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The Neurobiological Role of Lithium Salts

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Lithium salts have been the mainstay of treatment for bipolar disorder for more than 50 years, since approval by the FDA in 1970 for the treatment of this pathology. A variety of the molecular mechanisms of action of lithium have been well studied, primarily inhibition of the enzymes glycogen synthase 3β and inositol monophosphatase, with subsequent activation of cascades of cellular reactions, including induction of brain-derived neurotrophic factor and antiapoptotic proteins and suppression of calcium-dependent activation of apoptosis. Research over the last decade has focused on the effects of lithium on the regulation of autophagy and the accumulation of pathological proteins such as amyloid β and tau protein in neurons. Lithium is also thought to induce telomere elongation and to increase telomerase activity. Clinical studies of lithium have addressed the potential for its use for the prevention and treatment of neurodegenerative diseases, primarily Alzheimer's disease, with increasing emphasis on the use of lithium microdoses. A separate scientific problem is the search for safe and effective lithium salts using methods including chemoreactome analysis.

Keywords: lithium therapy, autophagy, telomerase, chemoinformatics, neurocytology, toxicology, neuroprotection, Alzheimer's disease.

History of the Use of Lithium. Lithium was first used as a drug – in the treatment of gout – by Garrod in 1860 [1]. The first therapeutic use of lithium in mental illness dates back to 1871, when Hammond began to use lithium bromide in patients with mania [2]. In the late 1890s, lithium carbonate was used in 35 patients with melancholic depression [3]. In 1949, the Australian psychiatrist Cade [4], believing excess uric acid to be the main cause of manic disorder, used lithium carbonate in 10 patients with manic syndrome. Cade noted positive treatment effects in some patients, to the extent that they could be discharged from hospital. The FDA banned the use of lithium chloride as a substitute for table salt in 1949 due to its high toxicity – reaching the level of death – with the result that further research on lithium was suspended. It as only in 1951 that studies of lithium carbonate in manic-depressive psychosis continued in Australia [5]. The results of numerous studies led to official FDA approval in 1970 for the use of lithium in bipolar disorder [3]. It should be noted that the use of lithium predominantly as the carbonic acid salt was due to the fact that Cade used lithium carbonate in his pioneering research.

There are currently more than 10 different lithium compounds that can be used in mental pathology. Most of these have received FDA approval for use in bipolar affective disorder. Lithium citrate has had FDA approval for use since the late 1970s [6]. There were no significant differences in its pharmacokinetic profile as compared with lithium carbonate. Lithium chloride is also officially approved by the FDA, but is rarely used in the treatment of bipolar affective disorder [7]. The great importance of lithium chloride lies in its use in experimental and molecular pharmacology, primarily due to the ease of i.p. administration. Lithium aspartate is not officially approved for use in bipolar affective disorder. Two studies on the potential for its use in alcohol and drug dependence have been reported [8, 9]. No comparative studies of the pharmacokinetics of lithium carbonate and aspartate have been reported. Lithium sulfate is also an officially approved lithium compound for bipolar affective disorder. Studies by Petersson [10] did not find any significant pharmacokinetic differences between lithium sulfate and lithium carbonate. Lithium hydroxybutyrate was used in an experimental study

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by Lyubimova et al. [11], though there were no clear data indicating an advantage over lithium carbonate. Shurygin et al. reported studies of lithium comenate in cerebellar granule neuron cell cultures [12]. Its antioxidant and neuroprotective effects were demonstrated. In 2014, Smith et al. [13] published a comparative study of lithium lactate, salicylate, and carbonate. These compounds were found to have lower bioavailability, with lower peak concentrations and a longer plateau which, as was previously established by a study reported by Lippman et al. [14], a characteristic which can reduce the toxic effects of lithium. At the same time, studies by Chokhawala et al. [15] and Couffignal et al. [16] showed that this effect could be achieved by using sustained release formulations. Lithium orotate is a lithium compound with a history going back half a century. In 1970, Nieper et al. [17] presented the results of a study showing that lithium orotate could be used in the treatment of manic disorder. Kling et al. [18] and Smith et al. [19] reported highly contradictory results: on the one hand, lithium orotate accumulates in the brain to significantly higher concentrations than lithium carbonate [18], while on the other, lithium orotate is more nephrotoxic [19].

