

The Role of Lithium in Neurological Health and Disease

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Abstract *Nutrition is the study of the human dependence on our environment. Lithium (Li) is found in all human cells and the notion that it is essential for physiologic function is well supported by the literature, although a syndrome associated with lithium deficiency has yet to be formally described. A literature review was conducted to identify all publications describing Li metabolism, physiologic roles, and nutrient–nutrient interactions. The evidence for clinical manifestations of deficiency, such as impulse control disorders, aggression, depression, and poor mood, is reviewed, as is the evidence for the notion that Li deficiency may increase risk of neuroinflammatory and neurodegenerative conditions via enhanced neuronal hyperexcitability and impaired autophagy. Li deficiency is an established, but poorly described, phenomenon that appears to be associated with impaired central nervous system function, at least on a community level. Whether fortification efforts would improve individual or public health cannot be determined without additional research.*

Introduction

Lithium (Li), the third element on the periodic table, is found in all cells in the human body.¹ It is an alkali metal that was first isolated as a salt by Swedish chemist Johan August Arfvedson in 1817. Minerals are considered essential if they are necessary for growth, reproduction, and health.² Of note, on the periodic table of the elements, Li is surrounded by other elements considered essential.

The determination of nutrient essentiality varies by discipline, organization, and agency, with each declaration having distinct scientific, political, and financial implications. Trace minerals (e.g., iron, magnesium (Mg), and selenium) are measured in milligrams per kilogram (mg/kg) of body weight and thus have been more frequently studied than ultratrace minerals. Li, like boron, germanium, and rubidium, has an estimated requirement lower than 1 mg daily¹ is thus considered an ultratrace mineral.

Dietary Intake

Li exposure varies both by the geographic region and the degree to which an individual consumes a plant-based diet. Li is found in trace amounts in soil, where it is unevenly distributed due to natural variation in the earth's crust. Intake between geographic regions varies greatly, and the standard deviations from the means within the same geographic area are large. (E.g., 1,485 + 1,009 µg/day in Tijuana, Mexico; 821 + 684 µg/day in Galveston, Texas; 348 + 290 µg/day in Vienna, Austria.¹)

The majority of Li comes to humans through the consumption of water, vegetables, and grains. In food, grains and vegetables are the primary source with Li content ranging from 0.5–3.4 mg per kg of food, compared to 0.5 mg/kg in dairy and 0.012 mg/kg in meat. Estimated Li intakes vary widely, from 430 to 2,900 µg per day.¹

Population intakes were recently evaluated for the first time in decades, a time during which there has been a notable reduction in the consumption of whole grains and vegetables in the diet of industrialized nations. A 2011 study conducted in Tokyo, Japan, showed 56% of individuals were below reference intakes;³ an estimated 64% reduction from a sample taken in Tokyo in 1992.⁴

Absorption, Distribution, Metabolism, and Excretion

Li is absorbed as a salt via Na⁺ channels in the small intestine and excreted through the kidneys. It is distributed ubiquitously throughout body fluids and deposited in bone and hair. Supplemental Li, in doses up to 2,000 µg/g, results in a direct dose-response relationship with hair Li concentrations, an established biomarker for ultratrace elements.⁴ The plasma concentration is approximately twice the concentration of the erythrocyte and cerebrospinal fluid concentration.⁵ When administered as Li chloride salt, it was shown to be well absorbed among all subjects.¹ Pharmacokinetic studies show that systemic absorption of topical Li gel is low and generally well tolerated. When given as a topical gel, most off-target effects were mild and included a burning sensation, erythema, and pruritis.⁶

Organ Li levels reach maximum levels during the first trimester of embryonic development.¹ After birth, Li levels do not seem to vary by age.³ Postmortem human studies revealed that the cerebellum, cerebrum, and the kidneys retain more Li than other organs, with women exhibiting 10–20% more Li than men in these areas.¹ Li-deficient adult rodents have been shown to retain Li concentrations in the pituitary, adrenal glands, hippocampus, mammary glands, ovaries, and thyroid, suggesting these organs have unique Li requirements.⁷

