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Article *in* Drugs & Aging · April 2012

DOI: 10.2165/11599180-000000000-00000 · Source: PubMed

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Drugs Aging 2012; 29 (5): 335-342
1170-229X/12/0005-0335/$49.95/0

Does Lithium Prevent Alzheimer's Disease?

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Abstract

Lithium salts have a well-established role in the treatment of major affective disorders. More recently, experimental and clinical studies have provided evidence that lithium may also exert neuroprotective effects. In animal and cell culture models, lithium has been shown to increase neuronal viability through a combination of mechanisms that includes the inhibition of apoptosis, regulation of autophagy, increased mitochondrial function, and synthesis of neurotrophic factors. In humans, lithium treatment has been associated with humoral and structural evidence of neuroprotection, such as increased expression of anti-apoptotic genes, inhibition of cellular oxidative stress, synthesis of brain-derived neurotrophic factor (BDNF), cortical thickening, increased grey matter density, and hippocampal enlargement. Recent studies addressing the inhibition of glycogen synthase kinase-3 beta (GSK3B) by lithium have further suggested the modification of biological cascades that pertain to the pathophysiology of Alzheimer's disease (AD). A recent placebo-controlled clinical trial in patients with amnestic mild cognitive impairment (MCI) showed that long-term lithium treatment may actually slow the progression of cognitive and functional deficits, and also attenuate Tau hyperphosphorylation in the MCI-AD continuum. Therefore, lithium treatment may yield disease-modifying effects in AD, both by the specific modification of its pathophysiology via inhibition of overactive GSK3B, and by the unspecific provision of neurotrophic and neuroprotective support. Although the clinical evidence available so far is promising, further experimentation and replication of the evidence in large scale clinical trials is still required to assess the benefit of lithium in the treatment or prevention of cognitive decline in the elderly.

1. Introduction

Lithium salts have been widely used for over 5 decades for the treatment of major psychiatric disorders,[1] particularly bipolar disorder and treatment-resistant depression. The clinical benefits are unequivocal, yielding symptomatic control of acute episodes and prevention of recurrence upon long-term use. Recent study has further suggested that lithium may have potential disease-modifying effects against Alzheimer's disease (AD) and other neurodegenerative conditions.[2] In this article, we critically review the literature addressing the putative neuroprotective properties

of lithium that may substantiate its use in the treatment and prevention of AD and other neurodegenerative conditions. The following keywords were used to search the PubMed database, without time constraints, until November 2011: lithium, GSK3B, neuroprotection, neurodegeneration, cognitive impairment, Alzheimer's disease, dementia. Secondary references obtained from selected publications were also included in the review.

The exact mechanism of action of lithium is not fully understood, and presumably does not involve the action of first and second messengers of neurotransmission through membrane receptors; rather, lithium targets downstream molecules, leading to the modification of intracellular signalling pathways and gene regulation. The inhibition of inositol monophosphatase (IMP) was one of the first mechanisms of action to be reported, and leads to the depletion of inositol triphosphate (IP_3). More recently, this effect has been shown to up-regulate autophagy.[3,4] While it may not be critical to the therapeutic effect of lithium in mood disorders, this effect may be particularly relevant in the prevention or attenuation of neurodegeneration, because autophagy is an intracellular protein degradation pathway that promotes the clearance of mutant and abnormally processed proteins that would otherwise accumulate in neurons. In fact, autophagy-related mechanisms can rescue a variety of animal models of neurodegenerative disease.[5]

Lithium is also a potent inhibitor of the enzymatic activity of glycogen synthase kinase-3 beta (GSK3B), a serine–threonine kinase that intermediates various intracellular signalling pathways, including Wnt/Notch signalling and cell cycle control. Two mechanisms of inhibition of GSK3B by lithium have been described: in the direct inhibition, lithium competes with magnesium at the cationic binding site, which is required for enzymatic activation; the indirect inhibition involves the activation of protein kinase B via Akt, usually in response to insulin or insulin growth factors, leading to the phosphorylation of the serine-9 residue of the regulatory amino-terminal domain.[6-8] The inhibition of GSK3B precludes the degradation of free β-catenin, a potent transcription factor, leading to the functional activation of the canonical Wnt/β-catenin signalling pathway. Other effects attributed to lithium involve the inactivation of proteasomes, down-regulation of E-cadherin, and up-regulation of transcription factors via non-canonical Wnt signalling (such as the nuclear factor of activated T-cells, NF-AT), which have been associated with cell proliferation both in neurons[9] and in non-neuronal cells.[10] The combined effect of lithium in multiple intracellular signalling systems ultimately inhibits apoptosis and promotes the synthesis of neurotrophic factors, in favour of mechanisms of synaptic plasticity, neurite outgrowth and neurogenesis.[11-13] Such mechanisms may be related to the therapeutic effects of lithium in psychiatric disorders[14] and underlie additional mechanisms of neuroprotection, as observed in models of AD and other neurodegenerative diseases. In the next sections, we will review the preclinical and clinical evidence of the neuroprotective effects of lithium in affective and neurodegenerative disorders.

