Review

Lithium: Occurrence, Dietary Intakes, Nutritional Essentiality

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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. Human dietary lithium intakes depend on location and the type of foods consumed and vary over a wide range. Traces of lithium were detected in human organs and fetal tissues already in the late 19th century, leading to early suggestions as to possible specific functions in the organism. However, it took another century until evidence for the essentiality of lithium became available. 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. In humans defined lithium deficiency diseases have not 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. 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. The biochemical mechanisms of action of lithium appear to be multifactorial and are intercorrelated with the functions of several enzymes, hormones and vitamins, as well as with growth and transforming factors. The available experimental evidence now appears to be sufficient to accept lithium as essential; a provisional RDA for a 70 kg adult of 1000 μg/day is suggested.

Key teaching points:

- Lithium is normally present in all organs and tissues. Lithium is absorbed from the intestinal tract and is excreted primarily by the kidneys. Absorbed lithium is uniformly distributed in body water, with only a small difference between the extracellular and intracellular levels.
- During embryonic development, organ lithium levels reach maximal values in the first trimester of gestation and subsequently decline. Animal studies have demonstrated that Li plays a role in the expansion of the pluripotential stem cell pool to more mature progenitor cells and blood elements.
- In Li deficient rats, behavioral abnormalities and a significant negative effect on litter size and litter weight at birth were observed. In Li deficient goats the conception rate was reduced, gravid lithium deficient goats experienced a higher incidence of spontaneous abortions.
- Defined human lithium deficiency diseases have not been observed. However, inverse associations of tap water lithium contents in areas of Texas with the rates of mental hospital admissions, suicides, homicides and certain other crimes suggest that low lithium intakes cause behavioral defects.
- The average daily Li intake of an American 70 kg adult ranges from 650 to 3100 μg. Major dietary sources are vegetables and, in some areas, the drinking water.
- Subjects at risk of developing lithium deficiency are patients with kidney diseases and dialysis patients.

Lithium (Li), the lightest of the alkali metals, was discovered in 1817 by Johan August Arfvedson in petalite, a tektosilicate of composition $LiAlSi_4Si_{10}$. The element occurs in numerous other minerals and was named after the Greek *lithos*, stone, because of its presence, in trace amounts, in virtually all rocks [1]. Mobilized by weathering processes, lithium is transported into soils, from which it is taken up by plants and enters the food chain. Lithium was detected in human organs and fetal tissues already in the late 19th century, leading to early suggestions of possible specific functions in the organism [2,3],

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but medical applications of lithium preceded studies on lithium as an essential micronutrient. From the mid 1800s to the early 1940s, lithium carbonate was used - without adequate substantiation or success - to treat gout and to dissolve urate bladder stones. The first legitimate medical application of lithium was introduced 1949, when lithium carbonate was found to be beneficial in manic depressive illness [4]. Today, lithium carbonate is one of the most widely prescribed psychiatric drugs. More recently, it has found other applications, notably in oncology [5,6] and in dermatology [7], for example. However, the present review focuses only on the nutritional aspects of this element.

LITHIUM IN THE ENVIRONMENT, UPTAKE BY PLANTS

Lithium is found in trace amounts in all soils primarily in the clay fraction, and to a lesser extent in the organic soil fraction [8], in amounts ranging from 7 to 200 μg/g [9,10]. It is present in surface water at levels between 1 and 10 μg/L, in sea water at 0.18 μg/L [9,10]. The lithium concentrations in ground water may reach 500 μg/L, in river water of lithium-rich regions of northern Chile, 1508 and 5170 μg/L, respectively [11]. In the latter regions, total Li intakes may reach 10 mg/day, without evidence of adverse effects to the local population. Still higher lithium levels, up to 100 mg/L are found in some natural mineral waters [1,12].