Lithium salts are first-line therapy for bipolar disorder. The therapeutic blood lithium concentration ranges from 0.4 to 1.0 mEq/liter, which requires prescription of large drug doses – from 1 to 3 g/day [20]. These doses increase the probability of developing adverse effects during therapy (kidney and thyroid damage). At the same time, the antisuicidal properties of lithium are obtained at significantly lower doses of lithium salts [21].

Numerous studies in recent years have convincingly indicated the potential of using lithium not only in psychiatric practice, but also in neurology, primarily to prevent and treat neurodegenerative diseases and, possibly, cerebrovascular pathology, because of the various effects of lithium on cellular signaling pathways. The first study initiating research on the neuropharmacology of lithium dates back to 1996. The classic work of Klein and Melton [22] on clawed frog embryos suggested that the mechanism of action of lithium is associated with the inhibition of glycogen synthase kinase 3β (GSK-3β). Many subsequent studies have revealed a multitude of effects of lithium on cellular signaling pathways and pro- and antiapoptotic proteins, influencing the mechanisms of neuroplasticity and neuroregeneration [23–28]. Molecular studies have more recently focused mainly on the ability of lithium to influence the accumulation of various pathological proteins within cells, to regulate autophagy, and to influence telomeres and telomerase activity.

Clinical studies of lithium in the last decade have addressed its potential to prevent and treat Alzheimer's disease, and, to a lesser extent, other neurodegenerative diseases such as Huntington's disease and amyotrophic lateral sclerosis. In addition, the interaction between sufficient amounts of lithium in water and food and the possibility of developing neurodegenerative pathology is being investigated. A number of studies have addressed the effects of lithium microdoses on neurodegenerative processes.

Lithium and Autophagy. Autophagy is a vital cellular process whereby cytoplasmic and subcellular organelles are delivered to lysosomes for destruction and recycling [29, 30]. The process of autophagy is induced by stressful conditions such as lack of growth factor and low intracellular oxygen and nutrient levels [31, 32]. Autophagy has been shown to have a neuroprotective role for brain structures, mediated by eliminating defective proteins and organelles, preventing the accumulation of protein aggregates, and maintaining neuroplasticity [33]. The effects of lithium on autophagy have been confirmed in numerous studies. Thus, Hou et al. [34] showed that lithium (lithium chloride, 10 mM) prevented the development of apoptosis in SH-SY5Y cell cultures by activating autophagy. Research reported by Kazemi et al. [35] using needle myography also provided evidence that lithium affects autophagy: significant increases in cell survival were observed in bone marrow stromal stem cell cultures in conditions of serum deprivation, the main role being played by induction of autophagy (by reducing P62 and increasing LC3II). It should be noted that the maximum effect was achieved at intermediate lithium chloride concentrations (5 mM; the range of concentrations in the study was 0–20 mM).

Experimental studies over the last decade have mostly addressed the effects of lithium on the formation and accumulation of pathological proteins within cells, as these play key roles in neurodegenerative pathology. Thus, Gomez-Ramos et al. [36] demonstrated that the use of lithium in *Spodoptera frugiperda* cell cultures prevents the formation of polymeric filamentous structures consisting of altered tau proteins, which are the basis of the pathogenesis of Alzheimer's disease. Sun et al. [37] studied the effects of different lithium concentrations on amyloid β secretion in COS7 cultures. Lithium induced dose-dependent decreases in amyloid β secretion, and also altered GSK-3β activity [37]. De Ferrari et al. [38] studied the neuroprotective effects of lithium in relation to intracellular accumulation of amyloid β. Inhibition of GSK-3β activity by lithium prevented the development of the neurotoxic effect of amyloid β in postmitotic neurons. Similar data were reported by Rametti et al. [39]: exposure of cortical neuron cultures to lithium reduced tau protein and mRNA levels. Furthermore, lithium was shown to reduce the protein phosphorylation, leading to its more rapid elimination [40].

