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Is lithium a universal inhibitor? Evidence arising from clinical neuroscience and oncology

Orestis Giotakos

Abstract

Lithium has been in the environment from the origin of life, interacting with almost all of the biological molecules that life invented. Lithium affects many components of intracellular signalling pathways, inhibiting more than ten cellular targets and displacing magnesium ions. Lithium modulates cell function via inhibitory effects on adenosine triphosphatase activity, cyclic adenosine monophosphate, and intracellular enzymes. Lithium is also an important inhibitor of the enzyme glycogen synthase kinase-3. Recent epidemiological findings strongly support the benefits of lithium use in both neuropsychiatry and oncology. Lithium is the first line drug used in the management of bipolar disorders, while natural lithium level intake may influence impulsiveness, a possible core factor mediating the manifestation of both suicidality and aggressiveness. Lithium is also useful in a broad range of diseases: neurological, such as epilepsy, Huntington chorea, Parkinson diseases, and headaches; endocrinological, such as hyperthyreosis, diabetes mellitus, and the inappropriate secretion of the antidiuretic hormone; haematological, such as neutropenia, and thrombocytopenia; and alergological, such as asthma. Moreover, lithium has been tested with promising results in oncology. Lithium reverts the apoptosis models by interfering receptor function, while a long-term lithium treatment has been shown to increase the expression of antiapoptotic genes. Lithium chloride has been also found to hold anticancer properties, while combination treatments with lithium can improve the efficacy of chemotherapeutic agents in apoptosis deficient cancer cells. Lithium can modulate autophagy in esophageal and colorectal cancer cells. A large retrospective study showed that lithium-exposed individuals were less likely to suffer melanoma-associated mortality and recent epidemiological findings showed a reduced overall cancer risk in bipolar patients treated with lithium. What we know about the effects of lithium seems to be a small fraction of what there is to know, but it seems that lithium has been central to survival in the process of biological evolution. Lithium demonstrates a broad range of inhibitory effects from the cell to the behavioral level. We may suggest that lithium operates like a natural universal inhibitor, helping the organisms to readjust balances and to survive, through the development of compensatory and readapting mechanisms.

Key words: *Lithium, bipolar disorder, inhibition, apoptosis, cancer, anticancer, oncology, neuropsychiatry*

Corresponding author: Orestis Giotakos, Psychiatrist (MD, MSc, PhD), Founder, The non-profit organization "obrela", 112 Imittou , 11634 Athens, Greece, www.obrela.gr, info@obrela.gr

Introduction

Lithium (from Greek: *lithos*: stone), with the symbol *Li,* is a chemical element with an atomic number of 3. 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 lithium chemistry is not common, since atoms are highly polarized, very small, and have a high charge density. The lithium biochemical properties are similar to those of magnesium, and it influences magnesium-dependent processes **[2].** As a natural trace element, lithium is washed out by rain from rocks and soil, reaching the food chain via drinking water. The available evidence indicates that the recommended dietary allowance for a 70 kg adult Is 1,000 microg/day **[3].** An average intake would result in a daily dose of approximately 1% of a therapeutic lithium dose for bipolar disorders **[4].** Lithium plays an important role in embryogenesis and biochemical mechanisms of action are related to the function of many vitamins, hormones, enzymes, and growth factors **[5].** 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 found that low doses of lithium demonstrate neuroprotective effects **[6]**, and improvements in mood and cognitive function **[7].**

Lithium is an integral drug used in the prophylaxis of bipolar disorders and the treatment of acute mania **[8].** Many other beneficial effects of lithium have been reported in neuropsychiatry, such as anti-suicidal and anti-aggressive properties, improvement of hyperactivity in schizophrenia, and behaviour benefits in intellectually disabled patients **[9].** The initial studies of molecular targets for lithium action were based on the assumption that this simple cation can interfere with transporting systems for sodium and potassium in the plasma membranes of neurons and alter the propagation of electrical signals. Some studies indicate that the lithium inhibition of the countertransport mechanism may be clinically significant and relevant to the lithium therapeutic action **[10].** Lithium has been found useful in a broad range of diseases from neurological (epilepsy, Huntington chorea, Parkinson diseases, and headaches) endocrinological (hyperthyreosis, diabetes mellitus, and the inappropriate secretion of the antidiuretic hormone), haematological (neutropenia, and trombocytopenia) to the alergological (asthma), **[11, 12].** Furthermore, lithium has now been tested with promising results in oncology (thyroid carcinoma) **[13],** infectious diseases (AIDS related dementia) **[14],** and dermatology, in seborrhoeic dermatitis, with topically application **[15].**