Lithium is taken up by all plants, although it appears not to be required for their growth and development. However, this question is not yet completely resolved, since, in the ppb range, stimulatory effects of lithium on plant growth have been observed [13]. At high levels in the soil, Li is toxic to all plants, causing a chlorosis-like condition. Uptake and sensitivity to lithium are species dependent. Some plants, notably *Cirsium arvense* and *Solanum dulcamera*, accumulate Li three- to six-fold over other plants. Halophilic plants such as *Carduus arvense* and *Holoschoenus vulgaris* may reach lithium contents of 99.6–226.4 μg/g [14]. Lithium is relatively toxic to citrus plants; nightshade species are remarkably lithium tolerant and may reach lithium contents of up to 1000 μg/g. Yeast (*Saccharomyces cerevisiae*) takes up limited amounts of lithium, high levels (115–400 ppm) in the medium cause growth inhibition [15]. In general, more lithium is taken up by plants from acidic than alkaline soils. Since soil acidity also increases the solubility of the heavier metallic elements, plant Li levels are directly and significantly correlated with those of iron, nickel, cobalt, manganese and copper, and to some extent also to those of aluminum, lead and cadmium [16].

DIETARY INTAKES AND SOURCES OF LITHIUM

The U.S. Environmental Protection Agency (EPA) in 1985 estimated the daily Li intake of a 70 kg adult to range from 650 to 3100 μg [17]. Primary dietary sources of lithium are grains and vegetables, which may contribute from 66% to more than 90% of the total lithium intake; the remainder is from animal-derived foods (Table 1).

In general, diets rich in grains and vegetables may be expected to provide more lithium than diets rich in animal proteins. However, due to the uneven distribution of lithium on the earth's crust, a predominantly vegetarian diet is not necessarily lithium rich. Accordingly, the estimated dietary lithium intakes in populations of different countries vary over a wide range and, as a rule, the standard deviations from the means are large (Table 2). Tap water and beverages may contribute significantly to the total.

In some parts of Texas, for example, tap water Li levels may reach 170 μg/L, adding about 340 μg of Li to the daily intake of lithium from foods. In these regions, urinary Li excretions of local residents vary inversely with rainfall, reflecting the dilution of drinking water supplies [18].

LITHIUM IN ORGANS AND TISSUES

Ingested Li in the form of its soluble salts is absorbed to virtually 100% from the small intestine via the Na^+-channels and is excreted primarily by the kidneys. Absorbed lithium is uniformly distributed in body water, with only a small difference between the extracellular and intracellular levels. Autopsy studies of adults revealed that the cerebellum retains more lithium than other organs, followed by the cerebrum and the kidneys. Organ lithium levels showed some unexplained gender differences, with women exhibiting 10% to 20% more Li than men in the cerebellum, cerebrum, kidneys and the heart and 13% less Li in the pancreas; the Li concentrations in the liver, lungs, ribs and thyroid were about the same for both genders [21] (Fig. 1). During embryonic development, organ lithium levels reach maximal values in the first trimester of gestation and subsequently decline, as is true for other trace elements. At the end of the third trimester, the lithium concentration of the fetus is 1/3 of that in the first. The lithium contents of the kidneys, the liver and the ribs continue to decline

Table 1. Sources of Dietary Lithium according to [10]

Food Group	Quantity ingested kg food/day	Li Level mg/kg food	Total μg/day
Grains and vegetables	0.85	0.5–3.4	430–2900
Dairy products	0.44	0.50	222
Meat	0.21	0.012	2.5
Total			650–3100

Table 2. Estimated Dietary Li Intakes (Adults, Averages for Males and Females) in Different Countries

	μg/day
China (Xi'an)[a]	1560 ± 980
Mexico (Tijuana, B.C.)[b]	1485 ± 1009
Sweden (Stockholm)[b]	1090 ± 324
Denmark (Copenhagen)[b]	1009 ± 324
Mexico (Culiacan)[b]	939 ± 928
USA (Galveston Texas)[b]	821 ± 684
Japan (Tokyo)[b]	812 ± 383
U.S.A., New York area	650 ± 740
Germany, District of Potsdam[c]	494 ± 421
USA (San Diego, California)[b]	429 ± 116
Germany (Munich)[b]	406 ± 383
Germany, District of Gera[c]	364 ± 326
Vienna (Austria)[b]	348 ± 290

