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Review Article

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Lithium: Implications for Neuropsychiatry and Wellness

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Abstract

Lithium is ubiquitous in the environment and probably an essential trace nutrient. The guidelines of major psychiatric association name lithium as a first-line therapy for bipolar disorder. Some studies have shown an association between low lithium intakes from water supplies and suicidality, as well as criminality. Other studies have shown that trace levels of lithium have neuroprotective abilities or improvements in mood and cognitive function. In animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor, nerve growth factor, neurotrophin-3, as well as receptors to these growth factors in brain. Lithium has been reported to be beneficial in animal models of brain injury, stroke, amyotrophic lateral sclerosis, spinal cord injury, and degenerative diseases. A wide range of intracellular responses may be secondary to the inhibition of glycogen synthase kinase-3 beta and inositol monophosphatase by lithium. 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, cortical thickening, increased grey matter density, and hippocampal enlargement. Many findings pose the question of whether the prospect of adding lithium to drinking water is realistic, weighing the benefits and potential risks. The bulk of evidence suggests that the optimum level of lithium intake is more than most people get from food and drinking water.

Keywords: Lithium; Neuropsychiatry; Bipolar disorder therapy

Introduction

Interesting questions about lithium abound at all levels of science, ranging from the microscopic to the cosmic. Lithium is at the heart of a deep so-far-unsolved problem in cosmology. It is one of the three elements (the other two are hydrogen and helium) produced in the initial condensation of matter from energy immediately following the Big Bang [1]. The overall abundance of hydrogen and helium in the observed universe agrees well with the predictions of big bang nucleosynthesis theory. However, the observed amount of lithium is too small [2]. Lithium is ubiquitous in our environment through being in both seawater and ground water, and hence in us and in everything we eat and drink. Because lithium is naturally present in only small amounts, it is often neglected in biological studies. However, even in small amounts lithium can have major biological effects. We know this both from its therapeutic effects, making it a first line therapy for bipolar disorder, and from its toxic effects, which for the average person emerge when the concentration in the blood is substantially over 1 millimoles/liter, a much lower blood concentration than that of other biologically significant inorganic ions in our blood. The actions of many biomolecules are modified by lithium, so many that it is difficult to identify in living cells just which biomolecules lithium is interacting with most strongly [3]. Between the 1880s and World War I, the most premium of all the mineral water brands were lithia waters because of their acclaimed health benefits. Research studies measuring the effects of trace levels of lithium, commonly found in lithia waters, have demonstrated neuroprotective abilities [4], as well as improvements in mood and cognitive function [5].

Biochemistry

It may be that the physical basis for the universality of the actions of lithium is the very small size of lithium ions, which as a corollary implies a very high charge density compared to other ions of biological importance such as sodium, calcium, potassium, magnesium, chloride, and bicarbonate to name the major ones. This hypothesis about the physics remains to be explored, but the fact that lithium is engaged in significant interactions with a very broad range of biological molecules is without question. Because lithium interacts with so many biomolecules, it is a universal modulator of biomolecular functions and interactions. One major pathway for lithium entry into cells appears to be through sodium channels [6]. Lithium efflux also appears to be sodium dependent, as lower concentrations of extracellular sodium cause a reduction in lithium efflux [7]. A major mechanism for lithium efflux is almost certainly the sodium-proton pump [8]. Thus the efflux of lithium appears to occur as an example of a general class of secondary active transport mechanisms that are driven by sodium gradients. In contrast to other ions, no specific transport mechanism selective for lithium has been discovered and it seems likely that other known transport processes play a role in moving lithium across the membrane [9].

The forces that govern biomolecular structure and function can be grouped into two major categories: (a) hydrophobic/hydrophilic, in which polar or charged regions of biomolecules are attracted preferentially towards water, resulting in the molecular exteriors being charged and polar, and (b) electrostatic, in which oppositely charged groups are attracted to each other. Lithium, being much smaller than other biologically significant ions has potentially much stronger short-range electrostatic interactions with both charged groups on macromolecules and with water than the larger ions. This is presumably relevant to its ability to modify biomolecular structure and function at relatively low concentrations. Since all of life on earth has evolved in the presence of lithium, and since lithium seems to affect many, perhaps all, biochemical interactions to some degree, biochemistry must be "tuned" to the presence of lithium. Lithium blood concentration varies normally from .00001 to .00009 moles liter, while the therapeutic target range for bipolar is .0005 to .001 moles/liter, which is about 100 times the high end of the normal range. Organic lithium salts is much safer than inorganic salts of lithium in terms of depletion of blood plasma glutathione (GSH) contents [10]. Symptoms of lithium toxicity begin, on the average, just a bit above the high end of the therapeutic range. Patient should be given a support to correct hypernatremia and even sodium levels should be tested serially-along with serum lithium concentrations-because high sodium

