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Lithium and Alzheimer's Disease: Experimental, Epidemiological, and Clinical Findings

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Abstract

Alzheimer's disease (AD) represents one of the greatest health-care challenges of the twenty-first century. Besides known pathologies such as intracellular accumulation of neurofibrillary tangles and extracellular deposition of amyloid-beta plaques, other factors, such as dysregulated GSK-3 activity, mitochondrial dysfunction, inflammation, and oxidative stress, have been shown to play a role in the pathogenesis of AD. Over the last two decades, the evidence accumulated for a neuroprotective effect of lithium, as an important mechanism of this ion in mood disorders, reflected by an increase in cerebral gray matter volume in lithium-treated subjects. Neurobiological mechanisms of lithium neuroprotective actions may also be relevant to the pathogenesis and treatment of AD, and they will be delineated. In most epidemiological studies, a negative association between lithium use and dementia has been shown, including two most recent papers regarding a concentration of lithium in drinking water. In this article, the results of initial studies using lithium in the treatment of dementia and showing some promise will also be presented. Therefore, considering the current paucity of treatments for the AD, further testing of lithium as a disease-modifying treatment in this illness may be warranted.

Keywords: Alzheimer's disease, dementia, lithium, neuroprotection, glycogen synthase kinase-3

1. Introduction

Alzheimer's disease (AD) represents one of the greatest health-care challenges of the twenty-first century. Nearly 50 million people over the age of 60 years are presently diagnosed with AD worldwide, and the projected figure is estimated to be 130 million in 2050 [1].

The main pathology of the AD includes the intracellular accumulation of neurofibrillary tangles, connected with abnormal tau protein phosphorylation, and extracellular deposition of amyloid-beta (Aβ) plaques. Such changes may be present even several years before symptom manifestation. However, in recent years, the evidence has been accumulated that some other factors may be both pathogenic and playing a role in the progress of the illness. They include, among others, dysregulated glycogen synthase kinase-3 (GSK-3) activity, mitochondrial dysfunction, inflammation, and oxidative stress [2].

Over the last two decades, the evidence accumulated for neuroprotective effects of lithium as important mechanisms of this ion in mood disorders. These effects were reflected by an increase in cerebral gray matter volume in lithium-treated subjects and also related to a possible influence of lithium on some pathogenic mechanisms operating in the AD. Such neurobiological mechanisms of lithium which may be relevant to AD pathogenesis, and treatment will be characterized in the first part of this article. They make lithium a candidate for use as a therapeutic drug in this illness [3]. In the recent decade, a negative association between lithium use and dementia has been shown in most epidemiological studies, including two most recent papers regarding a concentration of lithium in drinking water. In this article, preliminary studies of using lithium in the treatment of mild cognitive impairment (MCI) and AD that show some promise will also be presented.

2. Neuroprotective effects of lithium: relevance to pathology of Alzheimer's disease

The neuroprotective effect of lithium in bipolar patients has been reflected in neuroimaging studies, starting in 2000, when Moore et al. [4] in a research letter to the Lancet suggested a lithium-induced increase in human brain gray matter. Since then, several researches on this topic have been published. The prefrontal cortex, anterior cingulate, and hippocampus made the brain structures most frequently shown to be influenced by either short- or long-term lithium treatment. The results of cross-sectional and prospective studies on this issue were recently reviewed by Hajek and Weiner [5].

Among cross-sectional studies, the most frequently reported pattern was larger gray matter volumes in patients currently treated with lithium compared to those currently not on lithium. The association between lithium treatment and higher gray matter volume was reported regardless of mood state and diagnostic subtype [5]. Our research showed that bipolar patients receiving lithium had larger hippocampal volumes than non-lithium patients and comparable to healthy controls [6].

In a prospective study, Monkul et al. [7] performed a voxel-based morphometry analysis in healthy persons receiving lithium in therapeutic doses for 4 weeks. They found a significant increase in gray matter in the left and right dorsolateral prefrontal cortices and the left anterior cingulate region. Yucel et al. [8] made neuroimaging study in BD patients receiving lithium up to 2 months and for 2–4 years showing a bilateral increase in hippocampal volume in both groups. Moore et al. [9] extended their results published 9 years earlier as they found that an increase in total gray matter volume in the prefrontal cortex of depressed bipolar subjects after 4 weeks of lithium administration was significant only in lithium responders.