[a] Unpublished data, [b] [19], [c] [20].

during the first five to ten years of life, that of the prostate continues to decline over the entire lifespan. The serum lithium concentrations are approximately proportional to the lithium intakes. In adults receiving 0.25 mmol (1.74 mg) of lithium as the chloride per day for several weeks, for example, the mean serum lithium concentrations increased from a baseline concentration of 0.14 ± 0.03 μmol/L to 3.9 ± 0.8 μmol/L or 0.97 ± 0.21 to 27.0 ± 5.5 μg/L, respectively. At only half the dose, or 0.125 mmol (0.87 mg) of lithium per day, the serum lithium concentration at steady state was 2.6 μmol/L (18.0 μg/L). At the equal daily Li dosages, body weight and height of the study subjects were inversely correlated with the serum lithium concentrations; serum lithium decreased by 0.57 μmol/L for every 10 cm increase in height or by 0.38 μmol/L for every 10 kg increase in weight [22]. This indicates that the given dose of Li was equally well absorbed by all study subjects, giving rise to higher serum Li levels in shorter and lighter, than in taller and heavier subjects. Baseline serum lithium levels in adults typically range from 7 to 28 μg/L [10], corresponding to adult lithium intakes of 385–1540 μg/day. Scalp hair lithium levels reflect the average intakes of bioavailable lithium over a period of several weeks to months and represent a noninvasive means of determining the dietary lithium intakes [19]. The lithium content of hair also reflects lithium status in animals [23]. Hair lithium levels of adults from the New York area ranged from 0.009–0.228 μg/g (N = 206) [24]; the values were slightly higher for females than for males. This is also true for a number of other elements and was attributed to the generally higher inorganic (ash) content for hair from females [24]. The authors of this study furthermore showed that external contamination of hair by dustfall and housedust did not affect hair Li levels. From these data, the medium lithium intake of these adults was calculated to 650 μg/day, range 100–2645 μg/day [19]. In the same study, hair lithium levels were shown to increase in proportion to dose in human subjects receiving 1000 and 2000 μg of extradietary lithium in a supplement, reaching a steady state after three months of supplementation. However, the proportionality does not extend to pharmacological lithium intakes; hair lithium thus cannot be used to monitor the compliance of patients on lithium carbonate.

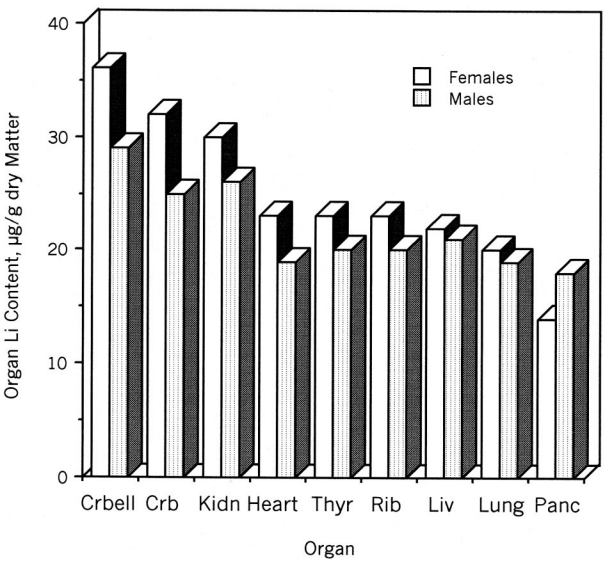

Fig. 1. Lithium levels of human organs according to autopsy studies of Baumann *et al.* [21]. Abbreviations: Crbell = cerebellum; Crb = cerebrum; Kidn = Kidneys, Thyr = thyroid; Liv = liver; Panc = pancreas.