Nutrient-Nutrient Interactions

Calcium

Li decreases the efficiency of alimentary calcium (Ca) absorption and inhibits tubular reabsorption of both Ca and Mg.² It was ob-

served that decreases in cerebrospinal fluid (CSF) Ca accompanied improvements in mood and motor activation in depressed patients undergoing treatment with Li. Based on the demonstration that progressive restriction of dietary Ca mitigated, and finally abolished, both rhythmic rises in serum Ca and periodic agitated episodes in one psychotic patient, it was hypothesized in 1979 that one of Li's therapeutic mechanisms was via the reduction of calcium. Depending on the dose and chronicity of Li intake, the effects of Li on Ca have been theorized to increase an individual's risk of hyperparathyroidism.⁸

Magnesium

Haavaldsen et al., published on the displacement of magnesium (Mg) by Li in *The Lancet* in 1973. Administration of 1.5 g Li per kg body weight for 14 days resulted in an increase in plasma Mg concentration and a reduction in erythrocyte Mg concentration. The authors concluded that the biological, and toxic, effects of Li in the treatment of manic-depressive psychosis were due to the displacement of Mg from erythrocytes into plasma. They also note that chemically, the high ionic potential of Li promotes the formation of complexes and that Li and Mg may antagonize one another, similarly to the antagonisms between Ca and Mg, resulting in a competition for binding sites.⁵

Sodium

Rodents fed Li-deficient diets were more likely to have reduced litter size and weight in the presence of normal- or high-sodium diets. This association was not seen when Li-deficient diets were also low in sodium.⁹ While this interaction has not been evaluated in humans, the high sodium content of industrialized nations may pose an additional risk factor for the negative effects of reduced Li intake.

B₁₂ and Folic Acid

Across populations, a highly significant association between hair Li and cobalt concentrations has been demonstrated. As

cobalt forms the center of the vitamin B₁₂ molecule, cobalamin, a role for Li in the metabolism of vitamin B₁₂ has been proposed.⁴ In cell lines, Li has been shown to enhance folic acid and vitamin B₁₂ transport into cell lines, a function that is compromised in the presence of Li deficiency.³ Both vitamin B₁₂ and folic acid are essential for methylation, and evidence exists of abnormal methylation in several CNS disorders.¹⁰

Inositol

The inositol depletion hypothesis has been suggested as a purported mechanism for Li's neuroprotective ability. Li has been shown to deplete inositol,¹¹ and via the inositol 1,4,5-triphosphate receptor (InsP3R), it has been shown to prevent chemotherapy-induced decreases in intracellular Ca signaling. In chemotherapy patients, Li pretreatment has been shown to inhibit the development of chemotherapy-induced peripheral neuropathy.¹²

Iodine

There is evidence of an interaction between Li and iodine in relationship to thyroid function. In a study conducted in Tokyo, Japan, the levels of hair iodine levels were directly associated with those of Li ($P < 0.0001$).³ The authors postulate that Li deficiency diminishes iodine retention, but it may be that these minerals share a common source (e.g., plant-based diet, water supply), or that iodine deficiency precedes or contributes to Li deficiency.

Assessment of Body Concentrations

In humans supplemented with pharmacological doses of Li, serum levels have been shown to rise approximately proportional to Li intake. Biologically, goats fed Li-deficient diets do not exhibit differences in blood concentrations, suggesting blood is a poor biomarker for detecting physiological concentrations of Li.¹

Scalp hair levels reflect the intakes of bioavailable Li over a period of weeks to months, in microgram per gram concentrations. **Table 1** (p. 104) shows the ranges of

lithium concentrations in the hair among selected cohorts from around the world. It has been established that Li concentrations in human hair increase in response to Li supplementation up to approximately 2,000 µg/d. The least-squares fitted line was determined to be: $[Li_{\text{intake}}] = 11.6 [Li_{\text{hair}}] - 0.43$.⁴ Hair as a biospecimen is a noninvasive method of determining the dietary Li intakes, representing the months prior to collection.^{1,4} The procedure for sample collection, shipping, washing, analyzing, and reporting has been described.¹³

