Lithium as a Nutrient

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ABSTRACT

In high doses, lithium acts as a drug, accompanied by potentially serious and debilitating side effects. In low doses, lithium acts as a nutrient required for B12 and folate transport and uptake, neuromodulation, and the function of many biochemical processes in both humans and animals. Studies since the 1970s have shown the ability of lithium to stimulate the proliferation of stem cells. Recent studies have described its ability to up-regulate neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve-growth factor (NGF), which are important in neuronal function, plasticity, and repair. With its newly described antioxidant and anti-inflammatory activity along with powerful neuroprotective effects, low-dose lithium therapy has largely unrealized potential to prevent or treat a wide-range of neurological disorders such as traumatic brain injury (TBI), Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), chronic pain, mercury toxicity, depression/anxiety, alcoholism, and drug addiction.

Lithium Is an Essential Element

For most people, the word "lithium" suggests images of mental unrest, imbalance, or overt mental illness. This is because societal perception of lithium for the last 100 years has almost exclusively been defined by its use in high doses (150-360 mg elemental Li) to treat bipolar disorder and various forms of mental illness.

Lithium was first discovered as a chemical element in 1817. Its first recorded medical use was in 1871 for the treatment of mania. In 1886, a highly ionizable form of inorganic lithium (carbonate), the currently used form, was introduced to treat depression.

A lithium requirement in human and animal nutrition is much less publicized, and rarely discussed in Western medicine, though it is fairly common knowledge among those involved in nutritional trace element research. It has been in the scientific database for many years.

In a 2002 review, researchers looked at silicon, aluminum, arsenic, and lithium, and their effect in human health and disease. The purpose was to take all of the research to date on these "ultra-trace minerals" and determine their overall nutritional significance and impact on health, taking into account their possible toxic effects. The researchers concluded that silicon and lithium have protective roles in human nutrition, while aluminum and arsenic have notably toxic effects.[1]

We have known for years that animals need small amounts of lithium for reproductive health and maintenance of general health and wellness.

Gerhard N. Schrauzer of the University of California at San Diego writes:

> In studies conducted from the 1970s to the 1990s, rats and goats maintained on low-lithium rations were shown to exhibit higher mortalities as well as reproductive and behavioral abnormalities. Lithium appears to play an especially important role during the early fetal development as evidenced by the high lithium contents of the embryo during the early gestational period….
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> Lithium is found in variable amounts in foods; primary food sources are grains and vegetables; in some areas, the drinking water also provides significant amounts of the element. In humans, defined lithium deficiency diseases have not (yet) been characterized, but low lithium intakes from water supplies were associated with increased rates of suicides, homicides and the arrest rates for drug use and other crimes. The biochemical mechanisms of action of lithium appear to be multifactorial…with [effects on] the functions of several enzymes, hormones and vitamins, as well as with growth and transforming factors.[2]

It appears that when people have deficient lithium intakes they experience poorer moods and are more easily agitated and reactive, as seen with increased rates of suicide, homicides, and violent crimes in areas with low lithium in their water supply.

Lithium is also important for enhancing transport of two other critically important brain nutrients, folate and vitamin B12, into cells. The transport of these factors is inhibited in lithium deficiency and can be restored by lithium supplementation. Schrauzer concluded,

> Since vitamin B12 and folate also affect mood-associated parameters, the stimulation of the transport of these vitamins into brain cells by Li may be cited as yet another mechanism of the anti-depressive, mood-elevating and anti-aggressive actions of Li at nutritional dosage levels.[2]

Schrauzer estimated that the minimum daily requirement for lithium at 1 mg per day (1,000 mcg), though I believe this is a very conservative estimate and doesn't reflect individual differences that could necessitate larger intakes for optimal health. In 1985, the EPA estimated that dietary intake of lithium in the U.S. varied from 0.6 to 3.1 mg per day.[2] People who live in the Andes of Northern Argentina have been estimated to consume between 2 to 30 mg per day, with 2 to 3 mg specifically from drinking water.[3]

Factors such as dietary sodium and caffeine intake increase

lithium excretion, and thus increase our requirement for this essential trace mineral. Along with these prevalent dietary factors, stress and excitotoxin exposure, which raise cortisol and other stress hormones, influence our physiological requirement for a variety of water-soluble nutrients (e.g. magnesium, zinc, B-vitamins), including lithium.