The signaling pathways Inhibition

Lithium affects many components of intracellular signalling pathways, like inhibiting of more than ten cellular targets and displacing magnesium ions. Lithium affects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase [**16].** Plenge (1985) **[17]** proposed the theory that lithium inhibits enzymes which have essential cofactor cations, such as Ca2+, Mg2+, Na+, K+, and Zn2+ by displacement of these cations from the enzyme. Lithium displaces magnesium ions, leading to the inability of the resulting very stable complex enzyme-phosphate-lithium to hydrolyse a further substrate molecule. Lithium competes for a magnesium binding site in glycogen synthase kinase-3, inositol polyphosphate 1-phosphatase, fructose 1,6-bisphosphatase, bisphosphate nucleotidase, and phosphoglucomutase **[18].** However, the targets inhibited by lithium at therapeutically relevant concentrations (0.6-1 mM) are inositol monophosphatase and glycogen synthase kinase 3ß. Thiruvengadam (2001) **[19]** proposed the understanding of the therapeutic effects of lithium and sodium valproate in bipolar disorder, modifying the known Goldman–Hodgkin–Katz equation in order to include a fourth ion, such as a lithium ion or a sodium ion. The author suggested that the resting membrane potential in bipolar patients may be hyperpolarized and the lithium ion depolarizes the resting membrane potential back to the normal state.

Lithium inhibits many of structurally similar magnesium–dependent phosphomonoesterases at levels within the therapeutically relevant range of concentrations, 0,6–1,2 mM. Most of the proposed mechanisms for lithium cellular action indicate an inhibitory effect on parts of various signaling

pathways, such as cyclic GMP and cyclic AMP formation **[20].** Lithium shows also an inhibitory effect on the G proteins, a ubiquitous family of proteins that serve the critical role of transducers of information across the plasma membrane, by coupling receptors to various neurotransmitters. By inhibiting inositol monophosphatase, lithium obstructs the enzymatic degradation of inositol trisphosphate (IP3), resulting in reduced availability of the second messengers IP3 and DAG, the derivatives of the PIP cycle. Some studies identified the upstream inositol polyphosphatase as an additional target for lithium **[21].** Molecular genetic studies in model systems suggested Ins (1, 4, 5) P3 as a clinically relevant target of lithium **[22].** Another possible therapeutic effect of lithium is to attenuate brain phospholipase A2 (PLA2) activity. Lithium therapy seems to decreases the turnover of arachidonicacid (AA) in several brain phospholipids, which is correlated with a significantly decrease of PLA2 activity **[23, 24].**

The thyroid system inhibition

Lithium treatment seems to contribute to the development of hypothyroidism, goitre, hyperthyroidism and autoimmune thyroiditis **[25, 26].** A meta-analysis of the potential toxicity of long-term use of lithium showed that lithium causes a five-fold increased risk of hypothyroidism **[27].** Goiter, due to increased thyrotropin (TSH), after inhibition of thyroid hormone release, occurs at various reported incidence rates and lithium-induced goitre reveals a prevalence of 0 to 60% **[28].** When more sensitive ultrasonographic scans are used to detect increases in thyroid volumes, prevalence is higher (30–60%) **[29]**. Although thyroid hormone basal levels are not usually high, lithium therapy is associated with exaggerated response of both TSH and prolactin to TRH in 50%-100% of patients. Clinical or subclinical hypothyroidism due to lithium is associated with anti-thyroid peroxidase (TPO) antibodies, although it may occur in their absence. Immunogenetic background and Iodine exposure may contribute to the occurrence of goiter and hypothyroidism during long-term lithium therapy **[30].**