The neuroimaging studies were also performed to compare lithium with valproate, carbamazepine, and antipsychotics, given to BD patients. In a paper of Lyoo et al. [10] including 22 BD patients treated with either lithium or valproate, the gray matter increased in lithium group, with maximum effect at weeks 10–12 which was still evident at 16 weeks of treatment. Such an increase was also associated with positive clinical response. On the other hand, patients receiving valproate did not show any significant changes in gray matter volume. Germana et al. [11] in their study of 74 remitted bipolar patients receiving long-term prophylactic treatment with lithium, valproate, carbamazepine, or antipsychotics observed that the volume of gray matter in some brain structures (the right subgenual anterior cingulate gyrus, the left postcentral gyrus, the hippocampus/amygdala complex, and the insula) was greater in patients receiving lithium than all other pharmacological treatments.

Thus, there is reasonable evidence showing that lithium administration can result in an increase of brain gray matter volume both in healthy subjects and in patients with BD which may be associated with its neuroprotective effect at a clinical level. The replicated substantiation for this has not been demonstrated for any other mood-stabilizing drug. The mechanism of the increase is not clear. The MRI changes are probably not related to the effect of lithium on tissue water or magnetic properties. Since the studies of magnetic resonance spectroscopy showed the association between lithium treatment and increased N-acetyl aspartate, localized in neurons, this may suggest an effect of lithium on neurons, which may involve an increase in the number of neurons, dendritic arborization, or neutrophil [5].

Several biochemical targets have been involved in the neurotrophic and neuroprotective effect of lithium which may be relevant to its possible disease-modifying treatment in the AD. The most important include the increased expression of neurotrophins [mainly brain-derived neurotrophic factor (BDNF)], the inhibition of glycogen synthase kinase-3 (GSK-3), modulation of the phosphatidylinositide (PI) cascade, inhibition of the protein kinase C (PKC), and increased expression of the B-cell lymphoma 2 (Bcl-2). As a result of such actions, lithium increases cell survival by promoting neurogenesis in the adult brain and by inhibiting cell death (apoptosis) cascades [12].

BDNF belongs to the neurotrophin family, along with nerve growth factor (NGF) and neurotrophin-3 (NT-3), NT-4, NT-5, and NT-6. These neurotrophins play an important role for the survival and function of neurons. BDNF regulates the activity of various neurotransmitters, e.g., glutamate, gamma-aminobutyric acid, dopamine, and serotonin. Experimental studies showed that lithium enhances the BDNF system. In clinical studies, lithium treatment increases the blood level of BDNF [13].

GSK-3 modulates a number of cellular processes, among others, cell apoptosis, and the inhibition of GSK-3 results in an antiapoptotic effect. GSK-3 is also a key enzyme in the metabolism of amyloid precursor protein and in the phosphorylation of the tau protein, the main pathological processes in AD. Lithium inhibits GSK-3 activity, and the evidence for this has accumulated in recent two decades, using various experimental models. Therefore, the GSK-3 can be considered as one of the most important therapeutic targets of lithium, and the GSK-3 inhibition by this ion can make an essential mechanism of its therapeutic action in mood disorders [14]. In experimental studies, using the cultures of rat neurons, it was shown that lithium reduces GSK-3 mRNA [15]. In mutant tau transgenic mice with neurofibrillary pathology, lithium delays the progress of neurofibrillary tangles, and in the *Drosophila* fly, adult-onset model of the AD, lithium alleviates

amyloid-beta pathology. Both these effects are thought to be obtained by lithium inhibition of the GSK-3 [16, 17]. About the GSK-3 inhibition by lithium, the effect of this ion on autophagy regulation should also be indicated, the signaling pathway of which is associated with the mammalian target of rapamycin (mTOR) [18].

The PI pathway plays a role in signal transduction mechanisms connected with the action of multiple neurotransmitters. Lithium significantly influences this pathway which resulted in the inositol-depletion hypothesis of lithium action, as an essential therapeutic mechanism in mood disorders. Lithium inhibits the inositol monophosphatase (IMPase) and many other phases of the PI pathway [12]. The effect of lithium on the PI pathway is also connected with enhancing autophagy by the mTOR-independent pathway [18].