ESSENTIALITY FOR THE RAT

For studies of the nutritional essentiality of lithium it was necessary first to formulate appropriate low-lithium diets. Patt, Pickett and O'Dell [25] succeeded in the mid 1970s to prepare a corn-casein diet for the laboratory rat whose lithium content was 5–15 ng/g. Growth rate and behavior of rats were found to be the same as in the controls maintained on a commercial feed whose lithium content was 350 ng/g or in animals receiving the low-Li corn-casein diet supplemented with lithium to 500 ng/g. The lithium deficient rats required a longer conception time in the first, but not in the second generation. Litter size was 20% to 30% smaller in all generations, and survival to one week was only 53% to 60% of that of controls. A key result of this study was that the mature, Li-deficient rats retained Li at control levels in the pituitary and adrenal glands, suggesting that these organs require Li for some functions. In other tissues, including blood, cerebrum, liver, kidney, spleen, heart and bone, a 20% to 50% reduction in lithium contents compared to the controls occurred, and all soft tissues contained less Li than the endocrine tissues. Fig. 2 shows the observed Li contents of select organs in the controls on the 350 ng Li/g feed and of the 1st and 2nd generation of animals on the 15 ng Li/g feed. In a second study [26], retention of Li was again seen in adrenal and pituitary, but this time also in hippocampus, mammary gland, ovary and thyroid. Retention in the thymus and the pancreas

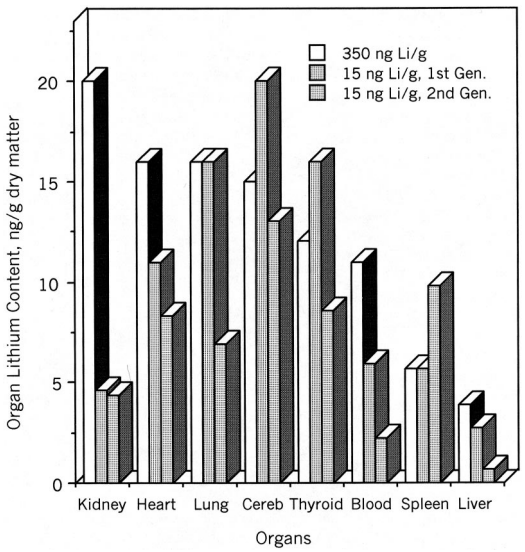

Fig. 2. Lithium contents of select organs of control rats on 350 ng Li/g feed and of 1st and 2nd generation rats on Li deficient feed, according to Patt *et al.* [25].

was less marked; the Li contents of other tissues were lower than in the controls. This study also revealed that Li is retained and released by bone. Whereas the femurs of the Li supplemented rats contained 0.21 ± 0.01 μg/g in the first and second generation, Li concentrations were below detection limit in the Li deficient rats. In a third study [27], rats were fed diets based on purified casein and corn containing only 2 ng Li/g and on purified casein and rice containing 0.6 ng Li/g. The controls received the same diets whose Li contents were increased to 500 ng/g. The dams and their offspring were maintained on these diets for five successive litters and three successive generations, respectively. A significant negative effect of lithium deficiency on litter size and litter weight at birth was observed. In addition, evidence for the interaction of lithium with sodium was obtained: Litter size and litter weight at birth were significantly lower among low Li-dams consuming diets with normal or high levels of sodium than those consuming low sodium diets.