2. Neuroprotective Effects of Lithium: Evidence from Preclinical Studies

Diverse preclinical models have provided consistent evidence supporting a key role for the neuroprotective effects of lithium. Lithium has a significant positive effect in synaptic plasticity and reduces Tau phosphorylation in neuronal cell culture studies.[15] Lithium treatment can also prevent and rescue the neurotoxic effects and cell death related to amyloid-beta (Aβ) protein exposure to neurons in cell culture.[16] These effects of lithium are allegedly mediated by the increased phosphorylation of the serine-9 epitope of GSK3B and subsequent inhibition of enzymatic activity. In addition, recent evidence suggests that lithium can significantly reduce GSK3B enzyme expression[17,18] and stimulate intracellular autophagic processes.[3,19] The deregulation of GSK3B metabolism leading to increased activity is an early pathological event in the pathophysiology of AD, triggering several downstream events culminating in increased production of Aβ and Tau hyperphosphorylation.[18] The latter evidence might contribute to the neuroprotective effects of lithium

in neuronal culture, but need to be further explored in additional studies.

Chronic lithium treatment stimulates the proliferation of progenitor cells in cultured neuronal cells and prevents cell loss induced by glutamate and glucocorticoids toxicity.[20,21] Lithium also increases the expression of anti-apoptotic proteins, such as B-cell lymphoma-2 protein (Bcl-2).[22,23] The higher expression of Bcl-2 inhibits mitochondrial release of cytochrome c, regulating its permeability while maintaining calcium homeostasis in the endoplasmic reticulum, which is essential for the maintenance of cell integrity and survival.

There are several lines of evidence, derived from animal studies, that also suggest a neuroprotective role of lithium. Long-term lithium treatment significantly reduces Tau phosphorylation and Aβ production, increases synaptic plasticity and facilitates long-term potentiation and cell firing, and most of these effects are due to GSK3B inhibition.[24-26] Lithium treatment can stimulate brain-derived neurotrophic factor (BDNF) synthesis and release, and hippocampal neurogenesis. There is also evidence of neuronal apoptosis inhibition, delayed age-associated cerebral glucose impairment and increased brain weight after lithium treatment.[27] Lithium treatment can additionally increase Akt activity, leading to higher expression of transcriptional factors β-catenin and CREB (cAMP response element-binding), which positively regulates cell survival.[27] These biological effects are accompanied by significant memory improvement and slow rates of age-related memory decline in these mice.

In animal models of AD, lithium treatment can prevent and/or rescue the amyloid-induced neurotoxic effects, such as Tau protein hyperphosphorylation and cell death.[25,28] This is also accompanied by improvement in memory impairment and decline in these animals. In transgenic mice bearing amyloid-precursor protein (APP) mutations, lithium treatment modulated APP processing and reduced Aβ production via GSK3B inhibition.[29] The inhibition of GSK3B and subsequent activation of Wnt/β-catenin signalling by lithium promoted hippocampal neurogenesis in double transgenic mice overexpressing the Swedish and Indiana mutations in the human APP.[30] A recent study suggested that neuroprotective effects of lithium in APP transgenic mice might be time-dependent.[27] The authors found that lithium treatment when started in 2-month-old mice had a significantly stronger effect in reducing AD-related neuropathology and memory impairment than when started in 6-month-old mice.

Therefore, lithium may exert its neuroprotective effects by modulating a large array of intracellular cascades and pathways, including the inhibition of GSK3B, stimulation of neurotrophic and transcription factors, hippocampal neurogenesis, reducing glutamate excitotoxicity and apoptosis-related cascades. More specific to AD, lithium significantly reduces Tau protein phosphorylation and modulates the APP processing, reducing $A\beta_{42}$ production.