In addition to in vitro experiments, many studies have addressed the effects of lithium in animals with various models of Alzheimer's disease. Thus, lithium prevented the formation of amyloid β from APP (amyloid precursor protein) in mice with traumatic brain injury by reducing β-secretase-1 (BACE-1) activity in the brain [41]. Another mechanism of the direct effect of lithium on amyloid β production via regulation of GSK3-β activity was found in a *Drosophila* model of Alzheimer's disease [42, 43]. Trujillo-Estrada et al. [44]

showed that the use of lithium at a dose of 1.2 g/kg for 71 days prevented memory loss, reduced the toxicity of amyloid β plaques, and reduced the intensity of tau phosphorylation in PS1xAPP transgenic mice. Pan et al. [45] demonstrated that use of lithium at a dose of 300 mg/kg/day for 21 days increased amyloid β clearance by 31% in APP/PS1 transgenic mice. Studies reported by Liu et al. [46] demonstrated that lithium chloride at doses of 5–17.5 mg/kg/day for two months prevented the development of memory disorders in APP/PS1 transgenic mice, and also decreased amyloid β and hyperphosphorylated tau protein levels.

A number of experimental studies have addressed the therapeutic potential of lithium microdoses in relation to neurodegenerative pathology. Thus, Pouladi et al. [47] demonstrated the effect of lithium-containing substance NP03 when given transmucosally for 10 months in mice with a model of Huntington's disease. Wilson et al. [48] also showed that NP03 for three months was effective against both the early and late stages of Alzheimer's disease in transgenic rats. Nunes et al. [49] showed that lithium carbonate was active in relation to the development of Alzheimer's disease in transgenic mice. Groups receiving lithium for eight or 16 months showed no memory impairment, had smaller numbers of senile plaques than controls, and experienced no neuron death in the cortex and hippocampus.

Effects of Lithium on Telomeres. Telomeres are nucleoprotein structures at the ends of chromosomes and consist of non-coding TTAGGG hexamer repeats combined with certain specific proteins. Telomerase expression and activity is limited in most cell types, with the result that telomere length consistently decreases throughout the life of the cell until it reaches a critical value, at which the corresponding signaling pathways are triggered [50]. Several studies have found that telomere length is reduced in bipolar disorder [51, 52]. A 2014 meta-analysis including 570 patients with bipolar affective disorder and 551 controls showed that telomere length was significantly shorter in patients with bipolar affective disorder, regardless of the phase of the disease and the method of measuring telomere length [52]. Several clinical studies have shown that lithium can attenuate telomere shortening and possibly cause telomere lengthening. The first data were obtained by Martinsson et al. [53], who found that telomere length was 35% longer in patients with bipolar affective disorder treated with lithium preparations than in controls. Moreover, telomere length correlated positively with the duration of lithium therapy. Similar data were subsequently obtained by other researchers [54]. A prospective study by Köse Çinar [55] on the influence of lithium on telomere length showed that patients with the manic form of bipolar affective disorder had a significantly shorter telomere length than controls, while telomere length increased significantly during remission and after lithium therapy. One study found that six weeks of lithium therapy resulted in an increase in telomerase expression in the hippocampus of rats with experimental depression [56]. Another study showed that telomerase expression was significantly greater in patients with bipolar affective disorder treated with lithium; a positive correlation was also found between the telomerase expression level and the duration of lithium therapy [57]. The increase in the BDNF level seen during lithium therapy presumptively induced c-Myc expression via the MAPK/PI3K signaling pathway, which in turn led to the increase in telomerase expression [58].

