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Review

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Neuroprotective effects of lithium: implications for the treatment of Alzheimer's disease and related neurodegenerative disorders

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Abstract

Lithium is a well-established therapeutic option for the acute and long term management of bipolar disorder and major depression. More recently, based on findings from translational research, lithium has also been regarded as a neuroprotective agent and a candidate drug for disease-modification in certain neurodegenerative disorders, namely Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and, more recently, Parkinson's disease (PD). The putative neuroprotective effects of lithium rely on the fact that it modulates several homeostatic mechanisms involved in neurotrophic response, autophagy, oxidative stress, inflammation and mitochondrial function. Such a wide range of intracellular responses may be secondary to two key effects, i.e., the inhibition of glycogen synthase kinase-3 beta (GSK-3β) and inositol monophosphatase (IMP) by lithium. In the present review, we revisit the neurobiological properties of lithium in light of the available evidence of its neurotrophic and neuroprotective properties, and discuss the rationale for its use in the treatment and prevention of neurodegenerative diseases.

Key words: Lithium, neuroprotection, GSK-3β, autophagy, bipolar disorder, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis.

Introduction

Lithium salts have long been used in psychiatry for the treatment of severe mental disorders[1]. Currently, the main medical indications of lithium are for the acute and long-term treatment of bipolar disorder (BD) and for the adjunctive treatment of major depression, given its well-established mood stabilizing properties[2]. More recently, there has been a growing body of evidence indicating that the neurobiological benefits of lithium may go beyond mood stabilization. In experimental and clinical models, lithium treatment has been associated with neuroprotection, due to its effects on several mechanisms of neuronal homeostasis involved in the activation of neurotrophic responses, modulation of oxidative stress, inflammatory cascades, up-regulation of mitochondrial function, and other specific biological effects implicated in the pathogenesis of neurodegenerative diseases such Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS)[3]. This article aims to review the mechanisms by which lithium may exert its neuroprotective effects, and how these mechanisms may help delay the progression of neurobiological changes in mood and neurocognitive disorders. Additionally, we address the potential of lithium as a disease-modifying agent for certain neurodegenerative and dementing conditions.

Neurobiological properties of lithium

The pharmacological mechanisms of lithium are not completely understood, but current evidence suggests the direct involvement of classic pharmacological targets affecting neurotransmission and signal transduction. These include the modulation of cell-surface receptors, the release of second-messengers and downstream signaling molecules, and the subsequent effect on the activity of important regulatory systems, with an impact on the release of transcription factors and gene expression[4]. Monovalent lithium (Li^+) competes with bivalent magnesium (Mg^{2+}) to the similar ionic radii of these cations (0.60Aº and 0.65Aº respectively), rendering the ability of lithium to bind to Mg^{2+}substrate sites. Therefore, lithium can inhibit a wide range of enzymes that depend on Mg^{2+} as a co-factor[5,6]. The competition between lithium and Mg^{2+} on these substrate sites has a significant influence on the activity of several enzymes and therefore the release of their metabolic products; in particular, glycogen synthase kinase-3 beta (GSK-3β), inositol monophosphatase (IMP) and Akt/β-arrestin2 (Akt) are important lithium targets. Therefore, the modification of these intracellular pathways through enzymatic inhibition is relevant to the understanding of the pathogenesis of certain neuropsychiatric and neurodegenerative disorders.

GSK-3 has two isoforms, alpha and beta, with distinct patterns of distribution and homeostatic roles. GSK-3β is more abundant in the brain, and is implicated in cytoskeletal organization and remodeling[7]. Conversely, cerebral GSK-3α is involved in