Symptoms of Li Deficiency and Toxicity

Li deficiency in humans and other animals has been poorly characterized. The daily requirement has been suggested to be as low as 25 µg/day,¹⁴ yet doses of 1,200 mg/day are commonly used in psychiatry. There is likely a continuum between the symptoms of Li deficiency and toxicity, with the ideal dose being that needed for maintenance, growth, and repair throughout the life cycle. It is possible that symptoms of deficiency are heterogeneous and manifest differently under different conditions, e.g., among genetically or environmentally susceptible individuals (**Figure 1**, p. 105).

A systematic review and meta-analysis of observational studies and randomized controlled trials was published in 2012. The authors concluded that, among individuals with mood disorders treated with lithium, there was an increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain.¹⁵

Physiologic Roles in the Central Nervous System

Li plays a role in electrolyte regulation across cell membranes, and thus membrane stabilization and maintenance of electrochemical gradients, all of which supports neuronal health and survival. Just as traditional seizure medications have come to be used in the management of bipolar disorder, so do Li's actions transcend disease specificity. In evaluating whether unique Li re-

Table 1. Range of Hair Lithium Concentrations from Various Cohorts

	Year	N	Median	Mean (SD) µg/g	ppm
New York, USA ¹⁵	1975	206		0.009–0.228	
Montreal, Canada ¹⁶		53			
Healthy control kids	1977	22			.40 ppm
<i>Kids with learning disorders</i>	1977	31			.22 ppm
Vienna, Austria	1992	20		0.030 (0.025)	
Munich, Germany	1992	18		0.035 (0.033)	
Tokyo, Japan	1992	20		0.070 (0.033)	
Galveston, Texas	1992	25		0.080 (0.059)	
Culiacan, Mexico	1992	21		0.081 (0.080)	
Copenhagen, Denmark	1992	20		0.087 (0.021)	
Stockholm, Sweden	1992	10		0.094 (0.028)	
Tijuana, Mexico	1992	60		0.128 (0.087)	
California, USA, healthy males		82		0.099 (0.126)	
<i>California, USA, violent offenders</i>	1992	49		0.028 (0.029)	
<i>Florida, USA, prisoners</i>	1992	48		0.032 (0.031)	
<i>Oregon, USA, prisoners</i>	1992	31		0.051 (0.052)	
<i>California, USA, heart patients</i>	1992	42		0.028 (0.025)	
National sample, USA, Doctor's Data, Inc. ¹⁷	1998	150	0.08	0.007–0.23	
*Tokyo, Japan ⁴					
Males	2011	100	0.011	0.019 (0.025)	
Females	2011	100	0.017	0.0275 (0.029)	

Disordered or diseased populations are in italics. *Tokyo is not a diseased population, but it should be noted that high regional suicide rates prompted the study.

quirements exist in neurological and psychological disorders, the guiding principle should be whether or not some cases or incidences of progression would not be there if Li concentrations were augmented.