Lithium affects thyroid functioning through multiple mechanisms. Lithium inhibits thyroidal iodine uptake and iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion. The lithium induced inhibition of the synthesis and release of thyroid hormones may result in an increase of TSH level, leading to enlargement of the gland and the goiter formation. At the thyroid cellular level, lithium decreases thyroid hormone synthesis and release. At the peripheral level, lithium decreases deiodination of tetraiodothyronine (T4) or thyroxine, by decreasing the activity of type I 5′ de-iodinase enzyme. Other mechanisms that explain the proliferation of thyrocytes in patients treated with lithium is the activation of tyrosine kinase by lithium ion, and lithium effects on intracellular signaling related with Wnt/ beta-catenin and adenylate cyclase **[31].** Lithium also increases the propensity to thyroid autoimmunity in vulnerable individuals, through the increased activity of B lymphocytes and the reduced ratio of circulating suppressor to cytotoxic T cells **[32].** In parallel with these anti-thyroid effects, lithium influences cell function via its inhibitory action on cyclic adenosine monophosphate (cAMP), adenosine triphosphatase (ATPase) activity, and intracellular enzymes. The known inhibitory effect of lithium on inositol phospholipid metabolism may affect signal transduction and may account for part of the effect in bipolar disorder. Lithium also alters the in vitro response of cultured cells to thyrotropin-releasing hormone (TRH) and can stimulate DNA synthesis **[33].**

However, the above described "disordered" thyroid-hypothalamic-pituitary axis seems to be temporary in most lithium treated patients, which suggests that the axis is adjusting in a new «state» during lithium therapy **[34].** Possibly, the lithium induced 'central hypothyroidism' activates a secondary action of the HPT axis, in order to re-activate and re-adapt the thyroid hormone availability and effect. This compensatory process may results to the correction of a possible peripheral resistance to thyroid hormones, as well as to the correction of an isolated CNS hypothyroidism. We may suggest that the compensatory mechanisms which operate to the final correction of the hypothyroidism, may represent a therapeutic process of lithium therapy in bipolar disorder, acting through the thyroid system resetting **[35].**

The GSK-3 inhibition

An important line of evidence has been connected with the discovery of the universal role of the enzyme glycogen synthase kinase-3 (GSK-3). Lithium has been found as the important inhibitor of GSK-3 **[36]** and activator of the Wnt signalling system **[37],** although this lithium effect occurs at high concentrations and may be related with a toxic effect **[38].** GSK-3 inhibition has been proposed as a therapeutic mechanism of action. Inositol is a metabolite that serves as a precursor for inositol phosphates and inositol lipids. Inhibition of inositol synthesis results in the inactivation of GSK-3α, which suggests a unifying hypothesis for the mechanism of action of mood-stabilizing drugs and that inositol synthesis and GSK 3α activity are intrinsically related. Ye & Greenberg (2015) **[39]** reported that inhibition of the rate-limiting enzyme of inositol synthesis leads to the inactivation of glycogen synthase kinase (GSK) 3α by increasing inhibitory phosphorylation of this kinase. Glycogen synthase kinase-3 (GSK3) affects over 100 known substrates, with many regulating mechanisms related to substrate priming, cellular trafficking, post-translational modifications, protein complexes, receptors and receptor-coupled signal transduction events. In addition, GSK3 is involved in many prevalent disorders, including inflammatory diseases, cancer, psychiatric and neurological diseases, and others **[40].**

The "GSK3 hypothesis of Alzheimer Disease" **[41]** integrates and extends the "amyloid cascade hypothesis" of Alzheimer Disease. This hypothesis strongly implicates GSK3 inhibitors as a novel treatment strategy for Alzheimer Disease, incorporating the known key molecular events and links these with outcomes such as memory impairment and inflammation. Phospholipase A2 (Pla2) is required for memory retrieval, while cognitive decline and memory deficits were shown to be reduced in animal models after lithium treatment, which suggests possible links between Pla2, lithium and memory. Mury et al (2016) **[42],** pointed to a significant perdurability of long-term memory after the chronic lithium treatment, which correlated with increased transcriptional and enzymatic activities of certain members of the Pla2 family (iPla2 and sPla2). The findings reinforced the possible use of low doses of lithium for the treatment of neurodegenerative conditions such as the Alzheimer's disease. On the other hand, not only is there no evidence about the increased prevalence of cancer in patients undergoing long-term lithium monotherapy **[43],** but lithium increases survival rates of patients with adenocarcinomas **[44].** Manji et al (2000) **[45]** demonstrated an increase of the cytoprotective factor Bcl-2 in the hippocampus, frontal cortex, and striatum in the brains of patients with bipolar disorder, after chronic lithium treatment. The mechanism of lithium action is not known, but its neuroprotective effect may be relevant in the long-term treatment of neurodegenerative disorders **[38].**