levels reduce the rate of elimination of lithium. Lithium-related central nervous system toxicity as well as the cardiovascular and thyroid changes are most likely due to the cations (Na^{2+} and K^{+}) competition [11]. In summary, proton concentrations are tightly regulated while lithium concentrations are not. In addition, cations in the body—sodium, potassium, calcium, and magnesium - are, like protons, tightly regulated in concentration. Significant deviations in concentration are diagnostic for, and causes of, pathology. Here is the paradox of lithium. It is clearly important in biology, it interacts with many biomolecules in ways that modify overall biological functioning, but it is not closely regulated in our bodies, and possibly not in other biological systems. Bodies' strategy for dealing with other biologically important cations includes regulating their concentrations closely through systems of specific carriers and transporters. However, bodies' overall strategy for dealing with lithium is to accommodate our biochemistry and cellular processes to widely varying concentrations. This accommodation is clearly imperfect, so that differing lithium intake levels and environmental exposure have both mental and physical health consequences [11].

Biology

Lithium inhibits the activity of glycogen synthase kinase-3 (GSK-3-beta), a kinase known for its activity on glycogen synthesis, that has in the last few years raised growing interest in biological psychiatry [12]. This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the nuclear factor of activated T cells (NFAT) and WNT/beta-catenin [13]. Strong inhibition has been shown with lithium via the proteic scaffold PP2A/β-arrestin/AKT, and with the rapid antidepressant effect of ketamine via p70S6K [14]. There are two versions of human GSK, GSK-3 alpha and GSK-3 beta, whose protein gene products are 78% identical. The human GSK-3 alpha and beta are two out of hundreds of human protein kinases. Other kinases are also affected by lithium, but the GSK-3's are the ones whose lithium effects are most studied. GSK-3 inhibitors are under consideration for a wide variety of diseases, including neurodegenerative disease, cancer, and inflammation [15]. This also means that lithium is a potential therapeutic agent for all of these conditions. The role of GSK-3 in many different pathways, plus the therapeutic potential of GSK-3 beta inhibitors, has motivated structural studies of GSK-3-beta complexed with many different organic molecules. GSK-3-beta inhibition has been shown specifically to inhibit prostate tumor growth [16]. A similar effect is found in ovarian cancer cells [17]. The possible use of lithium as an anticancer agent is reinforced by a retrospective study showing that psychiatric patients undergoing lithium therapy for bipolar disorder had a much lower incidence of cancer than a matched group not receiving lithium therapy [18]. Because of the promise of lithium as an anticancer drug, it is now the focus of a Phase I clinical trial in which lithium will be administered in conjunction with radical prostatectomy (Clinical trials). There is now a growing body of basic science literature on the cellular level showing that inhibition of GSK-3-beta by lithium can suppress various types of cancer. For example, lithium is lethal to neuroblastoma cells but not to normal nerve cells [19].

Evidence for the connection between lithium, GSK-3-beta, and neurodegenerative disease was strengthened by cell and animal studies [20,21]. It is noteworthy that recent work suggests a connection between BDNF and GSK-3-beta. Specifically it appears that BDNF inhibits GSK-3-beta [22]. It seems possible that lithium will play an analogous role with respect to neurodegenerative disease that it did in the development of the serotonin theory of depression. The ability of lithium to inhibit GSK-3-beta has been used to establish a critical role for GSK-3-beta in neurodegenerative disease. The pharmaceutical industry is searching for patentable or patented GSK-3 inhibitors in hope of uncovering one or more patentable blockbuster drugs against neurodegenerative disease, and a current example is the drug tideglusib [23]. In the meantime the possible effectiveness of lithium against neurodegenerative disease, no matter how promising, has so far remained the subject of preclinical, epidemiological, and retrospective clinical research and occasional reports of off label use [24], but no controlled clinical trials. Possible mechanisms alleviating negative impact of lithium on cognition in bipolar disorder can be connected with the prevention of affective recurrences, improvement of neural plasticity, antiviral action against herpes infection and using the drug in appropriate doses [25]. A recent paper [26] on potential lithium treatment for dementia concluded "In summary, new clinical data suggest lithium has the potential to prevent dementia development. With little evidence of novel therapeutics on the horizon for the millions of people at risk of dementia it would seem negligent not to investigate lithium in dementia prevention more thoroughly."