Protein kinase C (PKC) is an enzyme associated with the PI pathway and plays a role in the action of many neurotransmitters and other cellular mechanisms. It has been found that lithium inhibits the activity of PKC that may contribute to its regulation of intracellular signaling and increasing neuroplasticity [12].

Bcl-2 is a protein playing a significant role in cellular resilience and plasticity, among others, by inhibiting apoptosis. Experimental studies demonstrated an increase of Bcl-2 in the brain by lithium treatment. Enhancing by lithium the expression of Bcl-2-associated athanogene (bag-1) augments the antiapoptotic effect, by mitigating glucocorticoid receptor nuclear translocation [12].

Morris and Berk [19] suggested some additional mechanisms of lithium action which may be important in the treatment of AD, such as the effects on mitochondrial function, calcium homeostasis, inflammation, microglial activation, glutamate excitotoxicity, and oxidative stress. Most of these processes are connected with the mechanisms described above.

Lithium produces a significant increase in mitochondrial performance in human brain tissue, the main factors of such effect being the inhibition of GSK-3 and activation of mTOR [20]. This cation also desensitizes brain mitochondria to the damaging effects of calcium influx [21] and increases mitochondrial levels of Bcl-2 [22]. As peripheral and neuro-inflammation, together with the chronic activation of microglia, constitutes an important element in the development of the AD, there is evidence that lithium can ameliorate various aspects involved in the pro-inflammatory response. These include the generation of tumor necrosis factor-alpha and interleukin-1 beta by microglia, and this effect is obtained via the inhibition of GSK-3 [23]. Lithium also exhibits a protective effect against the development of glutamate neurotoxicity, which is a consequence of chronic microglial activation, and this effect is due to the upregulation of BDNF [24]. In clinical conditions, lithium administration causes a decrease in markers of oxidative stress such as catalase and superoxide dismutase [25].

3. Epidemiological studies of lithium in Alzheimer's disease

The results of population studies of an association between lithium and dementia were reviewed by Donix and Bauer [26]. Data from large cohort and most case–control studies suggest an association between lithium treatment and dementia risk reduction or reduced dementia severity.

In their publication in 2005, Dunn et al. [27] reported that among 19,328 participants selected from a General Practice Research Database, more subjects with dementia were treated with Li compared to control subjects without dementia. However, mood disorders are the most frequent indication for Li treatment and also belong to the strongest risk factors for dementia, and as this study did not control for compliance/optimal treatment, it may have simply detected the increased risk of dementia in mood disorders. Terao et al. [28] investigated clinical records of 1423 outpatients at a university psychiatric department and compared patient treated with lithium to age- and the gender-matched control group who had never been prescribed with lithium. Patients who had previously received lithium and/or were currently on lithium had significantly better Mini Mental State Examination (MMSE) scores than the control patients. Nunes et al. [29] studied the occurrence of AD in 66 elderly BD patients assessed during euthymia, receiving long-term lithium therapy, and in 48 age-matched patients who were not recently taking lithium. The percentage of patients with dementia was 19% in the first group and 7% in the second group. The diagnosis of the AD was made in three patients (5%) receiving lithium and in 16 patients (33%) who were not taking lithium, which suggests that lithium treatment may reduce the prevalence of AD in patients with bipolar disorder. Angst et al. [30] studied subjects with bipolar disorder (N = 220) and major depressive disorder (N = 186) followed from 1965 to 1985, receiving long-term treatment with lithium, clozapine, or antidepressants. In the whole group, the prevalence of dementia showed a significant association with age. However, when an analysis of the 88 patients with dementia was performed, the association with age was lost, and there was a trend to an inverse correlation between lithium administration and the severity of dementia.