neurodevelopment[8] and its inhibition by lithium has also been associated with disease-modification in a transgenic mouse model of AD[9]. The inhibition of GSK-3β is one of the most relevant mechanisms of action of lithium, and substantiates its putative role as a candidate for a disease-modifying drug in the treatment or prevention of AD[10,11]. Lithium inhibits GSK-3β activity by two distinct and interrelated mechanisms: directly, by preventing the binding of Mg^{2+} to the catalytic core of GSK-3β, and indirectly through inducing the phosphorylation of the serine-9 residue of GSK-3β, leading to conformational changes and inactivation, which is required for enzymatic activity. Therefore, by the competitive dislocation of Mg^{2+}, lithium reversibly inhibits the enzyme[12,13]. The indirect mechanism is followed by the activation of intracellular kinases (e.g. Akt) or the inhibition of intracellular phosphatases (e.g. PP2A) by lithium[14,15,16]. Finally, lithium can also reduce the availability of GSK-3β at the transcriptional level, therefore reducing its protein expression as a consequence of the inhibition of mRNA transcription[17].

Another relevant mechanism of action of lithium is the inhibition of inositol mono-phosphatase (IMP) and inositol polyphosphate-1 (IPP). As with GSK-3β, lithium directly inhibits IMP and IPP activity by the competitive displacement of Mg^{2+} from the catalytic site of the enzyme[18]. The inhibition of IMP and IPP prevents the re-uptake of inositol, leading to depletion of intracellular levels and subsequent inhibition of the phosphoinositol cycle. Another important consequence of IMP inhibition is the suppression of the formation of its metabolic product inositol triphosphate (IP3); IP3 is an intracellular messenger implicated in the regulation of many intracellular pathways relevant to neuropsychiatric disorders, including autophagy, an important homeostatic mechanism based on the degradation of cytoplasmic proteins and organelles[19]. Sarkar et al. (2005)[20] found in mammalian cell cultures that lithium induced autophagy as a downstream effect of the inhibition of IMP.

Lithium, in a dose-dependent manner, modulates autophagy through both the GSK-3β and IMPase pathways, with opposite effects. Lithium-induced IMPase inhibition at lower doses (≈0.8mM), up-regulating autophagy[20], while the inhibition of GSK-3β by higher doses of lithium (≈2mM) down-regulates autophagy via activation of the inhibitory regulator mTOR[21,22]. The overall ability of lithium to induce autophagy is due to the prevailing inhibition of IMPase[20]. Finally, lithium has been shown to act on other homeostatic pathways as well, such as extracellular signal-regulated kinase (ERK), PI3k/Akt and phospholipase C (PLC), which are proteins with further impact on the regulation of autophagy[23,24].

Preclinical evidence of the neuroprotective effect of lithium

As stated above, lithium has specific properties that may attenuate the effect of critical pathological changes that occur in AD, namely through the inhibition of the GSK-3β. In fact, this is the cornerstone to support the "GSK hypothesis of AD"[25], according to which the inhibition of GSK-3β activity by lithium is associated with the down-regulation of two central processes in the pathogenesis of AD, namely the reduction of the hyperphosphorylation of microtubule-associated Tau protein[26,27,28], and the induction of neuronal death via overproduction of the Aβ peptide [29,30] [31]. In transgenic mice overexpressing GSK-3β and in other animal models of AD, chronic lithium treatment significantly reduced Tau phosphorylation[32,33,34]. Likewise, chronic lithium treatment reduced $A\beta_{42}$ production by a direct modulation of APP processing and by inhibition of GSK-3β activity[35,36]. It is noteworthy that the attenuation or reversal of AD-related neuropathology was accompanied by a significant improvement in memory deficits in these animal models[37,38,39].

In addition to these disease-specific mechanisms, lithium may also protect neurons against the neurotoxic effects of $A\beta_{42}$ by favouring other neurotrophic and/or neuroprotective responses[40,41]. Chen and Chuang (1999)[42] showed that lithium increases the expression of p53 and Bcl-2, favouring neuronal survival. Chen et al. (1999)[43] showed the chronic administration of two structurally dissimilar mood stabilizing agents, lithium and valproate, increases Bcl-2 levels in the cortex, with beneficial neuroprotective effects. Also, lithium significantly stimulates the proliferation of progenitor cells in neuronal cell cultures [44,45], and increases the expression of anti-apoptotic proteins (e.g. Bcl-2)[46,47,48]. 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[49,50,51,52,53,54]. Lithium treatment also stimulates autophagic processes due to its inhibition of IMP/IPP activity and reduction of IP3 formation, in spite of GSK-3β inhibition[55,56].