Lithium Induces Stem Cell Production

Stem cells, undifferentiated cells capable of differentiation into specialized cell types, have tremendous potential for promoting neuronal repair and recovery. Stem cells come from two primary sources: embryos formed during the blastocyst phase of embryological development or from adult tissue (e.g. bone marrow, blood, neural, and adipose cells). Both types are able to differentiate into various cell types comprising the skin, nervous system, bones, muscle, and other tissues.[4]

Studies published since the 1970s have described the ability of lithium to stimulate blood-cell formation, thus counteracting the negative side effects associated with various medications, such as carbamazepine, zidovudine, and chemotherapeutic agents. Increases in blood neutrophils and eosinophils are regularly observed, though lymphocytes and erythrocytes remain unaffected.[7] This hematopoietic effect is thought to be a direct result of pluripotent stem-cell production[8-10] and/or enhanced colony stimulating factor production.[11, 12]

In 2011, Wang and colleagues revealed that lithium greatly enhances the generation of induced pluripotent stem cells from both mouse embryonic fibroblast and human umbilical vein endothelial cells. The authors found that lithium exerts its effect epigenetically via down-regulation of LSD1, a H3K4-specific histone demethylase.[13]

Rutgers researchers Dong Ming Sun and Wise Young filed a patent in 2013 using a lithium salt to stimulate cord blood stem cell proliferation and growth factor production.[14]

Lithium Effects on Neural Tissue and Blood

In his 2009 review,[15] Young cited the following biochemical effects and benefits:

- Lithium up-regulates neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT3), as well as receptors to these growth factors in the brain.
- Lithium stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum, and forebrain. The stimulation of endogenous neural stem cells may explain why lithium increases brain cell density and volume in patients with bipolar disorders.
- Lithium also remarkably protects neurons against glutamate, seizures, and apoptosis due to a wide variety of neurotoxins via N-methyl-D-aspartate receptor (NMDA) inhibition/modulation.
- Lithium causes granulocytosis and enhances immunological activities of monocytes and lymphocytes.

Young concludes, "Lithium has been reported to be beneficial in animal models of brain injury, stroke, Alzheimer's, Huntington's, and Parkinson's diseases, amyotrophic lateral sclerosis (ALS), spinal cord injury, and other conditions. A recent clinical trial suggests that lithium stops the progression of ALS."[15]

In 2014, Stenudd et al. demonstrated that endogenous neural stem cells restrict damage and promote repair of damaged spinal cord neurons.[16] Lithium's ability to stimulate neural stem cell production may prove to be of significant benefit in individuals recovering from spinal cord injury and neurological injuries caused by severe trauma (TBI, traumatic brain injury), dietary and environmental excitotoxins (mercury, aspartame, monosodium glutamate), and substance abuse.

Mechanism of Neuroprotective Effects

Three primary mechanisms have been identified over the last two decades for the wide-ranging neuroprotective effects of lithium on the brain and nervous system: up-regulation of the major neuroprotective protein Bcl-2, upregulation of BDNF, and inhibition of NMDA receptor-mediated excitotoxicity.

In 2002, Manji et al. found that lithium up-regulates the cytoprotective protein Bcl-2 in the CNS in vivo. They state: "Strategies that increase Bcl-2 levels have demonstrated not only robust protection of neurons against diverse insults, but have also demonstrated an increase in the regeneration of mammalian CNS axons. To date, lithium remains the only medication demonstrated to markedly increase Bcl-2 levels in several brain areas; in the absence of other adequate treatments, an investigation of the potential efficacy of lithium in the long-term treatment of several neurodegenerative disorders is warranted."[17]

At sub-therapeutic levels, lithium prevented glutamate-induced excitotoxicity through NMDA receptor inhibition. The neuroprotection observed was correlated with inhibition of NMDA receptor-mediated calcium influx.[18]

Part of lithium's protection against glutamate-induced excitotoxicity was conferred by a primary neural growth factor, BDNF, required for neuronal function, synaptic plasticity, and repair—and therapeutic doses of lithium result in a beneficial increase of BDNF in cortical neurons.[19]

Lithium's inhibition of the NMDA receptor parallels that of another essential (anxiolytic/anti-stress, anti-depressant) nutrient, magnesium—modulating and reducing the receptor hyperactivity associated with a number of disease states, including depression, anxiety, chronic pain, and sleep disorders.