Two papers coming from the University of Copenhagen employed the Danish nationwide register of lithium prescriptions. In the first one, a comparison was made for the diagnosis of dementia or AD between 16,238 persons who had purchased lithium at least once during inpatient or outpatient treatment and 1,487,177 persons from the general population who had never bought lithium. Those who had bought lithium at least once had the 1.5-fold higher rate of dementia than the persons not taking lithium. However, those who continued treatment with lithium had the rate of dementia decreased to the same level as that for the general population. Such a decrease was exclusive to lithium because persons receiving anticonvulsant drugs had the risk of dementia increased with the duration of treatment [31]. The second study followed up 4856 patients which received a diagnosis of a manic or mixed episode or bipolar disorder at their first psychiatric contact for the period of 1995–2005 (103.6/10000 person-years). The percentages of patients receiving given drug were as follows: lithium 50.4%, anticonvulsants 36.7%, antidepressants 88.1%, and antipsychotics 80.3%. During the follow-up period, 216 patients were diagnosed with dementia. It was found that a reduced rate of dementia in BD patients was connected with long-term treatment with lithium. On the other hand, such a phenomenon was not observed with continued treatment with anticonvulsants, antidepressants, or antipsychotics [32].

In 2015, Gerhard et al. [33] examined the association of lithium and dementia risk in a large claim-based US cohort of publicly insured older adults with bipolar disorder (n = 41,931), including individuals ≥50 years who did not receive dementia-related services during the prior year. Each follow-up day was classified by past-year cumulative duration of lithium use.

Authors, year, ref. no.	Design of study	Results
Dunn et al.[27]	9954 lithium-treated patients and 9374 not on lithium, selected from a General Practice Database	Lithium treatment associated with increased dementia risk
Terao et al. [28]	1423 psychiatric outpatients from a university clinic	Current or previous lithium treatment associated with better performance on MMSE
Nunes et al. [29]	66 elderly patients with bipolar disorder receiving lithium and 48 matched patients without lithium	Reduced AD prevalence associated with lithium treatment
Angst et al. [30]	220 subjects with bipolar disorder and 186 subjects with unipolar depression followed for 20 years	Reduced dementia severity among patients receiving lithium
Kessing et al. [31]	16,238 persons who had purchased lithium in the past and 1,487,177 not using lithium	Reduced risk for dementia associated with the continued use of lithium
Kessing et al. [32]	4856 patients with bipolar disorder, followed for 10 years	Reduced risk for dementia associated with the continued use of lithium
Gerhard et al. [33]	41,931 patients >50 years with bipolar disorder, followed for 3 years	Reduced risk of dementia with the long-term (10–12 months) use of lithium
Kessing et al. [34]	73,731 patients with dementia, 733,653 control subjects	Decreased incidence of dementia in subjects exposed to >10 µg/L of lithium in drinking water
Fajardo et al. [35]	Changes in AD mortality between 2000 and 2006, and 2009 and 2015 and lithium in drinking water	Increase in AD mortality negatively associated with lithium concentration in drinking water

Table 1. Epidemiological studies of lithium and dementia.

Compared with nonuse, 301–365 days of lithium exposure was associated with significantly reduced dementia risk No corresponding association was observed for shorter lithium exposures or any exposure to anticonvulsants that may suggest that long-term lithium treatment may reduce dementia risk in older adults with bipolar disorder.

Recently, two papers appeared studying a relationship between lithium in drinking water and dementia. Kessing et al. [34] performed a Danish nationwide, case–control research, studying an association between the municipality of residence and measurements of lithium in drinking water. The data were obtained from all patients between 50 and 90 years of age who had a diagnosis of dementia during hospitalization, from 1970 to 2013. A total of 73, 731 patients with dementia and 733, 653 controls were included in the study. Lithium exposure was statistically significantly different between patients with a diagnosis of dementia and controls, and a nonlinear association was observed. Compared with individuals exposed to 2.0–5.0 µg/L, the incidence rate ratio of dementia was decreased in those exposed to more than 15.0 µg/L and 10.1–15.0 µg/L and increased with 5.1–10.0 µg/L. Similar patterns were found for Alzheimer's disease and vascular dementia as outcomes. In the second study, Fajardo et al. [35] examined the relationship between trace levels of lithium in drinking water and changes in AD mortality

across several Texas counties. 6180 water samples from public wells since 2007 were obtained, and changes in AD mortality rates were calculated by subtracting aggregated age-adjusted mortality rates between 2000 and 2006 from those between 2009 and 2015. The authors found that the age-adjusted AD mortality rate was significantly (+27%) increased over time. Changes in AD mortality were negatively correlated with trace lithium levels, and statistical significance was maintained after controlling for most risk factors except for physical inactivity, obesity, and type 2 diabetes. Furthermore, the prevalence of obesity and type 2 diabetes positively correlated with changes in AD mortality but also negatively correlated with trace lithium in drinking water. The results suggest that trace lithium in water may be negatively linked with changes in AD mortality, as well as obesity and type 2 diabetes, which are important risk factors for AD.