The apoptosis inhibition

The programmed cell death named *apoptosis*, is an evolutionarily conserved form of cell death and an important factor for tissue homeostasis. The glutamate insult induces excitotoxicity, cell death and apoptosis, while this is triggered by an exaggerated and prolonged rise in intracellular Ca2+. Neurodegeneration after a cerebral trauma is associated with glutamate efflux and overstimulating of glutamate receptors. On the other hand, growth factors and neurotrophins have been shown to promote cell survival and inhibit apoptosis, a process mediated through the phosphatidylinositol 3-kinase/Akt cascade. This signaling pathway is usually activated by insulin factors, like the insulin-like growth factor 1 (IGF-1) and growth factors, like the platelet-derived growth factor (PDGF). Apoptosis may induced also in a low potassium-containing culture, a process mediated primarily by activation of NMDA receptors. Llithium can revert these apoptosis models by interfering receptor function, while a long-term lithium treatment has been shown to increase the expression of the antiapoptotic gene bcl-2 **[46].**

Inactivation or inhibition of the GSK-3 has revealed anti-apoptotic effects. The GSK-3 inhibitors may downregulate TGF-BIp expression by blocking TGF-β signaling **[47].** A number of studies demonstrated that lithium inhibits GSK-3 directly **[48-53],** or indirectly, by triggering the phosphorylation of GSK-3 at ser21/ser9 **[54-56].** Research suggests that lithium elicits its neuroprotective effects by inhibiting GSK-3 **[57].**

Lithium can block indirectly the GSK-3 activity through the phosphorylation of GSK-3α at ser21 and of GSK-3β at ser9 by multiple mechanisms, including the activation of PKA, phosphatidylinositol 3-kinase (PI3-K)-dependent AKT, and protein kinase C (PKC) **[58-59].** Choi et al (2011) **[60],** demonstrated also that lithium treatment reduces TGFBIp expression in a dose-dependent manner in corneal fibroblasts through the inactivation of GSK-3. Exposure of cells to glutamate induced a rapid and reversible loss of Akt-1 phosphorylation and kinase activity. Long-term lithium pretreatment suppressed glutamate-induced loss of Akt-1 activity and accelerated its recovery toward the control levels. Lithium also increased the phosphorylation of glycogen synthase kinase-3 (GSK-3), a downstream physiological target of Akt. Thus, modulation of Akt- 1 activity appears to play a key role in the mechanism of glutamate excitotoxicity and lithium neuroprotection **[61].** The PI 3-K/Akt signaling cascade has been linked to the pathogenesis of certain forms of leukemia, while lithium treatment is known to cause leukocytosis and has been used to suppress leukopenia in patients undergoing radiotherapy or chemotherapy **[61].**

Ceramide has been known as an apoptotic factor in a variety of cell types, through inhibition of the antiapoptotic kinase Akt, an enzyme that phosphorylates and inhibits GSK-3. Lithium could oppose the action of ceramide on GSK-3, as it has been shown to inhibit directly this enzyme **[62].** In another research area, glomerular renal dysfunction occurs after an average of twenty years of continuous lithium treatment, and the severity is related to the total lithium load as measured by dose and duration. Radiologically visible lithium-related microcysts are usually 1-2 mm. Khan & El-Mallakh (2015) **[63],** proposed that the mechanism of microcyst formation is related to the antiapoptotic effect of lithium. All the data mentioned above indicate that lithium may act as a neuroprotective drug whose action on GSK-3, either direct or mediated through the phosphatidylinositol-3-kinase pathway, by a yet unknown mechanism, may explain the broad range of apoptotic insults against which it is effective.