In animal experiments, lithium was shown to enhance the expression of brain derived neurotrophic factor (BDNF) [27]. Low levels of BDNF are shown to be correlated with both unipolar depression and bipolar disorder [28]. In addition, BDNF has been shown to play an important role in survival of adult and developing central neurons both in culture and in vivo [29]. The role of lithium in increasing expression of BDNF plus the role of BDNF in survival of neurons led to the suggestion that lithium might have a role to play in the treatment of neurodegenerative disease [30]. Also, a beneficial effect of lithium may be related to its anti-inflammatory properties [31]. In addition, lithium elicits opposing effects on endothelial functions representing a differential impact on the endothelium within the narrow therapeutic window. Lithium accumulation or overdose reduces endothelium-dependent but not endothelium-independent vasorelaxation. The differentially modified endothelium-dependent vascular response represents an additional mechanism contributing to therapeutic or adverse effects of lithium [32]. Wei et al. [33] found that lithium treatment normalized the telomerase activity. This was the first report showing telomere dysregulation in hippocampus of a well-defined depression model and restorative effects of lithium treatment. If replicated in other models of mood disorder, the findings will contribute to understanding both the telomere function and the mechanism of lithium action in hippocampus of depressed patients. On the molecular level, there is a significant body of evidence suggesting that prions are implicated in many types of neurodegenerative disease. The original prion hypothesis referred to infectious proteins that triggered or took part in destructive protein oligomerization, but was soon extended to genetic diseases that also involved oligomerization [34,35]. The key transformation postulated in prion disease is that a protein changes its structure from the alpha helical form to a beta sheet form [36], and a reasonable hypothesis is that lithium inhibits the structural change that enables the aggregation of the protein. Finally, Anderson, et al. [37] found that quasi-epigenetics mechanisms of lithium impacting autophagy of aberrant proteins and they suggested that "exploration of "pharmacoepigenetic" mechanisms can expand the breadth of the useful activity of a drug beyond the traditional drug targets such as receptors and enzymes".

Neurology

Lithium plays an important role in embryogenesis and biochemical mechanisms of action are related to the function of many enzymes, hormones, vitamins, and growth factors. Specifically, lithium exerts neurotrophic activity and involved activity in inhibiting the biochemical pathway, e.g GSK-3-beta and Wnt. In a recent study, post-ischemic introduction of lithium salts largely restored the neurological status of the rats [38]. The beneficial effect of lithium can be explained as following reduction of glial inflammation, increase pre- and post-synaptic protein, reducing stress which causes structural and functional damage to the dendrites. In a well-matched cohort of elderly (approximately 70 years old), 5% of those on long-term lithium therapy (continuous for the previous five years) were diagnosed with Alzheimer's disease (AD), while 33% of those not receiving consistent lithium therapy were diagnosed with AD [39]. Bipolar disorder has been reported to be associated with increased risk of dementia [40,41] and the risk may increase with every new affective episodes [42] while lithium, which is the first-line agent for bipolar disorder, may reduce the risk of dementia because long-term lithium treatment significantly reduces tau phosphorylation and amyloid β production, increases synaptic plasticity and facilities long-term potentiation and cell firing, most of which are due to GSK-3-beta inhibition [43]. De-Paula Vde [44] investigated the effect of lithium on cytosolic phospholipase A_2 (PLA_2) activity, a key player on membrane phospholipid turnover which has been found to be reduced in blood and brain tissue of patients with Alzheimer's disease (AD). Long-term lithium treatment increased membrane phospholipid metabolism in neurons and this effect was more prominent at sub-therapeutic concentrations of lithium. Because PLA_2 activities are reported to be reduced in Alzheimer's disease (AD) and bipolar disorder (BD), these findings provide a possible mechanism by which long-term lithium treatment may be useful in the prevention of the disease.