Another important neuroprotective effect of lithium is the stimulation of synthesis and release of neurotrophic factors, in particular brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). Increased availability of these factors protects neurons against neurotoxic insults, stimulates hippocampal neurogenesis, increases synaptic plasticity and long-term potentiation (LTP), and positively regulates cell survival[3]. Finally, lithium can regulate inflammatory processes by lessening the pro-inflammatory response. Lithium has also been shown to reduce the production of interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α), inducers of lipopolysaccharide (LPS)-induced inflammation in glial cells[57], and to reduce microglial activation secondary to ischemic insult in mice [58]. Chronic lithium treatment can attenuate arachidonic acid production, an essential feature of the innate inflammatory

response[59]. Therefore, the modulation of inflammatory processes by lithium is relevant in light of the prominent role of inflammation in neurodegenerative and mood disorders[60].

Complex interactions between genetic and environmental factors are believed to play a critical role in the pathophysiology of neuropsychiatric disorders. The epigenetic status is affected by environmental stimuli and insults, leading to DNA methylation and histone modifications. Therefore, a better understanding of the epigenetic mechanisms affecting neuronal cells will provide important insights into the pathophysiology of cognitive and mood disorders and clues to new treatment approaches[61,62]. Epigenetic studies conducted in the postmortem brains of patients with major depression found evidence of hypermethylation of several genes involved in neuronal response, such as *BDNF*, *DBN1*, *SLC6A4* and *PRIMA1* in the prefrontal cortex[63,64,65]. Studies further provided evidence implicating of GSK-3β in the regulation of DNA methylation in mouse embryonic stem cells (ESC)[66]. The *de novo* DNA methyltransferase gene (*Dnmt3a2*) is down-regulated in GSK-3β double knock-out ESCs, decreasing DNA methylation. The inhibition of GSK-3β activity by lithium mimics the effects of reducing DNA methylation in both wild-type ESCs and wild-type neural stem cells. In addition, the inactivation of GSK-3β via components of the insulin signalling pathway also results in reduced DNA methylation[67].

Clinical and imaging findings supporting the neurotrophic and neuroprotective properties of lithium in bipolar disorder:

In addition to the cumulative evidence derived from experimental models, clinical and neuroimaging studies with patients with bipolar and other mood disorders further corroborate the neuroprotective properties of lithium. Most of the current clinical evidence derives from studies using subjects with BD. Large case registry studies found that BD patients continuously treated with lithium had a significantly lower risk of dementia, compared to those on other mood stabilizers or without treatment[68,69]. In a retrospective study, Terao and colleagues (2006)[70] found that patients on chronic lithium treatment had lower rates of cognitive decline as measured by the Mini-Mental State Examination (MMSE). In a cross-sectional study from our group, we found that older bipolar patients on chronic lithium treatment had a significantly lower incidence of AD (3%) compared to those with no or minimal lifetime lithium exposure (19%)[71]. In this study, the incidence rates of AD in the group treated with lithium was comparable to those observed in the general population[72], suggesting that chronic lithium treatment can be protective against the development of dementia (particularly AD) in the long-term outcome of BD.

Acute and chronic lithium treatment of BD patients has been associated with the up-regulation of certain biological cascades related to neuroprotection. Lithium treatment

significantly increased plasma concentrations of BDNF, with influence on response to treatment[73,74]. In a clinical trial with patients in acute mania, a significant increase in plasma concentrations of BDNF was observed after 4 weeks of treatment with lithium; however, increased BDNF levels were not associated with treatment response[75]. In addition, maintenance treatment with lithium was associated with persistently higher levels of BDNF and reduced risk of relapse after a major affective episode[76].