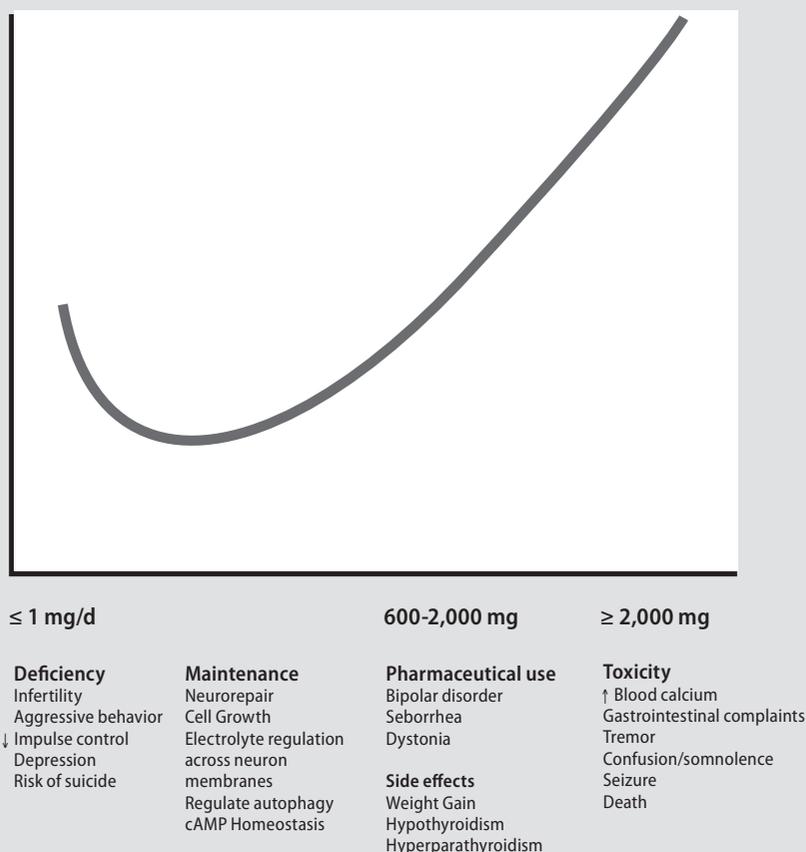
Mood and Behavior

The mood-enhancing properties of Li have been promoted for hundreds of years and have been theorized to be attributable to Li's enhancement of monoamine oxidase (MAO) activity, which is depressed in Li deficiency.^{1,16} Low municipal Li water concentrations have been associated with increased incidence of violent behavior, a finding supported by the feeding of Li-deficient diet to rodents.¹⁷

When 24 former drug users were administered 400 µg of Li per day in yeast in a placebo-controlled fashion, the Li group had mood scores that increased steadily over the 4-week intervention. Specifically, the authors reported an improvement in happiness, friendliness, and energy.¹⁸

Pharmacologic doses of Li, 500–1,500 mg or greater, have been used to manage mania of bipolar disorder for decades. The CNS depressant effect of Li has been well characterized, as has the toxicity associated with these dose ranges, but the mechanism of action remains poorly understood. Pharmacological use of Li, defined here as greater than 500 mg/day, are beyond the scope of this review.²

Figure 1. A theoretical model of a U-shaped relationship between lithium intakes and human health, deficiency, and toxicity.



Impulse Control

Prader-Willi syndrome is a genetic disorder associated with compulsive eating and other behaviors associated with poor impulse control, such as hoarding, anxiety, and skin-picking.¹⁹ Li levels have been shown to be deficient in Prader-Willi syndrome,²⁰ using discriminant function analysis to determine Li concentrations were effective in predicting category membership.

Learning and Development

A study evaluated hair element content of 31 learning disabled and 22 normal children using discriminant function analysis. Using cadmium, cobalt, manganese, chromium, and Li, the model could identify

subjects as learning disabled or normal with 98% accuracy. Li levels were lower in learning disabled children versus controls, $P < .01$ (mean 0.22 ppm, vs. 0.40 ppm, respectively, F ratio 7.29.²¹

Parkinson's Disease (PD)