Lithium salts have a well-established role in the treatment of major affective disorders. Epidemiological studies in bipolar patients revealed that continued lithium treatment was associated with reduction of the rate of dementia to the same level as that for general population and the effects were not found in anticonvulsants, antidepressants, or antipsychotics [45,46], suggesting a specific effect of lithium. Neuroimaging studies in humans have demonstrated that chronic use is associated with cortical thickening, higher volume of the hippocampus and amygdala, and neuronal viability in bipolar patients on lithium treatment. Chronic lithium intake is associated with a reduced risk of Alzheimer's disease in subjects with bipolar disorder, while chronic lithium treatment at subtherapeutic doses can reduce cerebral spinal fluid phosphorylated tau protein [47]. Therefore, lithium treatment may yield disease-modifying effects in AD, both by the specific modification of its pathophysiology via inhibition of overactive GSK-3-beta, and by the unspecific provision of neurotrophic and neuroprotective support [43]. Additionally, recent in vivo and in vitro studies indicate that lithium is able to ameliorate ethanol-induced neuroapoptosis, since lithium, as an inhibitor of GSK-3-beta, has been identified as a mediator of ethanol neurotoxicity [48].

A possibly useful adjunct to long-term controlled trials would be an epidemiological approach. Wright [49] comprehensively mapped the incidence and prevalence of Parkinson disease across the United States. The nonrandom distribution implies correlation with some environmental variable, but none of the specific environmental variables considered by the authors showed a compelling correlation with Parkinson incidence or prevalence. Completely independently, Ayotte, et al. [50] mapped the distribution of trace elements, including lithium, in groundwater across the United States. They suggest a correlation between Parkinson disease and lithium in the groundwater —the less lithium the more Parkinson. A rigorous statistical analysis is needed to either confirm or rule out such a correlation. It appears that there may be a correlation between low lithium levels in the well water and high Parkinson, for example on the New England coast, eastern Pennsylvania, southern Mississippi and Louisiana, and the west shore of Lake Michigan. On the other hand, high lithium levels in well water in southern California seem to be correlated with low prevalence of Parkinson there. More rigorous and comprehensive statistical analysis is needed, in which lithium levels in local drinking water and food supplies around the nation are correlated with prevalence of various diseases and other measures of mental and physical health.

Psychiatry

Lithium was shown several decades ago to increase serotonin levels in animal brains [51-55]. Knowledge of this action of lithium, plus the efficacy of lithium in alleviating depression, was a major tool in establishing the serotonin theory of depression [52]. The serotonin theory of depression in turn led to Prozac and the family of selective serotonin reuptake inhibitors (SSRI's)—not only a medical but also a cultural revolution [53]. Lithium has the strongest research evidence for efficacy to augment the primary SSRI, but in the great majority of cases other drugs such as anticonvulsants and newer antidepressants with less research support are prescribed in this role. Valenstein, et al. [54], in a study on prescription practices suggest as one possible reason "…unlike lithium, the newer antidepressants and antipsychotic agents are backed by large advertising budgets and are the subjects of numerous recent articles. Providers may have difficulty ascertaining the level of research evidence for alternative augmentation strategies and may be more influenced by newer than by older studies when making prescribing decisions." Leucht, et al. [55] in a meta-analysis of 13 studies examined whether the augmentation of antipsychotic drugs with lithium salts is more effective than antipsychotic drugs alone, and the y found that more participants who received lithium augmentation had a clinically significant response, however, this effect became non-significant when we excluded participants with schizoaffective disorders. More recently Hayes, et al. [56] examined 5,089 patients with bipolar disorder in lithium (N=1,505), valproate (N=1,173) olanzapine (N=1,366) or quetiapine (N=1,075) as monotherapy. They concluded that lithium is often avoided because of its side effect profile, but alternative treatments may reduce the time to being prescribed more than one drug, with potential additive side effects of these treatments.

Almost 3% of Americans will suffer from at least one bipolar disorder episode in any given year [57]. A smaller number, perhaps 1% (about 3 million people) suffer from recurrent bipolar cycling and should definitely receive treatment. The same study finds that over half of bipolar disorder sufferers are treated with inappropriate medication, most often an antidepressant without an antimania medicine. An array of anticonvulsant drugs have emerged as effective mood stabilizers to either augment or, in some cases where lithium is ineffective, to replace lithium as the primary mood stabilizer in treating bipolar disorder [58]. A recent analysis of the National Comorbidity Survey Replication found that not even one of the 167 black Americans in the survey diagnosed with bipolar disorder received appropriate medication [59]. These statistics add up to the fact that fixing the problem of

inappropriate medication of bipolar disorder is a matter of life or death for millions of people, although the guidelines of all major international psychiatric associations recommend lithium as a first-line therapy for bipolar disease. These include the American Psychiatric Association [60], The World Federation of Societies of Biological Psychiatry [61], the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) [62]. A comprehensive evidence-based review of the incidence of lithium toxicity confirmed that lithium's benefits far outweigh its risks [63] and prompted an editorial in The Lancet [64] that concluded ".. this study provides timely clarification of the toxicity associated with lithium therapy and, on balance, reaffirms its role as a treatment of choice for bipolar disorder."