The metastasis inhibition

In 1981, Lyman et al **[64]** studied patients with small cell lung cancer who received radiation therapy, chemotherapy, with or without lithium. They found that patients who received lithium (900 mg per day) experienced significantly less mid-cycle leukocyte and neutrophil count depression, spent fewer days with leukopenia and neutropenia than control patients regardless of age or extent of disease, spent fewer days hospitalized and fewer days with fever in the presence of severe neutropenia than control patients. Although anti-angiogenic agents have been used for treating cancer, the overall survival in patients with advanced cancer has not been improved substantially, possibly because cancer metastasis occurs preferentially via lymphatic rather than hematogenous spread. There is an unmet need to develop therapies to block lymphangiogenesis as well as angiogenesis, in order to efficiently block tumor growth and metastasis. Saghiri et al (2016) **[65]** reported that the elements Li, Ti, Hg, Va, Nb, Ce, As, and Pb can promote and/or inhibit angiogenesis through different mechanisms, while lithium affects vasculogenesis but not angiogenesis. In 2016, Maeng et al **[47]** reported the *in vitro* and *in vivo* activities of lithium in inhibiting tumor lymphangiogenesis, TGFBIp expression, and metastasis. They found that lithium reduced the expression of TGFBIp in SW620 colon cancer cells via GSK3β inactivation and inhibited lymphatic endothelial cell migration induced by TGFBIp. Furthermore, lithium activity against lymphangiogenesis and angiogenesis, had no effect on the growth of a primary colon cancer tumor xenograft, and strongly inhibited its metastasis to the lungs, liver, and lymph nodes by blocking lymphangiogenesis in primary tumors.

Asgari et al (2017) **[66]** examined the association between lithium use and melanoma risk, conducting a retrospective cohort study on 2,213,848 adult white Kaiser Permanente Northern California members for the period 1997-2012. Melanoma incidence per 100,000 person-years among lithium-exposed individuals was 67.4, compared to 92.5 in unexposed individuals, while no lithium-exposed individuals presented with advanced-stage melanoma. Among melanoma cases, lithium-exposed individuals were less likely to suf-

fer melanoma-associated mortality. The authors found that lithium treated patients (n=11,317) had reduced melanoma risk and associated mortality and they concluded that lithium may reduce melanoma risk and associated mortality. Wang et al (2017) **[67],** found that lithium can suppress proliferation and induces apoptosis in pancreatic cancer cells, while lithium and ESI-09 synergistically inhibit pancreatic cancer cell growth and survival. The authors suggested the lithium's ability to suppress cAMP/protein kinase A signaling as a novel mechanism for the synergistic action of lithium and ESI-09, in addition to the known inhibitory effect of lithium toward GSK3β.

The cancer cell inhibition

The supratherapeutic doses of lithium chloride (LiCl) has been shown to demonstrate anticancer properties. Novetsky et al (2013) **[68]** suggested that inhibition of glycogen synthase kinase 3β and lithium is a potential therapy for ovarian cancer. The authors pointed that the combination treatment with LiCl and cytotoxic agents can reduce ovarian cancer cell metabolism but does not appear to affect cellular proliferation. Erguven et al (2016) **[69],** investigated the effect of different concentrations of LiCl on prostate cancer stem cells, after incubating of human prostate stem cells and non-stem cells, with low and high concentrations of LiCl for 72 hours. They found that cell stimulated with low concentrations had low apoptotic indices, high proliferation, high MK levels and more healthy ultrastructure, while opposite results were obtained at high concentrations. Li et al (2015) **[70]**, reported that lithium chloride promotes apoptosis in human leukemia NB4 cells by inhibiting glycogen synthase kinase-3 beta. Moreover, in a dose-dependent manner, LiCl significantly increased the level of Ser9-phosphorylated glycogen synthase kinase 3β (p-GSK-3β), and decreased the level of Akt1 protein.

O'Donovan et al (2015) **[71],** reported that lithium modulates autophagy in esophageal and colorectal cancer cells and increases the efficacy of therapeutic agents. Mutations of the *PTEN* gene, that encodes the phosphatase and tensin homolog (PTEN) protein, are a step in the development of many cancers. Recent findings indicate lithium and PTEN as potential candidates for the identification of new therapeutic approaches for colorectal cancer treatment. de Araujo et al (2016) **[72],** reported that PTEN overexpression cooperates with lithium, increasing cell death and reducing malignancy in colorectal cancer cells. It should be noted that the role that lithium plays in cancer is controversial, since lithium can inhibit or activate survival signaling pathways, depending on the cell type. In this recent study, de Araujo et al (2016) **[72]** investigated the mechanisms by which lithium modulates the progression of the colorectal cancer and the role of the survival signaling pathways PI3K/Akt and PTEN. Lithium was found to decrease the proliferative potential of colorectal cancer cells and increased apoptosis, which was accompanied by decreasing proteins levels of Akt and PTEN.