Lithium can also modulate other important biological processes related to inflammation and oxidative stress. Lithium treatment of acute mania episodes was associated with a reduction of pro-oxidative stress markers, namely TBARS[77]. In addition, lithium treatment increased anti-oxidative, and reduced pro-oxidative, markers in healthy subjects[78]. The reduction in pro-oxidative stress markers was associated with significant clinical improvement in depressive symptoms after lithium treatment[79]. Finally, a recent study demonstrated that patients with BD who had a good response to lithium also had a significant reduction in plasma concentrations of TNF-α; in contrast, patients who did not respond well to lithium showed a significant increase in TNF-α levels[80]. Lithium can restore the balance between the production of IL-1β and IL-6 in monocytes of bipolar patients *in vitro*; this effect is similar to those observed *in vivo*[81].

Neuroimaging studies have provided further support for the neuroprotective effects of lithium. Structural neuroimaging studies showed that short and long-term lithium treatment was associated with a volumetric increase in the hippocampus and amygdala, in addition to increased cortical thickness[82,83,84,85]. In a recent multicentre, observational study, BD patients on continuous lithium treatment had significantly larger hippocampi compared to those with no or minimal lifetime exposure to lithium[86]. Finally, lithium treatment was associated with increased N-acetyl aspartate (NAA) and myo-inositol levels as shown by magnetic resonance spectroscopy[87,88]. These imaging and neurochemical findings suggest that long-term lithium treatment may have a significant effect on synaptic density, neuronal vitality, and mitochondrial function in BD patients.

Clinical evidence of neuroprotective effects of lithium in neurodegenerative disorders:

Alzheimer's disease (AD):

The rationale for the clinical use of lithium as a neuroprotective therapy derive from preclinical models of AD, indicating that lithium can preclude or attenuate Aβ and Tau pathology, and improve cognitive function in transgenic mice. These results encouraged the conduction of clinical studies in patients with AD; however, few studies have been presented thus far. In a small open label trial with 25 patients with mild to moderate AD conducted in the United Kingdom, MacDonald- et al. (2008)[89] found no significant effects of lithium on cognitive function after one-year of treatment. Nonetheless, the authors

concluded that lithium was a safe drug in older adults as most of the side effects and dropouts from the trial were due to mild and reversible side effects. In a single-blind, multicenter clinical trial with 71 patients with mild to moderate AD conducted in Europe, Hampel et al. (2009)[90] did not find any significant benefits of lithium on cognitive performance associated with ten weeks of treatment at therapeutic levels (0.5–0.8mmol/L). In this study, the authors evaluated the effect of lithium on biomarkers related to AD, and did not find any significant changes in cerebrospinal fluid (CSF) concentrations of $A\beta_{42}$ and phosphorylated Tau, nor in phosphorylated GSK-3β (i.e. the inactive form of this enzyme) levels in leukocytes. The authors hypothesize that their negative results, in light of the short duration of treatment, were insufficient for lithium to exert its neuroprotective effects, or at least for these effects to be represented by changes in biomarker levels. Secondary analysis of this trial showed that lithium treatment was associated with increased plasma concentrations of BDNF. In this subset of AD patients, lithium treatment restored low baseline BDNF to levels similar to controls, and patients who displayed an increase in BDNF also had significant cognitive improvement[91]. The effect of lithium was specific to the BDNF response, as no significant changes were observed in levels of glial cell-derived neurotrophic factor (GDNF) both in the CSF and serum of AD patients after 10 weeks of lithium treatment[92].