The risk of suicide is many times higher among those who suffer from depression and bipolar disorder than the general population [65]. But among the subgroup of bipolar patients who are treated with lithium maintenance for several years the suicide rate drops to approximately the same level as the general population [66]. Although lithium is known to prevent suicide in people with mood disorders, it is uncertain whether lithium in drinking water could also help lower the risk in the general population. It is known that in therapeutic doses, which are more than 100 times higher than natural daily intakes, lithium has been proven to be a mood-stabilizer and suicide preventive. Lithium carbonate (Li_2CO_3), lithium sulfate, lithium citrate ($Li_3C_6H_5O_7$) and lithium orotate ($C_5H_3LiN_2O_4$) are in clinical use, lithium bromide and lithium chloride, are out of use since 1940s, and lithium fluoride and lithium iodide, are out of use because of toxicity. The therapeutic measures of plasma lithium levels are between 0.6-1.1 mmol/L, which corresponds to recommended doses of 600-1,200 mg/d lithium carbonate by mouth. According to the arachidonic acid (AA) cascade hypothesis, the brain Arachidonic Acid (AA) cascade is a common target of lithium, as well as other mood stabilizers, and that bipolar symptoms are associated with an upregulated cascade and excess AA signaling via D2-like and NMDA receptors [67]. Recently, Helbich, et al. [68] found some interesting associations investigated the relation between suicide mortality, lithium levels in drinking water, and the altitude above sea level. These new research and methodological approaches contribute to the induction of new avenues in the collaboration between biology, chemistry, psychiatry, geographic information science, and even criminology, by exploring the association between lithium content in drinking water and mental health, and especially suicide mortality, as well as violent or impulsive crime [69].

Some studies have shown an association between low lithium intakes from water supplies and suicide, as well as homicide rate [70]. Schrauzer & Shrestha [71], using data from 27 Texas counties for the period 1978-1987, found that the incidence rates of suicide, homicide, and rape were significantly higher in counties whose drinking water supplies contain little or no lithium than in counties with water lithium levels ranging from 70-170 μg/l. Ohgami, et al. [72] examined lithium levels in tap water in the 18 municipalities of Oita prefecture in Japan, in relation to the suicide standardised mortality ratio in each municipality. They found that lithium levels were significantly and negatively associated with suicide standardised mortality ratio averages for 2002-2006 and suggested that even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population. Similarly, Kapusta, et al. [73] evaluated the association between local lithium levels in drinking water and suicide mortality at district level in Austria. The overall suicide rate as well as the suicide mortality ratio were inversely associated with lithium levels in drinking water and remained significant after sensitivity analyses and adjustment for socioeconomic factors. Recently, Blüml, et al. [74] evaluated the association between lithium levels in the public water supply and county-based suicide rates in 226 Texas counties, with a state-wide sample of 3123 lithium measurements from the public water supply. The findings provided evidence that higher lithium levels in the public drinking water are associated with lower suicide rates. However, Kabacs, et al. [75], measuring lithium levels in tap water in the 47 subdivisions of the East of England and correlating these with the suicide standardized mortality ratio in each subdivision, found no association between lithium in drinking water and suicide rates across the East of England for the period 2006-2008. A recent study found that lithium levels in drinking water were significantly ($\beta = -0.169$, $P = 0.019$) and inversely associated with male but not total or female suicide standardized mortality ratios, in 274 municipalities of Kyushu Island in Japan [76].