Dyskinesia The first reported use of Li in PD came following reports of Li reducing tardive dyskinesia and Huntington's chorea. Li was tested in two patients with levodopa-induced dyskinesias (then referred to as "hyperkinesias in parkinsonism"). Levodopa-induced dyskinesia was significantly reduced in both patients, with an increase in PD symptoms in one. The authors concluded the findings supported the view that Li reduces

receptor supersensitivity in extrapyramidal disorders.²²

Dystonia The Lancet reported in 1974 Li carbonate, started at 250 mg and increased to “optimal dose, determined by blood levels and the appearance of side-effects,” seemed to result in the alleviation of painful muscle spasms and cramps.²³ In 1986, The Lancet again reported that the nighttime administration of slow-release Li carbonate resulted in reduction or abolishment of painful dystonia cramps in 19 of 21 experimental treatment periods (13 open, 6 double-blind). Effects of Li initiation and cessation were observed with a 1–17 day latency.²⁴ Due to a perception of toxicity, this treatment has never gained widespread acceptance; dystonia of PD remains largely untreated.

On-Off Phenomenon A 1981 case report describes a patient with PD with disabling on-off phenomenon which was reduced while taking Li carbonate.²⁵ In 1982, The Lancet published the results of a double-blind crossover trial of Li versus placebo, followed by an open trial of Li therapy in six patients with severe disease complicated by the on-off phenomenon. The authors reported that five of the six patients had marked reductions in slowness (mean, 70%) and improved by one grade in Parkinson staging.²⁶

Neurogenesis, Repair, and Differentiation

Chronic use of Li has been shown to increase neurogenesis in adult rodent and human brains. In culture, Li has been shown to stimulate the proliferation of progenitor cells in neurons.²⁷ In humans, Moore et al. postulated that the neurotrophic effects of Li would result in an increase in grey-matter volume as measured by magnetic resonance imaging and quantitative brain tissue segmentation. They compared magnetic resonance imaging of 10 individuals with bipolar disorder before and after four weeks of masked administration of Li carbonate at doses targeting serum concentrations of approximately 0.8 meq/L. In eight out of 10 patients, Li treatment increased total grey matter volume, with a mean change of approximately 3%.²⁸

That Li levels reach peak concentrations

during embryonic development supports the notion that the element plays a role in brain development. That said, Li has been shown to stimulate neurogenesis in the hippocampus into adulthood.²⁹ The mechanism of enhanced neurogenesis is unclear, but expansion of the neuropil content is evident.²⁸ Chronic use of Li has been shown to increase N-acetyl-aspartate, a putative marker of neuronal viability and function.³⁰ This is especially exciting given recent advances that permit the quantitative assessment of N-acetyl-aspartate in isolated brain regions using MR spectroscopy.^{31,32}

Autophagy, the process by which lysosomes degrade and recycle cellular debris, is an essential function for cellular survival and is dysregulated in neurodegenerative diseases.³³ One mechanism by which Li manifests neuroprotective action is via the regulation of autophagic processes, which has been demonstrated by the clearance of α -synuclein, ubiquitin, and superoxide dismutase 1 in a rodent model.^{34,35}

Excitotoxicity is the pathological process by which neurons are damaged or killed by over activation of receptors. Li has been shown to reduce excitotoxicity in vitro and in vivo by a variety of mechanisms. Li pretreatment has been shown to offer protection against glutamate-induced, N-methyl-D-aspartate (NMDA) receptor-mediated Ca influx of CNS neurons.³⁶ Additional protection against excitotoxicity occurs via increased glutamate uptake.²⁹

In addition to offering protection against the pathophysiological processes involved in neurodegeneration, Li has been shown to exert neurotrophic effects. Li treatment has been shown to induce the secretion of brain-derived neurotrophic factor,³⁷ improve axonal sprouting of spinal cord lesions, and promote functional recovery.³⁸

Conclusion

The essentiality and toxicity of Li remain undisputed in the published medical literature, and yet no formal guidelines exist for appropriate target intakes, either among healthy populations, or for those with sus-

pected or confirmed deficiency. The published data supports the hypothesis that Li deficiency is associated with impulse control disorders, poor mood, learning disorders, and neuropsychological disease, all of which plague public health. An evaluation of nationwide intakes and adequacy as well as formal evaluation of supplemental Li in deficient populations is warranted.

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Competing Interests

The author has no relevant competing interests to declare.

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