Alzheimer Disease

Recent findings implicate changes in BDNF levels in the pathogenesis of Alzheimer's disease. An early increase may reflect a compensatory repair mechanism in early neurodegeneration and could also contribute to increased degradation of β-amyloid. During the course of the disease, BDNF decreases, correlating with the severity of dementia.[20]

Strategies that increase BDNF levels in the brain could thus

be a primary target in the prevention, slowing, and perhaps reversal of fundamental biochemical deficits and changes that drive Alzheimer's disease. Some studies have suggested that coffee intake and exercise, both powerful inducers of BDNF release, possess cognitive-enhancing, neuroprotective properties.

A coffee fruit extract was associated with a 143 percent increase in plasma BDNF levels in healthy subjects over baseline controls levels.[21] Authors of a 2014 review concluded: "Coffee intake demonstrated a protective effect against cognitive decline with 6.25 fold lower risk with increased coffee intake."[22]

A 2014 study of subjects with a mean age of 67 showed that exercise-increased BDNF levels correlated with improved executive function.[23]

These simple lifestyle factors could help reduce cognitive impairment with age, while providing immediate benefits in cognitive performance.

Forlenza et al. stated that 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. In addition, lithium's inhibition of glycogen synthase kinase-3 beta (GSK3B) may modify biological cascades involved in the pathophysiology of Alzheimer's disease. 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 Alzheimer's disease, both by the specific modification of its pathophysiology via inhibition of overactive GSK3B, and by the unspecific provision of neurotrophic and neuroprotective support.[24]

In a follow-up study, Forlenza et al. state: "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."[25]

In a landmark study, Nunes et al. found that a small dose (0.3 mg) of lithium administered once daily to Alzheimer's disease patients prevented cognitive decline over a 15-month period, with significant differences seen in the treatment and control groups by the third month and progressing through the course of treatment.[26]

Additional studies and clinical trials will be needed to determine the most effective dose.

Anti-Inflammatory Activity

Julian Lieb described lithium's anti-inflammatory and anti-prostaglandin effects.[27]

Basselin et al. stated that a portion of lithium's therapeutic activity can be explained by its ability to reduce inflammation through a reduction in brain arachidonic acid metabolism, and an increase of the anti-inflammatory metabolite and docosanoid precursor, 17-hydroxy-DHA.[28] Along with lithium, docosanoids are increased by common anti-inflammatory agents such as aspirin. This is a very significant finding because all chronic diseases possess some degree of inflammation as a defining feature in their etiology and progression.

Lithium, with its ability to reduce inflammation—in small, nutritional doses, devoid of the side effects commonly seen with high-dose therapy—may serve as a powerful adjunctive therapy in the treatment of a wide-range of chronic inflammatory diseases.

Antioxidant, Anti-Aging Activity

Along with elevating stress hormones, chronic stress is known to increase free-radical production. Coupled with its anti-inflammatory activity, lithium has been shown to possess antioxidant effects[29,30] through the inhibition of free-radical production, while increasing the activity of endogenous antioxidant systems such as glutathione peroxidase.[30]

Suggesting a potential link between lithium's neuroprotective, antioxidant effects and cognition, Vo et al. state that animal studies have shown positive results regarding the neuroprotective and antioxidant properties of lithium, while human studies indicate a potential benefit of lithium for improving cognition.[29]

Lithium has also been shown to be a longevity ("anti-aging") nutrient. It's been observed that populations who consume higher amounts of lithium in their water show reduced all-cause mortality.[31]

Lithium and Mercury Toxicity

Lithium may benefit those with elevated mercury levels from fish consumption or dental amalgams. Symptoms of mercury toxicity include irritability, depression, anxiety, sensitivity to stress, and emotional lability, which interestingly enough are similar to the proposed symptoms of lithium insufficiency in humans. This similarity likely results from the fact that along with increasing oxidative stress, mercury increases levels of the excitatory neurotransmitter glutamate in the brain by impairing glial function, while lithium has a modulating and opposing action on glutamate (NDMA) receptors.[18]

Lithium, Magnesium, and Trace Elements

Both lithium and magnesium are known to possess anti-inflammatory and antioxidant activities along with their specialized ability to inhibit NMDA receptor overactivation. The latter is believed to play a strong role in their antioxidant (free-radical reducing), and anti-inflammatory effects. Another essential trace mineral, zinc, which is known to exert powerful inhibitory effects on the NMDA receptor, also has antidepressant[32, 33] and neuromodulatory effects, along with magnesium[34] and lithium.[35]

Mlyniec et al. write that the deficiency of essential elements can lead to the development of depressive and/or anxiogenic

behavior, and that supplementation can enhance therapeutic effect of antidepressants and anxiolytics.[35] To lithium and magnesium they add zinc, iron, calcium, and chromium.