Lithium and Neurodegenerative Diseases. In 2006, Terao et al. [59] conducted a study assessing Mini Mental State Examination (MMSE) scores in patients who had received/were receiving treatment with lithium therapy for bipolar disorder and controls. Patients receiving lithium therapy were shown to have higher MMSE scores (27.5 vs 25.8). However, the small sample size (110 patients) did not allow any definitive conclusions to be drawn. Nunes et al. [60] assessed the prevalence of Alzheimer's disease in patients with bipolar disorder treated with lithium (group 1, $n = 66$) and in patients with bipolar disorder treated with other drugs (group 2, $n = 48$). Alzheimer's disease was diagnosed in 5% of cases in the first group and 33% of the second. In 2009, Hampel et al. [61] presented data from a randomized placebo-controlled trial of lithium in Alzheimer's disease. Lithium was used for a short period (10 weeks) in patients with Alzheimer's disease, reaching the standard therapeutic concentration (0.5–0.8 mEq/liter). MMSE scores were assessed, along with biomarkers such as GSK-3β activity, cerebrospinal fluid (CSF) tau, and plasma amyloid β. The use of lithium did not lead to any changes, though this could have been due to the short follow-up period. Kessing et al. [62] performed an epidemiological study in Denmark including 4856 patients with bipolar disorder. Patients received lithium or other drugs (antidepressants, antiepileptic drugs (AED), antipsychotics). The development of dementia was noted in 216 patients from different groups during follow-up observations. It should be noted that patients receiving lithium had a significantly lower risk of developing dementia. On the basis of a retrospective population-based cohort study conducted in the United States, Gerhard et al. [63] demonstrated that the use of lithium in bipolar disorder for at least 300 days significantly reduced the risk of dementia. It should be noted that shorter periods of lithium use, like use of AED, did not affect the development of dementia.

Forlenza et al. reported an important clinical study of the effectiveness of lithium in relation to the development of dementia [64]. A total of 61 patients with moderate amnestic cognitive impairments were included in a double-blind placebo-controlled study. Patients of the main group received lithium to a concentration of 0.25–0.5 mEq/liter. Cognitive functions were studied for two years, with determination of amyloid β levels at 12, 24, and 36 months from the start of the study. The state of cognitive functions remained stable throughout the study in patients of the main group, while dementia developed in patients of the reference group. In

addition, patients of the reference groups also differed in showing a progressive increase in the CSF amyloid β level. The first clinical study of the effects of low-dose lithium in Alzheimer's disease was run by Nunes et al. in 2013 [65]. A total of 113 patients with Alzheimer's disease were randomized. Patients in the study group ($n = 58$) received lithium at a dose of 300 μg/day for 15 months, while patients in the control group ($n = 55$) received placebo. Starting from three months from treatment initiation, MMSE scores in the study and placebo groups differed: scores remained stable in the study group. Pepelyaev et al. [66] studied the effects of microdoses of lithium ascorbate (780 μg/day for two months) in middle-aged patients on cognitive functions and the severity of depression. Lithium ascorbate microdoses were found to lead to regression of the signs of subclinical depression, which was apparent as a decrease on the Beck Depression Scale from 10.3 to 8.4 points, along with improvements in cognitive functions, seen as increases in the MMSE score from 26 to 26.8 points and in visual-spatial gnosis from 7.3 to 8.1 points.

Several studies have been carried out on the effects of lithium levels in drinking water on the likelihood of developing dementia and the course of Alzheimer's disease. Thus, in 2017 Kessing et al. [67] published the results of a population study run in Denmark in 1995–2013. The study included a total of 807,653 people, of whom 73,731 were patients with Alzheimer's disease. Lithium levels were assessed in drinking water from 151 water supplies, representing about 42% of those in Denmark. Statistical analysis found that drinking water lithium levels of >15 μg/liter displayed a significant association with a lower risk of dementia (incidence rate ratio (IRR), 0.83; 95% CI, 0.81–0.85; $p < 0.001$), and conversely, lithium contents of <5 μg/liter were linked with a statistically greater likelihood of developing dementia (IRR, 1.22; 95% CI 1.19–1.25; $p < 0.001$). Fajardo et al. [68] evaluated the effects of lithium levels in drinking water on mortality in patients with Alzheimer's disease. Water samples were studied in 234 of the 254 counties in the state of Texas (USA), along with the rates of death due to Alzheimer's disease in these communities. Mortality in Alzheimer's disease was found to correlate negatively with the drinking water lithium level: the less lithium in the drinking water, the higher the mortality from Alzheimer's disease ($p = 0.01$, $r = –0.20$).

It should be noted that drinking water lithium levels also correlate with the prevalence of mental illness and antisocial behavior. Thus, Schrauzer et al. [69] found as early as 1990 that there is a negative correlation between drinking water lithium levels and the incidences of suicide, violent crime, and drug addiction. Barjasteh-Askari et al. [70] reported a meta-analysis of 13 environmental studies in 939 different regions and a total population of 3,740,113 people which showed that the drinking water lithium level correlated negatively with the incidence of suicide (OR = 0.63; 95% CI 0.47–0.83; $p < 0.01$).