3. Neuroprotective Effects of Lithium: Evidence from Clinical Studies in Affective Disorder

In the last decade, distinct studies have suggested that the therapeutic use of lithium salts is associated with significant neurotrophic and neuroprotective effects in patients with affective disorder.[29] From a clinical perspective, lithium is a first-line mood stabilizer, preventing the relapse and recurrence of new episodes of mania and depression and reducing suicide risk.[31-35] By reducing the number of affective episodes, it might lessen the stimulation of deleterious cascades such as increased inflammation, oxidative stress and decreased neurotrophic support observed in these patients.[35-40] These effects reduce the risk of progressive changes in the central nervous system (CNS), observed in patients with mood disorders,[40] providing indirect, but strong, evidence that lithium treatment is protective to the CNS.

Clinical studies have also demonstrated that lithium can modulate *in vivo* cellular cascades related to neuronal resilience and neuroprotection. Lithium treatment is associated with increased phospho-GSK3B levels and, consequently, reduced enzymatic activity in leukocytes of patients

with bipolar disorder and recurrent major depression.[41-44] The inhibition of GSK3B may have protective effects as it can reduce apoptosis, improve mitochondrial function and reduce both Tau phosphorylation and $A\beta_{42}$ production.

In addition to the effects on GSK3B activity, lithium augments peripheral BDNF levels after acute and chronic treatment in bipolar patients.[44-47] Also, lithium treatment sensitizes the tyrosine kinase b (TrKb) receptor, amplifying the response of the BDNF signalling system.[48] Few studies have addressed the impact of lithium on oxidative stress parameters. Lithium treatment is associated with a reduction in pro-oxidative and an increase in anti-oxidative stress markers.[35,49]

Short- and long-term lithium treatment was associated with an increased hippocampal volume and cortical thickness in patients with bipolar disorder in structural magnetic resonance studies.[49-55] Higher N-acetyl-aspartate and myo-inositol levels have also been described after chronic lithium treatment in magnetic resonance spectroscopy.[55,56] These findings altogether suggest that lithium has a significant positive effect on synaptic density and function in bipolar patients.

Another compelling line of evidence of the neuroprotective properties of lithium derives from observational epidemiological studies. Several studies so far suggest that chronic lithium treatment is associated with lower rates of dementia and AD in older patients with bipolar disorder.[57] Case registry studies have also found that the reduction in incidence of dementia in these subjects is correlated with the longer time of lithium intake.[57] Furthermore, areas naturally enriched with lithium in the water and soil show lower rates of suicide.[58,59]

Taken together, these converging lines of evidence suggest a significant neuroprotective role of lithium in patients with affective disorders. The exact mechanistic links are largely unknown, but may involve the regulation of GSK3B and of other critical cascades related to neurotrophic support and oxidative stress. In turn, this might provide substantial long-term neuroprotective effects, preventing the progressive nature of pathological brain changes and reducing the higher risk of dementia that is associated with affective disorder.

4. Neuroprotective Effects of Lithium: Evidence from Studies in Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI)

The evidence that lithium, by its inhibitory effect on GSK3B activity, could modulate cascades related to AD pathophysiology set the stage to consider this drug as a candidate for the treatment and prevention of AD. However, few trials examined the efficacy of lithium in patients with mild to moderate AD and, in fact, the initial studies presented negative results. In a case-control study using primary care patient records in the UK, Dunn et al.[54] showed that patients who received lithium had actually a higher risk of a diagnosis of dementia, with a trend toward increasing risk with increasing numbers of lithium prescriptions. In a small, open-label trial, including 25 patients at baseline, Macdonald et al.[60] reported no significant benefit on cognitive performance after 1 year of lithium treatment. However, the all-cause dropout rates were very high and only eight patients completed the trial.

A larger, single-blind, placebo-controlled clinical trial including 71 patients with AD also did not find a significant benefit of lithium treatment on cognition over 10 weeks of treatment.[61] In this study, lithium did not significantly inhibit GSK3B activity, nor did it change cerebrospinal fluid (CSF) levels of the AD-related biomarkers $A\beta_{42}$ and total Tau protein (T-Tau). However, they found a trend toward reduced CSF phosphorylated Tau (P-Tau) levels in the lithium group. On the other hand, additional analyses showed that lithium treatment was associated with a significant increase in BDNF serum levels as compared with placebo-treated patients or healthy controls,[62] but not in glial-derived neurotrophic factor (GDNF).[63] Some possible explanations for these negative findings include the small sample size included[60] and the short duration of treatment.[61] Furthermore, and most importantly, both trials recruited patients with mild to moderate AD, in which the core patho-

logical changes are well-established and possibly less prone to benefit from the disease-modifying effects of lithium. Recently, our group conducted a double-blind placebo-controlled clinical trial of lithium on patients with mild cognitive impairment (MCI).[64] In this study, we recruited 45 older adults with MCI according to the Mayo Clinic criteria.[65] Subjects were randomized to receive low doses of lithium (to achieve serum levels between 0.2 and 0.4 mEq) or placebo for 2 years. Baseline and outcome measures included the assessment of CSF biomarkers $A\beta_{42}$, T-Tau and P-Tau, and cognitive performance, and a safety analysis.