Lithium inhibits glycogen synthase kinase (GSK)-3, which activates NFAT1/FasL signaling, while temozolomide inhibits GSK-3 and activates Fas in tumour protein wild-type (TP53wt) glioma cells. Temozolomide, in combination with low-dose lithium, induces TP53wt glioma cell death, via NFAT1/FasL signaling, and this may represent a therapeutic strategy for the treatment of TP53wt glioma **[73].** Neurocognitive impairment is an important issue in patients with cancer, due to the direct or indirect involvement of the nervous system or due to the chemotherapy-related complications. Neuroprotection is a realistic goal in preventing these neurocognitive sequelae and lithium seems to have a neuroprotective effect in such patients **[74].** Due to apoptotic effects of the psychotropic drugs on immune and neural cells, opioid abusers are more likely to be infected. Sahebgharani et al (2008) **[75],** had been found that lithium chloride protects PC12 pheochromocytoma cell line (as a model of neural cells) from morphine-induced apoptosis. Activation of glycogen synthase kinase 3beta (GSK3beta) is thought to promote tumor growth and neuroendocrine peptide secretion, while inhibition of this signaling pathway with lithium, could be a potential therapeutic strategy to control tumor growth and hormone production. In the Kappes et al (2007) **[76]** study, pheochromocytoma PC-12 cells were treated with varying concentrations of lithium chloride, and the levels of active and inactive GSK3beta and NE peptides

chromogranin A (CgA) and Mash1 were determined. The authors suggested that GSK3beta inhibition may be a novel strategy to treat catecholamine-producing neoplasms, like pheochromocytoma.

The regeneration of the muscle fibers of experimental hepatocarcinoma-29 transplanted into the hip in CBA mice was tested, after treatment with nanosized lithium carbonate particles on muscle tissue. The regeneration of the muscle fibers was found to be associated with a significant increase in activation of fibroblasts, number of microvessels, and recovery of the organ structure **[77].** Oxidant-antioxidant status in tumor tissue of male-mice CBA at spontaneous course of hepatocarcinoma-29 and after repeated injections of lithium carbonate nanosized particles was evaluated by Konenkov et al (2015) **[78].** The authors investigated the changes of lipid peroxidation products level reacted with 2-thiobarbituric acid, as indicator of oxidative stress and the activity of superoxide dismutase and catalase enzymes, as indicators of antioxidant defense. They concluded that lithium carbonate nanosized particles supports the balance between the oxidant and antioxidants and helps to limit the progression of precancerous condition toward malignancy **[78].**

Inhibition of impulsive behavior

Lithium, a naturally occurring element, has a wide use in psychiatric treatment. Inositol cycle has been suggested as a common action substrate of the bipolar medications lithium, valproate and carbamazepine. Berridge's (1989) **[20]**, with the 'inositol depletion hypothesis' suggested that the lithium induced inhibition of inositol monophosphatase may lead to Ins1P accumulation and inositol depletion.

Regeneration of phosphatidylinositol 4,5-bisphosphate requires recycling of inositol from Ins1P, and lithium seems to dampen signaling, using a G-protein-coupled receptor linked to phospholipase C **[79].** Moreover, lithium's antidepressant action may be linked with reduced phosphoinositide cycle-coupled 5-HT_2 receptor function **[80].** Lithium also reduces 5-HT_2 receptor function in mouse as demonstrated by a 5-HT_2 agonist-evoked head-twitch response **[81].** This effect is mediated at the prefrontal cortex **[82],** where it is believed to be the target of lithium in the treatment of bipolar disorder **[83].**