More recently, we conducted a double-blind, placebo controlled, clinical trial to evaluate whether long-term treatment with lithium at sub-therapeutic levels (serum levels of 0.2–0.5 mmol/L) could delay the progression from amnestic mild cognitive impairment (MCI) to dementia, and to evaluate the disease-modifying properties as illustrated by the modification of clinical and biological markers of AD in patients with MCI [11]. This study recruited 45 older adults with amnestic MCI, and the preliminary analysis after one year of follow-up showed that amnestic MCI subjects receiving lithium presented stable cognitive performance and lower conversion rates to AD compared to subjects on placebo, although the latter difference was not statistically significant. However, significant differences in favour of the lithium group were observed on multiple cognitive parameters, namely memory, attention and global cognitive function. In addition, lithium use was associated with a significant reduction in CSF concentrations of phosphorylated Tau as compared to subjects in the placebo group. 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 upon follow-up. Overall, these results suggest that long-term lithium treatment may have disease-modifying properties on the core pathophysiologic features of AD and deliver a marginal clinical benefit, mostly if started at the earlier stages of the disease process. In another recent clinical trial conducted by a different Brazilian group, Nunes et al. (2013) demonstrated a significant improvement in global cognitive performance (as shown by the MMSE) using continuous microdoses of lithium

(300µg daily) for 18 months. The authors state that these benefits started after 6 months of treatment and persisted until the end of the trial.

As stated earlier, autophagy is a key intracellular pathway dedicated to the degradation of mutant proteins, some of which are associated with neurodegeneration[93]. Lithium ultimately induces autophagy via its effect on the dominant regulatory mechanism, which is dependent on the inhibition of IMP[20]. Autophagy is also induced by active GSK-3β[93]; therefore, the inhibition of GSK-3β by lithium leads to the attenuation of autophagy. This effect has been shown to occur via the activation of mTOR[21]. Therefore, there is a clear interplay between distinct regulatory mechanisms that may be differentially affected by lithium depending on the prevailing pathological process of the neurodegenerative disease. The overall effect of lithium on these mechanisms and their clinical implications still need to be clarified by future controlled studies.

Amyotrophic lateral sclerosis (ALS):

The potential neuroprotective effects of lithium were also evaluated in ALS, a severe progressive neurodegenerative disorder that affects motor neurons leading to premature disability and death[94].

Dill et al. (2008)[95] suggested the potential neuroprotective effect of lithium in ALS by demonstrating the ability of lithium to induce the sprouting of pyramidal neurons in the corticospinal tract following mechanical injury. In primary neuronal cultures obtained from the ventral spinal cord, Busceti et al. (2008)[96] suggested that the neurotrophic response and synaptogenesis induced by lithium could be relevant for the treatment of ALS, with a possible impact on disease progression. This effect was related to the inhibition of GSK-3β (and subsequent decrease in Tau phosphorylation) and upregulation of autophagy, which may further increase the clearance of hyperphosphorylated Tau. Therefore, it is likely that distinct pathways may contribute to the neuroprotective effects of lithium on neurodegenerative diseases associated with hyperphosphorylated Tau, such as AD, ALS and some forms of frontotemporal dementia[97].

Preclinical studies have shown a significant improvement in motor function in animal models of ALS treated with lithium. The main hypothesized mechanism for such improvement was the stimulation of autophagy by lithium[98,99]. In an early clinical trial, lithium treatment for 15 months was shown to be safe and significantly associated with a slower rate of disease progression and death in these patients[98]. However, more recent and larger trials failed to show a significant benefit of lithium for this condition[100,101].

In animal models of ALS, the co-treatment of lithium with valproate (another mood stabilizing drug) has been shown to produce more beneficial effects than the treatment

with either drug alone[102]. Similar findings were presented by other authors addressing animal models of Huntington's disease[103] and traumatic brain injury[104].

Chiò et al. (2013)[105] recently conducted a phase 3 multicenter, double-blind, placebo-controlled trial of lithium versus placebo in ALS. Patients were randomly assigned into two groups to receive either lithium (n=107) or matched placebo tablets (n=107). 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. The primary endpoint was the rate of survival after 18 months, which was ascertained by intention to treat analysis. Unfortunately, the study results did not support any evidence of increased survival associated with lithium treatment.