The chronological arrangement of epidemiological studies on lithium and dementia is presented in **Table 1**.

4. Clinical studies of lithium in MCI and AD

In 2008, Macdonald et al. [36] first attempted to assess the safety and feasibility of prescribing long-term lithium (up to 1 year) to 22 elderly people with mild to moderate Alzheimer's disease (AD) in an open-label study. A comparison group not receiving lithium therapy was matched for cognition and age. The mean duration of treatment for 14 patients who discontinued prematurely was 16 weeks and for those continuing treatment at the end of the study was 39 weeks. The reason for discontinuation in three patients was possible side effects which disappeared on stopping therapy. The intensity of side effects did not differ between patients discontinuing therapy and the subjects remaining in the study. Two patients receiving lithium died; however, in neither case the treatment with lithium was related to the cause of death. The lithium and non-lithium groups were not different as to deaths, drop outs, or change in MMSE.

In 2009, the first randomized lithium trial in patients with mild AD appeared [37]. Seventy-one patients were randomized to receive either lithium (0.5–0.8 mmol/l) (n = 33) or a placebo for (n = 38) 10 weeks. The results obtained showed that there were no differences as to global cognitive performance, as measured by the ADAS-Cog subscale, depressive symptoms, as well as plasma activity of GSK-3 and disease biomarker concentrations in the cerebrospinal fluid (CSF), between lithium and placebo groups [42]. However, interesting results were obtained by an analysis of a single site subsample (Tübingen) containing 27 patients, 13 of which were randomized to lithium and 14 to placebo. In AD patients treated with lithium, in comparison to placebo-treated patients, a significant increase of BDNF serum levels and a significant decrease of cognitive impairment measured by the ADAS-Cog sum scores, inversely correlated with lithium serum concentration, were found [38].

Two Brazilian studies performed in 2011 and 2013 brought about some promising results. Forlenza et al. [39] employed lithium in placebo-controlled trial of 45 patients with amnestic mild cognitive impairment (MCI), randomized to lithium (n = 24) or placebo (n = 21) for 12 months. They found that lithium treatment (0.25–0.5 mmol/l) was associated with significantly better performance on the cognitive subscale of the Alzheimer's Disease Assessment

Scale and with a significant decrease of P-tau protein in cerebrospinal fluid (CSF). In the second study, Nunes et al. [40] assessed the effect of a microdose of 300 μg lithium, given to AD patients in one daily dose, for the period of 15 months. During this time, the group receiving lithium microdose showed no decrease in performance in the MMSE test. On the other hand, such a decrease was observed in the control group.

In a meta-analysis performed by Matsunaga et al. [41], three clinical trials including 232 participants that met the study's inclusion criteria were identified. The results obtained suggested that lithium significantly decreased cognitive decline (standardized mean difference = −0.41) as compared to placebo. There were no significant differences in the rate of attrition, discontinuation due to all causes or adverse events, or CSF biomarkers between treatment groups.

5. Conclusions

There is robust and highly replicated evidence for positive association between Li treatment and gray matter volumes. There has also been a strong experimental background for biochemical underpinnings of lithium's neuroprotective effect that may have possible relevance for therapeutic action of this ion in the AD. A negative association between lithium use and dementia confirmed in most epidemiological studies, including the recent ones on lithium in drinking water, has also been quite substantial. All the same, the results of using lithium in the treatment of AD involve some methodological and clinical issues, which complicate the interpretations. One must acknowledge the heterogeneity of studies regarding of methodology, duration of intervention, dose regimen, and also outcome variables. Nonetheless, three of the four available studies meta-analyzed by Matsunaga et al. [41] suggested some benefits from lithium treatment on amnestic mild cognitive impairment or early stages of the AD, including effects on illness biomarkers.

Despite the wide range of supporting evidence, the neuroprotective effects of lithium are mostly neglected and little known outside of the mood disorders field. However, considering the current paucity of treatments for neurodegenerative disorders, we cannot afford to let the research into neuroprotective effects of lithium come to a halt. The evidence presented in this chapter would warrant further testing of lithium as a disease-modifying treatment for the AD.

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