We evaluated the association between lithium levels in the public water supply and prefecture-based suicide rates in Greece. Analysis were conducted with respect to lithium levels in 149 samples from 34, out of 52, prefectures of Greece. The average lithium level was 11.10 μg/l (range 0.1 to 121 μg/l). The results indicated a tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water [77]. Extending this study [78], we found a tendency of lower mean number of homicides in the prefectures with high levels of lithium in drinking water (R^2=0.054, $\beta = -0.38$, $p = 0.004$). Considering these results, we suggested that natural lithium level intake may influence impulsiveness, a possible core factor that mediate to the manifestation of both suicidality and aggressiveness. Helbich et al. [69] also concluded in similar suggestions. In addition, based on findings that lithium inhibits both glycogen synthetase kinase-3 isoenzimes, Jiménez, et al. [79], analyzed the potential impact of genetic variants located at the GSK3 α and β genes on impulsivity levels. They found that genetic variability at GSK3β gene was associated with increased impulsivity in bipolar patients. Furthermore, a recent meta-analysis [80] in 48 randomized control trials comparing lithium with placebo or active drugs in long term treatment for mood disorders found that lithium is an effective treatment for reducing the risk of suicide in people with mood disorders, and the authors suggested that impulsivity might be a mechanism mediating the antisuicidal effect. John Cade [81], the Australian psychiatrist credited with discovering the effects of lithium carbonate as a mood stabilizer in the treatment of bipolar disorder, reported the original paper with the title "Lithium salts in the treatment of psychotic excitement". Thus, we can suggest that Cade's concept of excitement may fit better with that concept of impulsiveness [78].

Side effects

Toplan, et al. [82] found that treatment with lithium carbonate in rats may result in liver and kidney tissue abnormalities and oxidative damage. Long-term treatment with lithium may suppress the activation of regenerative processes by reducing the number of Very Small Embryonic Like (VSEL) Stem Cells circulating in peripheral blood [31]. Lithium treatment is associated with a decline in renal function, hypothyroidism, and hypercalcaemia. Women younger than 60 years and people with lithium concentrations higher than median are at greatest risk. Because lithium remains a treatment of choice for bipolar disorder, patients need baseline measures of renal, thyroid, and parathyroid function and regular long-term monitoring [83]. Aiff, et al. [84] retrieved serum lithium and creatinine levels from 4879 patients

examined between 1981 and 2010. From them, 630 adult patients (402 women and 228 men) with normal creatinine levels at the start of lithium treatment. There was a yearly increase in median serum creatinine levels already from the first year of treatment, but only 5% were in the severe or very severe category. Hayes, et al. [56] examined renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder. They found that lithium use is associated with more renal and endocrine adverse events but less weight gain than commonly used alternative mood stabilizers, and they suggested that risks need to be offset with the effectiveness and anti-suicidal benefits of lithium and the potential metabolic side effects of alternative treatment options. Finally, renal dysfunction seems to appear after decades of treatment and to progress slowly and irrespective of lithium continuation [85].

Exposure to lithium via drinking water and other environmental sources may also affect thyroid function, consistent with known side effects of medical treatment with lithium [86]. In addition, thyroid abnormalities occur frequently during lithium treatment, as well as in patients with bipolar disorder regardless of treatment. Lambert et al. [87] compared hypothyroidism risk for lithium versus the anticonvulsants and second-generation antipsychotics in 24,574 patients with bipolar disorder. They examined the stabilizing anticonvulsants lamotrigine, valproate, oxcarbazepine, and carbamazepine, and the antipsychotics aripiprazole, olanzapine, risperidone, and quetiapine. They found thet the risk of hypothyroidism for lithium (8.8%) was 1.39-fold that of the lowest risk therapy, oxcarbazepine (6.3%), while lithium was non-statistically significantly different from quetiapine. In another field, Chouhan, et al. [88] studied the impact of low-dose oral lithium therapy on Radioactive iodine (RAI) uptake and retention parameters in different subgroups of hyperthyroidism patients, and thus explore its potential role in enhancing the therapeutic efficacy of RAI in these groups of patients. The results suggested that a short course of lithium is safe and could be beneficial for hyperthyroid patients considered for RAI therapy as it increased the RAI retention in thyroid, and thus had the potential to increase the effect of RAI therapy. Finally, Harari, et al. [89] found that lithium exposure through drinking water during pregnancy may impair the calcium homeostasis, particularly vitamin D and the results reinforce the need for better control of lithium in drinking water, including bottled water. However, Uguz, et al. [90] found that lithium and mood stabilizers like lamotrigine, can be prescribed without any adverse events in most infants in lactating women.