ESSENTIALITY FOR THE GOAT

Experiments to prove the essentiality of lithium in goats were initiated by Anke and his school in 1976 and continued until 1988 [20,28,29]. The animals were maintained on a semi-synthetic feed; the feed of the controls contained 12.7 μg Li/g, that of the experimental group $<1\mu$g Li/g. Lithium deficient goats required repeated inseminations for conception, exhibited a reduced conception rate and increased barreness. Gravid lithium deficient goats experienced a higher incidence of spontaneous abortions and produced kids with the female to male ratio of 1:1.9, significantly different from the ratio of 1:0.9 observed in the controls. In lactating, lithium deficient goats, milk production was not reduced during the first five weeks of lactation, but dropped below that of the controls in the sixth week. Although Li deficiency did not significantly alter the fat content of the milk, the overall fat production during the first 56 days of lactation was significantly reduced. These effects of Li deficiency were accompanied by atrophy of the spleen, lowered immunological status, chronic inflammations, hemosiderosis and calcification of the blood vessels. The newborn kids had lower birth weights and showed slower weight gains than control kids during the subsequent lactation period. Lithium deficiency did not affect the mortality of the kids during the 8th and 91st day of life, but resulted in a significantly higher mortality of adult goats during the first year. In the Li-depleted mature goats, the Li contents of skeletal muscle, pancreas and of cardiac muscle were the same as in the normally fed controls, while the serum Li levels dropped to 19% of the controls. The Li contents of hair, lungs and milk were reduced to 30%, of spleen, carpal bone to 40%, of rib to 42%, of ovary to 45% and liver to 48%. The Li contents of the kidneys, uterus, aorta and cerebrum remained at 48% to 69% of those of the controls. Fig. 3 shows the Li contents of select organs in the Li-normal and Li-deficient kids, revealing evidence of Li retention under conditions of Li deficiency in the pancreas, heart and cerebrum. Compared to the organ Li contents of the Li-deficient rats (Fig. 2), those of the Li-deficient kids were somewhat higher, indicating that their degree of Li deficiency was not as extreme.

Lithium deficiency in the kids and goats had no effect on blood parameters, with possible exception of the lymphocyte count, which was slightly lower. Lithium deficiency reduced the activity of enzymes of the citrate cycle such as isocitrate dehydrogenase (ICDH), malate dehydrogenase (MDH), of glycolysis such as aldolase (ALD) and of N-metabolism. Creatine kinase, a stress-indicating enzyme, was elevated. The monoamine oxidase (MAO-) activity in liver was significantly reduced [20]; serum levels such as glycerol, glucose, lipids, fatty acids, lactate and cholesterol of the Li deficient goats were normal. A morphological examination of organs and tissues of

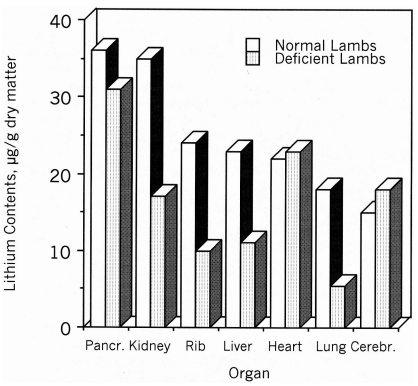

Fig. 3. Lithium contents of select organs of normal kids and of Li-deficient lambs, according to Arnhold and Anke [29].

a lactating lithium deficient goat revealed a cystadenoma of the mamma. In the other goat Investigated, the mamma was underdeveloped and exhibited manifestation of a chronic inflammatory process. Adenomatous structures of the salivary glands were found in the tongue of this goat. In the adrenal glands, examination revealed adenomas of the capsule and zona glomerulosa. In addition, some portions of the cortical substance tissue penetrated the substantia medullaris. There also were multiple follicular cysts in the ovaries [30]. These findings provide a clue as to the origin of the effects of lithium deficiency on lactation and reproduction in goats.

EFFECTS OF LITHIUM DEFICIENCY ON BEHAVIORAL PARAMETERS

Effects of Li deficiency on behavioral parameters were demonstrated in studies with rats. Ono and Wada [31] found that rats on a Li-deficient diet (0.0066 μg Li/g diet) exhibited suppressed level-press avoidance behavior as compared to animals on a Li-supplemented diet (0.11 Li μg/g diet). The behavior of the Li-deficient rats normalized on Li supplementation at nutritional dosages. In another study, Klemfuss and Schrauzer showed that rats on a Li-deficient diet ($<$0.01 μg Li/g) and drinking water containing 31 μM NaCl exhibited diminished wheel-running activity, decreased response to handling and lower aggression in social interactions with other rats compared to rats receiving the same diet but 31 μM (215 μg Li/L) of LiCl in the drinking water [32].