After 1 year of follow-up, lithium-treated MCI subjects showed stable cognitive performance and lower conversion rates to AD as compared with MCI subjects on placebo (though not statistically significant). More strikingly, lithium-treated subjects showed a significant reduction in P-Tau levels as compared with subjects on placebo. Additional analyses revealed that the reduction in P-Tau levels was even more significant in MCI subjects who did not progress to AD after 1 year. No significant changes were observed for $A\beta_{42}$ and T-Tau.[64] Overall, these results highlight the potential of lithium as a disease-modifying agent in AD. This effect is more evident in subjects at the earlier development stages of the pathological disease process (i.e. in subjects diagnosed with MCI), when they are more likely to benefit from the disease-modifying effects of lithium.

5. Neuroprotective Effects of Lithium: Evidence from Studies on Non-AD Neurodegenerative Disorders

In addition to AD, other neurodegenerative conditions may also benefit from the therapeutic effects of lithium. In particular, a few studies have addressed its utility in patients with amyotrophic lateral sclerosis (ALS), which is a severe progressive neurodegenerative disorder that affects motor neurons, leading to premature disability and death.[66,67] The neuroprotective effect of lithium in ALS seems to be related to the activation of autophagy, an increased number of mitochondria in motor neurons and suppressed reactive astrogliosis, which are features associated with the pathophysiology of motor neuron degeneration in ALS.[68] Lithium treatment has been associated with improvement of pathological changes in ALS animal models[69,70] and slower rates of disease progression in human patients,[59] in spite of the fact that that negative findings have also been described.[71,72] Thus, more studies are needed to address the potential of lithium as a treatment drug for delaying the progression of ALS.

In addition, lithium has been studied in preclinical models of other neurodegenerative disorder such as Parkinson disease[73,74] and Huntington disease.[23,75,76] Despite these studies showing a potential neuroprotective effect against the neurodegenerative features of these disorders, no clinical trial has been conducted in human patients to date.

6. Limitations to the Long-Term Use of Lithium

As reviewed in the above sections, the neuroprotective effects of lithium for AD and other psychiatric disorders are more pronounced upon long-term treatment. This can be problematic to older subjects because of safety concerns regarding its long-term use.[27] Older adults may be more sensitive to lithium side effects, such as hand tremor and nausea, and this may lead to early discontinuation of treatment. Also, lithium-induced thyroid and renal dysfunction might be problematic in elderly subjects and requires close monitoring. Thyroid dysfunction is usually easily managed with hormone replacement, but renal dysfunction may require drug discontinuation. The potential for drug interactions is another major concern. Concomitant use of lithium with some drugs can potentiate the adverse events related to lithium either by increasing serum drug concentrations (e.g. thiazide diuretics) or by potentiating renal dysfunction (non-steroidal anti-inflammatories).

On the other hand, the lower doses of lithium needed to provide neuroprotection may be associated with a reduced risk of emergent side effects in older subjects. In our clinical trial, lithium was

well tolerated by patients with MCI, with very few drop-outs due to drug intolerance. The most common side effects were of mild intensity and transient. Also, lithium-treated subjects did not show a higher incidence of severe adverse effects related to treatment.[77] Thus, low dose lithium seems to be safe and well tolerated by older subjects.

7. Conclusions

Overall, a large bulk of data suggests that lithium yields neuroprotective effects against psychiatric and neurodegenerative disorders. Trials conducted in samples of MCI patients have presented preliminary, but promising results, as long-term lithium treatment was associated with stabilization of cognitive decline and a reduction of CSF P-Tau. This beneficial effect can be accomplished at lower drug doses than those usually needed to treat patients with acute affective episodes, reducing the risk of treatment emergent adverse effects and improving treatment adherence. However, additional trials with longer treatment and follow-up time are necessary to confirm these findings. Also, the beneficial effects of lithium may not be restricted to AD, as it has shown potential neuroprotective effects in ALS, a devastating neurodegenerative disorder.

Acknowledgements

The authors have no conflicts of interest that are directly relevant to the content of this article.

Funding for the present work was provided by Conselho Nacional de Pesquisa Científica (CNPq, Project 554535/2005-0), Alzheimer's Association (NIRG-08-90688), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Project 02/13635-7 and 09/52825-8) and Associação Beneficente Alzira Denise Hertzog da Silva (ABADHS).

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