Based on the findings that lithium inhibits both (α and β) glycogen synthetase kinase-3 isoenzymes, Jiménez et al (2014) **[84],** analyzed the possible association of the genetic variants located at the GSK3 α and β genes on impulsivity levels in patients with bipolar disorder. They found that genetic variability at GSK3β gene was associated with increased impulsivity levels in these patients. Evidence indicates that lithium, the most effective mood-stabilizers in bipolar patient, decreases impulsivity levels not only in bipolar patients, but also in other impulse control disorders **[85-89].** Since GSK-3β, a common target for both lithium and valproate, plays a critical role in the central nervous system, by regulating various cytoskeletal processes and long-term nuclear events, its inhibition could be the subject of future research **[45].** Although impulsivity has been associated with serotonin and dopamine dysregulation, some authors suggest that lithium could reduce impulsivity levels through the regulation of the aforementioned neurotransmitter systems **[90].** The inhibition of GSK3 has been suggested to play a key role of the therapeutic action of most of the pharmacological agents used to treat mood disorders **[91].** Lithium inhibits the glycogen synthase kinase-3 (GSK3) β isoenzyme, which in turn act as a mediator of serotonergic function **[92].** The above mechanisms may be also related to the lithium superior antisuicidal effects, in relation to other mood stabilizers **[93-94].**

A recent meta-analysis **[95]** in 48 randomized control trials, which compared lithium with active drugs or placebo for the treatment for mood disorders, has found that lithium is the more effective treatment for reducing the risk of suicide in people with mood disorders. Moreover, the authors suggested that *impulsivity* might be the mechanism that mediates this antisuicidal effect. John Cade (1949) **[96],** the Australian psychiatrist who discovered the lithium carbonate effects in mood stabilizing during the treatment of bipolar disorder, had published the original paper with the title "Lithium salts in the treatment of psychotic excitement". On the other hand, lithium may increase the volume of the prefrontal cortex and

the anterior cingulate gyrus **[97],** which indicates that lithium may at least partially exert its antisuicidal effect *via* reinforcing "top-down brakes" of impulsive action. Moreover, since lithium has been shown to increase the volume and function of the limbic system, such as hippocampus **[98],** we can suggest that lithium antisuicidal effects may consist of both reinforcing "top-down brakes" and decreasing "bottom-up drive."

Some ecological studies have shown an association between low lithium intakes from water supplies and suicide, as well as homicide rate. Schrauzer & Shrestha (1990) **[99],** 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 (2009) **[100]** 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, Blüml et al (2013) **[101]** 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 (2011) **[102]** , measuring lithium levels in tap water in the 47 subdivisions of the East of England and correlating these with the suicide standardised 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 showed that lithium levels in drinking water were significantly and inversely associated with male but not total or female suicide standardized mortality ratios, in 274 municipalities of Kyushu Island in Japan **[103].** Another recent research by Liaugaudaite et al (2017) showed also that the higher levels of lithium in public drinking water systems from 9 cities of Lithuania were associated with lower suicide rates in men **[104].**

Following the above studies which investigated the relation between low lithium intakes from water supplies and suicide, we evaluated the association between lithium levels in the public water supply and prefecture-based suicide rates in Greece. Analysis was 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 **[105].** Extending this study, we found a tendency of lower mean number of homicides in the prefectures with high levels of lithium in drinking water **[106].** 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, or even criminality. In summary, several studies had shown that low-dose lithium, such as lithium intakes from water supplies, could have anti-manic and anti-suicidal effects, or even anti-dementia effects, although, anti-psychotic or anti-cancer effects are yet to be determined. Further studies would need to determine those levels that are required to maintain mental health **[107]** or whether a "lithium deficiency state" may precipitate the above situations **[108].**

Epilogue - Is lithium a universal inhibitor?

Many lithium mechanisms are responsible for its therapeutic effect, which results in supporting neural plasticity and neuroprotection. Lithium modulates neural plasticity at multiple levels and enzymes, including glycogen synthase kinase-3β, cyclic AMP-dependent kinase, and protein kinase C. Lithium modulates neurotransmitters and readjusts balances between excitatory and inhibitory actions. Lithium also modulates signaling activities, through the regulation of second messengers, the transcription factors, and the gene expression. The neuroprotective effects may be derived from its modulation of gene expression, while the outcome of its inhibitive actions seems to result in limiting the magnitudes

of fluctuations, contributing to a stabilizing influence **[109].** Lithium, for example, demonstrates two entirely separate actions, inhibition of phosphoinositide signaling and inhibition of GSK-3β. Through these actions, lithium is able at the same time to decrease the highest, stimulus-induced transcription factor activator protein1–DNA binding activity, and to raise the lowest, basal activator protein1-DNA binding activity, respectively. This bimodal action of lithium provide a stabilizing influence on signal fluctuations, ensuring that the activity of activator protein1 is not too low while at the same time protecting the cell from an overly extreme increase in AP1 activity **[109].**