LITHIUM DEFICIENCY IN HUMANS

As Li deficiency in humans is unlikely ever to reach the degree of severity observed in experimental Li-depleted animals, any symptoms of lithium deficiency in humans, if at all observable, would be expected to be mild and manifest themselves primarily by behavioral rather than physiological abnormalities. Evidence linking low lithium intakes with altered behavior and aggressiveness in humans was reported by Dawson *et al.* [18,33,34]. These authors compared the regional mental hospital admission rates and homicide rates for 1967-1969 with the lithium concentrations in tap water samples and in urine samples obtained from 24 county sites in Texas. The highest significant inverse associations of water Li levels were observed with first mental hospital admissions for psychosis, neurosis and personality disorders. The decreasing order of magnitude of the associations was neurosis, schizophrenia, psychosis, first admission, all admissions, personality, homicide and secondary admissions. Urine lithium concentrations showed the statistically most significant inverse associations with the schizophrenic diagnosis, secondary with the first mental hospital admission for psychosis, neurosis and with homicide; associations with the suicide rates were inverse but not significant. Using crime rate data for 1978-1987, Schrauzer and Shrestha observed statistically highly significant inverse associations (p = 0.005 to 0.01) between water lithium levels and the rates of homicide, suicide and forcible rape. Significant inverse associations (p = 0.05 to 0.01) were also observed with the rates of arrest for burglary and theft, possession of narcotic drugs and, in juveniles, for runaway from home [35,36]. In a subsequent study [19], the mean scalp hair Li levels of incarcerated violent offenders in California were found to be 0.028 $\pm$ 0.029 μg/g, significantly lower than the 0.099$\pm$0.126 μg/g observed in hair of nonincarcerated controls, although this does not necessarily establish a causal relationship.

Lithium deficiency may not only be caused by low dietary Li intakes but can also be secondary to certain diseases. Fig. 4 shows that organ Li contents of kidney disease and, especially, of dialysis patients are approaching deficiency levels.

LITHIUM SUPPLEMENTATION STUDIES

In a placebo-controlled study with former drug users (mostly heroin and methamphetamines) [37], 24 subjects (16 males and 8 females, average age 29.4 $\pm$ 6.5 years) were randomly divided into two groups, one receiving 400 μg of lithium per day in yeast, the other placebo, for four weeks. All subjects completed weekly self-administered mood test questionnaires. In the Li group, the total (positive) mood test scores increased steadily during the four weeks of supplementation and specifically in the subcategories reflecting happiness, friendliness and energy. In the placebo group, the combined mood scores showed no consistent changes; the happiness scores actually declined.

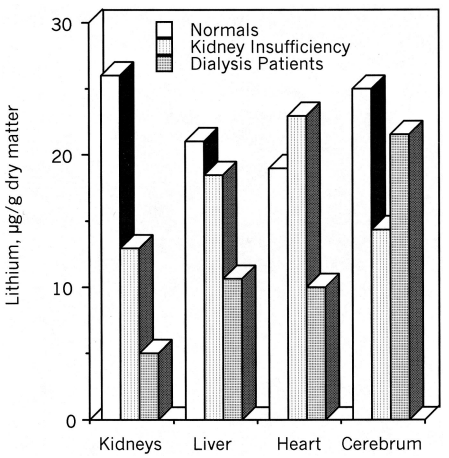

Fig. 4. Lithium contents of organs of kidney disease and dialysis patients compared to those of normals, plotted with data of Baumann *et al.* [21].