Dietary intakes

Lithium, as a natural trace element, is washed out by rain from rocks and from the soil, dissolving in ground water and reaching the food chain via drinking water. In some regions, its concentrations may reach up to 5.2 mg/l, corresponding to a natural daily intake of lithium of up to 10 mg/l [69]. The biochemical mechanisms of action of lithium are considered to be connected with the functions of several enzymes, hormones and vitamins, as well as with growth and transforming factors [70]. All seawater contains lithium, with an average content of 194 micrograms/liter [91]. Both tap and bottled drinking water contains some lithium, with widely varying amounts depending on the location; since plants readily take up lithium from the soil can be as high as just one order of magnitude (factor of ten) less than common therapeutic doses, although in most locations natural lithium intake is several orders of magnitude lower [92]. Natural lithium contents of tap water range up to 1 mg or more of dissolved lithium per liter per day (1 L of water with 1 mg/L lithium per day corresponds to 6.9 mg lithium carbonate per day), depending on the geographic origin of the drinking water. Under the assumption that individuals drink not more than 2 L water per day (corresponding to a daily dose of 13.8 mg lithium carbonate by mouth), such an intake would result in a daily dose of approximately 1% of a therapeutic lithium dose for bipolar disorders [93].

Based on experiments in which experimental animals are lithium-deprived and suffer a decline in fertility, lithium is probably an essential trace element in the diet [94,95]. Schöpfer & Schrauzer [96], found in more than half of two samples of 100 persons of both genders, Li levels were below the instrumental detection limit or below or the lower limit of the laboratory reference ranges. Among other elements, the concentrations namely of cobalt were also frequently below the laboratory reference range, suggesting that low circulating levels of vitamin B_{12} were common in this study population. The authors also suggested that as vitamin B_{12} deficiency is associated with depression and other psychiatric conditions, and there is evidence of interactions between Li and vitamin B_{12}, Li deficiency as well as suboptimal vitamin B_{12} status must be considered as potential suicide risk factors. In view of its established positive effects on mood and brain function, an adequate supply of selenium (Se) is important as well. A clinical pilot study using lithia water (natural spring from the Rocky Mountains wish contains trace amounts [0.68 mg/litre] of lithium) from British Columbia was underway at the University of British Columbia, but was terminated. It was a study on the effects of Lithia water on BDNF and oxidative stress markers in healthy male participants.

Schrauzer [70] suggests that the available experimental evidence appears to be sufficient to accept lithium as essential; a provisional RDA for a 70 kg adult of 1,000 microg/day is suggested. Lithium is found in variable amounts in grains and vegetables, while drinking water provides significant amounts of that element. Human dietary lithium intakes vary over a wide range and depend on location and the type of foods consumed. The evidence indicates an intake of 1,000 microg/day for an adult of 70 kgr. 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 behavioural abnormalities factors [70]. 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. For example, a significant direct association was observed between the hair lithium and cobalt concentrations, which suggests a role of lithium in the transport and distribution of vitamin B_{12} [97]. Lithium appears to play an especially important role during the early foetal development as evidenced by the high lithium contents of the embryo during the early gestational period. A recent study showed that the exposure to lithium may exert anti-aging capabilities and unambiguously decreases mortality in evolutionary distinct species [98].

Current findings and suggestions

A total of 682 samples of drinking water were collected during the year 2014 from the different sites of the city of Athens. Lithium levels were analyzed by inductively coupled plasma mass spectrometry (ICP-MS). We found (unpublished data) that the average lithium level was 1.8 μg/l (range 12.0-0.0). It should be noted that the average lithium level in our previous studies [77,78], as evidenced by the raw values for

the 34, out of 54, prefectures of Greece, was 11.10 μg/l (SD=21.16), while the analysis of 21 samples of different kind of bottled waters showed that their mean lithium levels was 6.21 μg/l (SD=16.35). This was the first time we investigated lithium levels of Athens, the capital of Greece, with more than 3 million residents. Athens uses an urban water supply system originated from the Marathon Lake. We suggest that the mean lithium level 1.8 μg/l is too low, in comparison with the lithium levels of the rest regions in Greece, as well as with other findings from other European countries, USA, and Japan. On the other hand, since 2008, Greece entered a deep and longstanding financial crisis, which has raised concerns about severe public health consequences, economic downturns historically being associated with increases in mortality. In 2012, there were 116 670 deaths in Greece, the highest number since 1949. The 2011-12 increased mortality in people older than 55 years (about 2200 excess deaths) constitutes one more short-term consequence of austerity on mortality in Greece [99]. We suggest that increasing lithium levels of drinking water as a public health measure, through the urban water supply system, could potentially increase wellness and health markers in Athens citizens.