Dietary Salts with Potential for Correcting Deficiency of Lithium Supply. There is value in finding anions for the synthesis of lithium salts, as this would help maximize the intake of lithium ions into neurons and have the most suitable spectrum of pharmacological activities without producing toxic effects even if used in the long term. It should be noted that all studies conducted to date have used lithium compounds empirically, without any preliminary modeling of their pharmacokinetics and pharmacodynamics.

Torshin et al. [71] studied organic lithium salts in 2016 using a chemoreactome method. The chemoreactome approach to the analysis of the "structure–property" problem of molecules is the latest means of applying artificial intelligence systems to the field of postgenomic pharmacology. A set of algorithms was used to evaluate more than 350 pha macological properties of lithium salts (toxicity, pharmacokinetics, pharmacodynamics, etc.). A list of the lithium salts (water-soluble organic lithium compounds with molecular weight < 300 Da) studied, along with structural formulas, was downloaded from the PUBCHEM database (1245 compounds). At the first stage, 38 minimally toxic lithium salts (LD_{50} >1000 mg/kg) were selected; the second stage selected 11 lithium salts with maximum bioavailability (>20%): these were lithium ascorbate, nicotinate, hydroxybutyrate, orotate, citrate, gluconate, comenate, pyroglutamate, glycinate, asparaginate, and lactate. The third stage involved evaluation of the various biological and pharmacological effects of the selected lithium salts and analysis of possible interactions of the lithium ion with proteins of the human proteome. Overall, chemoreactome analysis showed that lithium ascorbate has promise for further research: it was found to have higher affinity for dopamine, serotonin, benzodiazepine, and adrenergic receptors than other anions (nicotinate, hydroxybutyrate, comenate), such that the activity of these receptors could be modulated and more intense entry of lithium into cells could be obtained.

It should be noted that an earlier study conducted by Pronin et al. [72] identified the pharmacokinetic properties of lithium ascorbate, including the presence of a prolonged plateau in the serum concentration, presumably due to release from organ depots (spleen, adrenal glands, femur, aorta). In addition, there was a predominant accumulation of lithium ascorbate in the frontal lobes of the brain. Previous studies of the pharmacodynamics of lithium ascorbate showed it to have extremely low acute and chronic toxicity, even at a dose of 3000 mg/kg. These data suggest that lithium ascorbate is safe to use, without concerns relating to adverse effects due to overdosage or side effects of the test substance. Ostrenko et al. [73] studied lithium ascorbate in rats with a model of alcohol intoxication: lithium ascorbate reduced ischemic damage to neurons and contributed to maintaining the normal state of the myelin sheath of their axons, which ameliorated withdrawal symptoms, blocked the occurrence of seizures, and improved the survival of the animals.

Conclusions. Experimental studies over the last decade have shown that lithium has positive effects on the regulation of autophagy and inhibits the accumulation of amyloid β, tau protein, etc. in brain cells. The toxic properties of the widely used compound lithium carbonate have led to a search for new salts for lithium therapy. Systematization and analysis of literature data shows that lithium ascorbate is a highly assimilable organic lithium salt with low toxicity. A neurocytological study on cultured cerebellar granule neurons using a glutamate stress model demonstrated that lithium ascorbate was more effective in supporting neuron survival (+11%) than lithium chloride or carbonate. Assessments of the biodistribution of lithium have shown that administration of lithium ascorbate is followed by lithium ion accumulation mainly in the brain. Lithium ascorbate has extremely low acute and chronic toxicity. Studies using models of Alzheimer's disease and ischemic brain damage in animals have shown that lithium chloride and organic lithium salts (citrate, orotate, comenate, asparaginate, ascorbate) are effective in slowing neurodegenerative processes. Epidemiological studies have established a link between insufficient lithium supply and the occurrence of mental disorders, neurodegenerative diseases, and the risk of accelerated brain aging.

The authors declare no conflict of interest.

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