MECHANISTIC CONSIDERATIONS

The biochemical mechanisms of action of Li appear to be extraordinarily complex, multifactorial and strongly intercorrelated with the functions of other elements, drugs, enzymes, hormones, vitamins, growth and transforming factors. Some of the known biological actions of Li are shown in Table 3. Although these were mostly observed at pharmacological levels, they could also occur at nutritional levels, accounting for the unusually broad activity spectrum of Li. For example, the mood-elevating action of supplemental Li may be related to the increase monoamine oxidase (MOA) activity, which is depressed in Li deficiency [20]. However, Li has been shown to enhance folate and B_{12} transport into L1210 cells [38], the transport of these factors is inhibited in Li deficiency and can be restored by lithium supplementation. 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 antidepressive, mood-elevating and antiaggressive actions of Li at nutritional dosage levels. Recognition of the intercorrelated nature of all biological actions of Li may result in improved therapeutic concepts. Thus, the joint administration of Li with vitamin B12 and folate may prove more effective than Li or the vitamins alone.

Ultimately, many of the biological actions of Li are probably attributable to the powerful polarizing effect caused by its small ionic radius. Lithium may displace Na^+, K^+, Mg^{+2}, Ca^{+2} from its membrane or enzyme binding sites [39], interactions with aluminum, manganese or vanadium which have been discussed elsewhere [19]. The fact that embryonal Li concentrations are the highest during early fetal development suggests that it is specifically needed. Animal studies have demonstrated that Li plays a role in the expansion of the pluripotential stem cell pool [40–42]. In mice, lithium chloride increased pluripotential stem cells, followed by increases of more mature progenitor cells and later of hematopoietic growth factors and mature blood elements [43].

Table 3. Known Biological Actions of Lithium, according to Klemfus and Greene [38] and their References

Inhibits adencylate cyclase	Inhibits cyclic GMP
Inhibits inositol phosphatase	Binds to G protein complex
Stimulates tyrosine hydroxylase	Desensitizes 5-HTP receptor
Stabilizes tryptophane hydroxylase	Increases the viscosity of water
Increases GABA activity	Increases ACh turnover
Increases enkephalin release	Promotes actin assembly
Inhibits vasopressin release	Prevents supersensitivity
Antagonizes aldosterone	Inhibits PKC translocation
Delays melatonin onset	Increases membrane fluidity
Suppresses thyroid	Decreases intracellular K^+
Stimulates parathyroid	Inhibits choline transport
Decreases sensitivity of retina	Stimulates Na^+,K^+-ATPase
Interferes with cation binding	Inhibits Na^+,K^+-ATPase
Depolarizes neurons	Inhibits Na^+/Ca^{+2} antiport
Damps circadian rhythms	Stimulates PGE_1 synthesis
Delays circadian rhythms	Inhibits PGE1 synthesis
Blocks ion channels	Alters neurotransmitters
Alters lipid composition	Blocks vanadate binding

Abbreviations: ACh = acetylcholine, GABA = gamma-aminobutyric acid, 5-HT = serotonin, ATPase = adenosine-triphosphatatase, PKC = calcium-dependent protein kinase, PGE_1 = prostaglandin E_1, GMP = guadinine monophosphate.

PERSPECTIVES FOR THE ESTABLISHMENT OF AN RDA FOR LITHIUM

Although Li is clearly essential for higher animals, the Li requirements for different animal species still remains to be accurately determined. Although there is presently no evidence that Li deficiency causes serious problems in animal production, the possibility that inadequate Li intakes cause behavioral defects should be considered. For humans, the available evidence suggests that assuring adequate Li intakes for the general population could provide substantial health and societal benefits. The minimum human adult (physiological) Li requirement was estimated [44] to <100 μg/day, higher intakes are apparently needed to utilize "beneficial" effects of Li. Based on Li intake data in different countries, a provisional RDA of 1 mg Li/day for a 70 kg adult can be proposed, corresponding to 14.3 μg/kg BW, which can be reached by diet alone in Li- adequate regions. For subjects subsisting on special diets or for populations residing in naturally low Li areas, Li supplementation or other appropriate measures to meet this RDA would be required. Special attention should be accorded to the potentially higher relative Li needs of children, adolescents and lactating mothers. Lithium needs furthermore may be higher after physical exertion, in certain diseases and in dialysis patients. An adequate supply of Li should also be assured for subjects on formula diets and or on total or home parenteral nutrition.

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