Other neurodegenerative diseases:

Lithium has been also studied in preclinical models of other neurodegenerative diseases, including Parkinson's[106,107] and Huntington's disease[108,109,110]. The pattern of cell death in Parkinson's disease is complex, having features of apoptosis and necrosis in addition to accumulations of autophagosome-like structures[111]. Using an *in vitro* model of Parkinson's disease, Chen et al. (2004)[112] demonstrated that 6-OHDA activates GSK-3β in cultured human neuroblostoma SH-SY5Y cells as well as in cultures of rat cerebellar granule neurons. Lithium and other specific GSK-3β inhibitors effectively protected against neuronal death after exposure to 6-OHDA, indicating that GSK-3β is involved in 6-OHDA-induced apoptosis of SH-SY5Y cells and cerebellar granule neurons. However, other studies in dopaminergic neurons have presented conflicting results: 6-OHDA treatment was not associated with GSK-3β activation, and 6-OHDA-induced degeneration was not inhibited by lithium[113]. These results suggest that GSK-3β activity may not be centrally involved in 6-OHDA-induced dopaminergic neurodegeneration in the substantia nigra (pars compacta) of rats. In a rat model of Huntington's disease, a protocol of chronic subcutaneous injections of lithium showed that lithium treatment may protect against brain damage caused by focal cerebral ischemia and suppresses excitotoxicity-induced striatal lesions[114]. Despite the promising neuroprotective potential against disease mechanisms described in these studies, no clinical trials have been conducted so far in human patients to test these findings.

Conclusions:

Converging lines of evidence derived from preclinical and clinical models support the rationale for the study of the protective effects of lithium in neuropsychiatric conditions associated with chronic degeneration of the central nervous system. This effect is probably due to the modulation of multiple biological cascades that are involved in cell survival, neuronal plasticity, transcriptional control, energetic metabolism, and resilience

against neurotoxic insults. Some of these mechanisms may be represented as core pathological processes of mood and neurodegenerative disorders. The knowledge on the specific effects of lithium on distinct pathways critically relevant to neuronal homeostasis, and the broad understanding of their interactions, will guide the development of novel therapeutic strategies against neurodegeneration, aiming at both symptom reduction and attenuation of disease progression.

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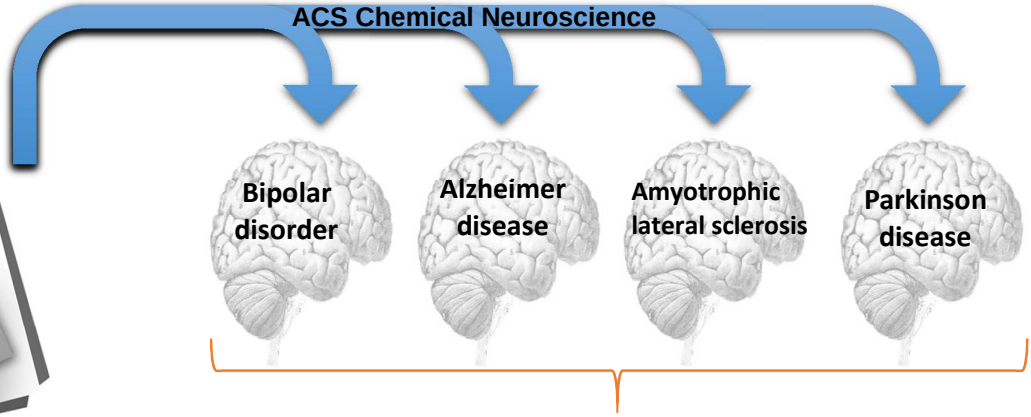

Neuroprotective effects of lithium

Bipolar disorder	Alzheimer disease	Amyotrophic lateral sclerosis	Parkinson disease
↑pGSK3β	↑pGSK3β	↑pGSK3β	↑pGSK3β
↑ BDNF	↑ BDNF	↓pTau	↑ BDNF
↑ autophagy	↓pTau	↑ autophagy	↓pTau
↓ TNFα	↑ autophagy		↑ autophagy
↑ TBARs	↑ mTor		
	↓ inflammation		
	↓ IMP		