Concha, et al. [92] found in Andean villages in Argentina, that besides confirmation of elevated arsenic concentrations in the drinking water (up to 210 μg/L), remarkably high concentrations of lithium (highest 1000 μg/L), cesium (320 μg/L), rubidium (47 μg/L), and boron (5950 μg/L). They suggested that there is an apparent risk of toxic effects of long-term exposure to several of the elements, and studies on associations with adverse human health effects are warranted, particularly considering the combined, life-long exposure. Lithium occurs in barely trace amounts in groundwater with few major exceptions. One of these is the Northern area of Chile where all potable water and many of the food stuffs contain high levels of lithium; between 100 and 10,000 times higher than most rivers in North America [100]. Inevitably, the local population has been exposed to these levels in their drinking water for as long as the region has been populated. Figueroa et al (2014) suggested that this population would provide important insights into the potential neuroprotective effects of lithium or even help to assess the risks from high dose environmental exposure. Neuroradiological studies of the historically lithium loaded populations in the north of Chile should provide unique insights into the role of lithium particularly as a putative hippocampal neurogenic agent [101].

Andean villages have elevated lithium concentrations in the drinking water, highest 1000 μg/L [92,100,102]. This was the land of Incan Empire, the largest empire in pre-Columbian America, with the known Inca civilization, people and culture. Different health maps from World Health Organization and Neuroscience Communities, show that the countries around the Andes, like Venezuela, Colombia, Ecuador, Peru, Bolivia, and north Chile and Argentina, seem to have a more "healthy" profile with high life expectancy and low levels of neurodegenerative diseases. The maps for the "Healthy life expectancy", as well as the "Life expectancy at birth", show the more favorite in Chile, Canada, some European and Australian countries. Perou is a country with the lowest "suicide rates" (per 100.000 population) in the world. Interactive Charts and Maps that Rank Alzheimers/dementia as a Cause of Death show that Peru, Colombia, Paraguay, are some of the few countries with the lowest rates of Alzheimer Disease in the World. Finally, the global burden of Parkinson's disease, measured in disability-adjusted life years (per 100,000 inhabitants) show that South America is the continent with the lowest incidence of Parkinson's disease.

In addition to being ubiquitous in food and drinking water and being strongly advised for bipolar disorder therapy by national and international professional psychiatric associations, it appears that sub therapeutic levels of lithium may have a beneficial effect on mood disorders. Multiple independent studies based on populations from different parts of the world show that lithium concentration in drinking water is inversely correlated with per capita rate of suicide [69,72,74,76,77,103]. Research results have supported also the potential of lithium for treatment of neurodegenerative disease [21], while Zarse, et al. [98] found an inverse correlation between lithium concentration in drinking water and age adjusted mortality from all causes. The neuroprotective effect has led some to suggest that lithium may provide protection against neurodegenerative disease [43,104]. Perhaps it is significant in interpreting these results to note that numerous studies have now confirmed that lithium and other mood stabilizers have a neuroprotective effect, inhibiting apoptosis of neurons. An editorial suggested the addition of lithium to drinking water as a public health measure [105]. By contrast, some environmental toxicologists seem to view lithium in ground water solely as a pollutant, but this seems to be a minority viewpoint [106]. Grof & Muller-Oerlinghausen [107] reviewed decades of research and clinical experience on the effectiveness of lithium as a treatment for bipolar disorders, and suggested an answer to this question. They pondered the apparent paradox that "despite its well-proven efficacy, the use of lithium has to some extent gone into disrepute, particularly in North America" and suggest as a possible answer "the push from pharmaceutical companies wanting to sell their new and more expensive products."

Many findings pose the question of whether the prospect of adding lithium to drinking water is realistic, weighing the benefits and potential risks [97,98,108,109]. Terao, et al. [110] suggested that even very low but sustained lithium intake can prevent suicide in the general population, and that if this is the case, increasing lithium levels of drinking water could potentially reduce the risk of suicide, and justify administering lithium to tap water. Having in mind all the above mentioned evidence for possible long-lasting neurobiological effects of low-dose lithium, regular lithium supplementation would be recommended to take place under a monitoring by a physician [93]. Lithium, far from a contaminant in the environment, is an essential nutrient and there should be a concerted attempt to establish optimum levels for lithium intake by multiple criteria (Schrauzer & Gerhard). What we know about the effects of lithium is only a small fraction of what there is to know, but the bulk of evidence suggests that the optimum level of lithium intake is more than most people get from food and drinking water. From the origin of life, lithium was in the environment, interacting with all of the biological molecules that life invented. Biological evolution had to accommodate to the presence of lithium to survive. In the competition for survival, those entities that best minimized lithium toxicity and maximized the benefits of lithium action had an edge in the competition to survive and reproduce.

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