Nutritional Forms of Lithium

The two most common, low-dose forms of lithium that are readily available over the counter (OTC) are the aspartate and orotate forms. In terms of chelate stability and ionizability (how easily they ionize, or generate ions in an aqueous medium), both are very stable, and are thought to be absorbed and transported largely intact (un-ionized) through the intestinal lumen, and delivered to their sites of action within the cell. In contrast, the pharmaceutical forms of lithium, carbonate and citrate, have a "loose" ionic association and readily ionize producing extracellular lithium ions, which diffuse less efficiently into the cell via sodium channels.

Clinical support for the relative differences in the ionizability of different organic chelates (e.g. citrate, aspartate, glycinate, orotate, threonate, gluconate, etc.) and inorganic complexes (i.e. carbonate, oxide, and sulfate) can be readily observed in the body's response to oral forms of magnesium.

Low-to-moderate doses of readily ionizable forms of magnesium (e.g. oxide, sulfate, gluconate, and citrate) produce an osmotic effect in the intestines (exploited for this very property in clinical medicine), resulting in a laxative effect. Well-absorbed forms of magnesium (e.g. glycinate, lysinate, threonate, orotate, aspartate) are stable chelates with relatively low ionizability, and are absorbed largely intact from the intestines. These forms have high bioavailability (estimated to be greater than 60–70 percent) with virtually no intestinal side effects.

In general, the more ionizable forms of minerals cause greater side effects and "biological disruption" due to their extracellularly irritating nature. For example, copper and zinc can produce nausea in relatively small doses, and poorly absorbed forms of iron (e.g. sulfate) can cause intestinal irritation, nausea, and constipation.

From a firmer understanding of the various forms of lithium and other mineral nutrients, one can navigate the nutritional and pharmacological realm with greater precision and desired effect, yielding fewer unwanted side effects, and more positive clinical outcomes.

High-Dose vs. Low-Dose Lithium

Vastly different mechanisms govern high and low doses of lithium. In high doses, approximately 50–300 times greater than our dietary intake from naturally occurring lithium in food and water, lithium acts as a drug.

The high doses are needed to "force" lithium into the body's cells via a crude concentration gradient. If the extracellular concentration is high enough (at potentially toxic levels), sufficient lithium will enter via simple diffusion primarily through sodium channels to reach a therapeutic level. Like anything at a high enough level, including water and vitamins, lithium can be toxic.

For low-dose lithium, the highly bioavailable orotate chelate[29, 30] functions as a targeted delivery system. The stable, intact, un-ionized chelate is believed to transport the lithium efficiently through the cell membrane to its various sites of action within the cell. Stability studies of the orotate chelate conducted in the 1970s by the German physician Hans Nieper concluded that the orotate chelate was able to pass through cell membranes intact without dissociating into its component ions (Li+ and orotate-), and once inside the cell, the orotate mineral complex dissociated, releasing the lithium to its sites of action.[36]

Kling and Pollack found that lithium orotate was three times more effective at raising brain concentrations of the mineral than lithium carbonate. Based on the data, the authors concluded that lower doses of lithium orotate may achieve therapeutic brain lithium concentrations and relatively stable serum concentrations.[37]

The safety of low-dose lithium is comparable to low-dose forms of other nutrients such as zinc. In fact, lithium has a much wider therapeutic and biologically compatible (nontoxic) window than zinc. Starting with a dose at Schrauzer's provisional RDA of 1 mg for lithium with nutritional doses up to 20 mg (representing a 20-fold difference in the "low-dose supplemental range" employed by functional medicine practitioners for many years now) is very safe with a very low incidence of side effects.[38]

In contrast, a 20-fold increase in the dose of zinc from the RDA of 15 mg to 300 mg would cause numerous adverse effects such as nausea, vomiting, abdominal cramps, diarrhea, headaches, weakness, irritability, immune suppression, and copper depletion.[39, 40, 41] Even low-to-moderate doses (15 mg to 30 mg) of zinc, which is considered relatively nontoxic, may still promote copper depletion. Lithium is not known to cause any mineral imbalances or depletion.

