithium to exert its neuroprotective effects in these patients. Secondary analysis of this trial showed that lithium treatment was associated with increased serum levels of BDNF and that in a subset of patients who had increased BDNF levels it showed significant improvement in cognitive performance.[83] The effect of lithium was selective to BDNF as there was no significant change in the levels of glial-derived neurotrophic factor either on cerebrospinal fluid or serum of AD patients after 10 weeks of lithium treatment.[84]

Recently, a double-blind, placebo-controlled clinical trial was carried out to evaluate whether lithium at subtherapeutic levels (serum levels of 0.2–0.4 mmol/L) could delay the progression of amnestic MCI subjects to AD. It also evaluated the disease modifying properties in cascades related to the core physiopathologic features of AD in MCI subjects.[85] This study recruited 45 amnestic MCI subjects and preliminary analysis of the 1-year follow-up showed that amnestic MCI subjects on the lithium regimen presented stable cognitive performance and lower conversion rates to AD compared to subjects on placebo, although the difference was not statistically significant. Despite the lack of clear clinical benefit, amnestic MCI subjects on lithium showed a significant reduction in phosphorylated tau levels compared to subjects on placebo. Additional analyses revealed that the effect size of lithium on phosphorylated tau levels was even greater in MCI subjects who did not progress to AD on follow-up. Overall, these results suggest that long-term lithium has disease modifying properties on core physiopathologic features of AD and a marginal clinical benefit, mostly if started at the earlier stages of clinical and pathological disease processes.

Are we ready to use lithium in AD?

Despite the robust evidence for disease modifying properties of lithium on AD, derived from preclinical and clinical studies, its use is still not recommended. Larger, multicenter, long-term clinical trials are needed to assess the benefits of lithium on cognitive and functional performance as well as its power to delay the progression from preclinical to clinical states of AD. To evaluate the impact of chronic lithium treatment on the core physiopathologic processes in AD, these studies must include, as a primary and/or secondary outcome, biomarkers related to the core features of AD (eg, cerebrospinal fluid amyloid-β_{42} and phosphorylated tau proteins in structural neuroimaging, and/or amyloid imaging). Also, it is of the utmost importance to evaluate the optimum serum level to combine potential clinical benefit and patient safety.

Another important issue relates to patient safety and long-term lithium use. Older patients are particularly vulnerable to the side effects of lithium, with gastrointestinal disturbances and tremor the most common side effects reported. In general, they are mild and reversible but can be troublesome to patients and are common reasons for drug discontinuation. Also, renal dysfunction (including asymptomatic elevation of creatinine and renal insufficiency) and hypothyroidism can emerge during long-term treatment. They are, in general, manageable medical conditions but often lead to lithium discontinuation. In a safety analysis from a trial in older subjects with MCI, subtherapeutic doses of lithium (0.2–0.4 mmol/L) were safe and there were no significant changes in laboratorial parameters related to renal and thyroid function, hematologic parameters, and energetic metabolism.[86]

Drug interaction is another major concern. Concomitant use of lithium with some drugs can potentiate the adverse events related to lithium either by increasing serum drug levels (eg, thiazide diuretics) or by potentiating renal dysfunction (eg, nonsteroidal antiinflammatory drugs). However, the use of subtherapeutic levels can minimize such risks.

Conclusion

Current evidence points to a potential role of lithium as a drug with disease modifying properties in AD. Nonetheless, it is very important to emphasize that the risk/benefit ratio of using lithium for neuroprotection is still very unclear and

lithium should not yet be used for neuroprotection in older adults. Additional clinical trials are necessary to establish its efficacy from the clinical and biological perspective and also to establish the optimal dose regimen/plasma levels and length of drug use to attain the best clinical benefit.

Disclosure

The authors report no conflicts of interest in this work.

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