Concerns about the safety of lithium supplementation were raised in a letter to the editor.[42] A resident physician at a university clinic evaluated a patient who reported using lithium orotate, 240 mg/d, for self-diagnosed bipolar disorder. The diagnosis was not confirmed, and the patient did not show signs of toxicity.[42] Toxicity at this dose would not be expected, based on the long history of safe use of lithium throughout Europe and the U.S. for more than 40 years. Jonathan V. Wright, M.D., reports the exceptional safety of lithium (orotate) as used at the Tahoma Clinic in low, nutritionally relevant doses (5–20 mg/d).[43]

We need to remember the often-disregarded truism that the dose determines the poison. Water intoxication (intentional consumption of large amounts of water producing hyponatremia and subsequent organ failure) has caused many fatalities,[44,45] whereas there are no reported cases of death or serious side effects in more than 40 years of lithium orotate use in Europe and the U.S. There is one case report of a woman who intentionally ingested 18 tablets of Find Serenity Now (each tablet containing 120 mg of lithium orotate, supplying 3.83 mg of elemental lithium per tablet), for a total dose of 68.9 mg. She complained of nausea with one episode of emesis,

and presented with normal vital signs and a slight tremor. Symptoms resolved within three hours of observation.[46]

Lithium Use in Alcoholics and Drug Abusers

Schrauzer and de Vroey reported on 42 alcoholic patients undergoing treatment at a private rehabilitation clinic who were given 150 mg of lithium orotate per day (4.8 mg elemental lithium). Ten of the patients had no relapse for more than three and up to 10 years; 13 patients remained without relapse for one to three years; and the remaining 12 had relapses between 6 and 12 months. The adverse side effects noted were minor: eight patients out of the 42 total developed muscle weakness, loss of appetite, or mild apathy. The symptoms subsided when the dose was decreased from daily to four to five times weekly.[47]

In 1994, Schrauzer reported a placebo-controlled study of former drug users. Using a lithium-rich brewer's yeast providing just 400 mcg (0.4 mg) per day of lithium, he found that in the lithium group, the total mood test scores increased steadily and significantly during the period of supplementation. He concluded, based on these results and the analysis of voluntary written comments of study participants, that lithium at the dosages chosen had a "mood-improving and-stabilizing effect."[37]

Dietary Sources of Lithium

Foods traditionally regarded as "neurotonics," defined as having a nourishing effect on the brain and nervous system, such as cacao, oats, seafood, seaweed, goji berries, various fruits and vegetables (depending on the soil in which they're grown), and egg yolks are significant sources of lithium, along with other trace minerals such as iron, copper, and manganese, which are known to co-migrate along with lithium from the soil to the plant.

Toxic Challenges and Deficiencies

Potential toxins from diet and environment include mercury (e.g. from large fish, vaccines, dental amalgams)[48-50], aspartame (present in more than 6,000 consumer products), monosodium glutamate (e.g. from canned foods, processed foods, flavorings), Bisphenol A or BPA (e.g. from canned foods and beverages, plastics, store receipts), and other neurologically damaging excitotoxins.[51-53]

These neurological "assaults" are cumulative and over time can manifest in a variety of symptoms ranging from depression, anxiety, memory problems, learning difficulties, sleep disturbances, sensitivity to stress, chronic pain, and other signs of a "stressed" or compromised nervous system.

Persons with any type of neurologic injury often have deficiencies in neuroprotective nutrients such as magnesium, zinc, selenium, vitamin B12, folate, and lithium. These deficiencies exacerbate the underlying conditions, while simultaneously undermining fundamental healing processes in the brain and nervous system.

Conclusion

An optimal, nutritional intake of lithium may prevent or ameliorate many neurologic and psychiatric conditions through effects on nervous system metabolism and generalized anti-inflammatory and antioxidant effects. Pharmaceutical agents often mask symptoms without correcting underlying problems. Nutritional supplementation is safe—with wide-ranging neurological benefits—and should benefit overall health.

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Disclosure: Dr. Marshall willl be marketing products containing lithium as a nutritional supplement.

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