The collapsin response mediator proteins (CRMPs) are mainly expressed in the nervous system during development and play important roles in axon formation from neuritis and in growth cone guidance. They are involved in cell migration, axonal guidance, dendritic spine development and synaptic plasticity through its phosphorylation. The intracellular phospho-proteins CRMPs mediate signals for numerous extracellular enzymes, like neurotrophins, semaphorins, and Reelin. **[110].** Tobe et al (2017) **[111],** using human-induced pluripotent stem cells from patients with bipolar disorder responsive to lithium, found that lithium alters the phosphorylation state of collapsin response mediator protein-2 (CRMP2). Especially, lithium lowers phosphorylated CRMP, which results in increasing spine area and density. Lithium therapy seems to normalize the ratios and spines of bipolar patients' brains, which have elevated ratios and diminished spine densities. The authors suggested that lithium in bipolar patients normalize the CRMP2's phosphorylation, which regulates cytoskeletal organization, particularly in spines, resulting in neural networks modulation. Recently, Ferensztajn-Rochowiak et al (2017) **[112],** investigated the effect of long-term lithium treatment on very-small embryonic-like stem cells and the mRNA expression of pluripotency and glial markers, in peripheral blood, in 15 patients with bipolar disorder not treated with lithium, in comparison with 15 patients with bipolar disorder treated with lithium and 15 controls. They found that long-term treatment with lithium may reduce the activation of regenerative processes of bipolar patients, by reducing the number of VSELs circulating.

Recent epidemiological findings strongly support the benefits of lithium use in both psychiatry and oncology. Martinsson et al (2016) **[113]** investigated the cancer risk in 5,442 lithium treated patients with bipolar, in comparison with the general population. The overall cancer risk in lithium treated bipolar patients was similar with the general population. In addition, the cancer risk in the digestive organs, in the intrathoracic organs, and in the endocrine glands, was significantly increased in not lithium treated bipolar patients in comparison with the lithium treated bipolar patients and the general population. Similar results were found in a retrospective study by Huang et al (2016) **[114],** who investigated the association between lithium and cancer risk in patients with bipolar disorder. They found a reduced overall cancer risk in lithium treated patients with bipolar disorder, while a dose-response relationship for cancer risk reduction was observed.

Recently, Ge & Jakobsson (2018) **[115]** conducted a pathway and network analysis exploring the role of lithium in multiple cancers. The results show that for the large majority of such cancers, there is high mutual enrichment between the interactomes of lithium-sensitive enzymes and the pathways associated with those diseases, indicating that lithium is very likely to affect the incidence and course of the disease. Three genes stand out as being not strongly connected to cancer pathways: BPNT1, DISC1, and PGM1. Of the cancer pathways, breast cancer stands out as being not likely to be strongly influenced by lithium levels. For the remainder of the genes and the remainder of the cancers, the relationship between the lithium-sensitive interactome and the cancer phenome is strong. Ge & Jakobsson **[115]** pointed that unlike other pharmaceuticals that are far more specific and inhibit or activate one gene or a small number of genes, the model for lithium action is that it alters the balance between a large number of interacting processes and pathways. Thus, a dose-response curve for lithium is likely to be highly nonlinear and not always monotonic. In the light of all these factors, the authors suggested that the correct question to ask with respect to lithium and a particular disease is not, "Should lithium be administered for this particular disease?" but rather, "What is the optimum blood level of lithium for this individual, given his or her disease history, status, ge-

netic propensities, and other medications?" Table 1 summarizes the broad range of lithium inhibitory effects, from the cell to the behavioral level, and its therapeutic implications.

In conclusion, lithium treatment has been associated with many neurochemical and structural evidence of neuroprotection, like the synthesis of brain-derived neurotrophic factor, the increased expression of anti-apoptotic genes, and the inhibition of cellular oxidative stress, which results in cortical thickening, increased grey matter density, and hippocampal enlargement. Unlike other ions, lithium is not regulated by selective membrane transport processes. Unlike other pharmaceuticals, lithium is an essential nutrient and is wildly nonselective in its biochemical effects. The question with lithium is not whether it should be ingested or not, but rather how much. Extreme lithium deprivation results in failure to thrive, while too much lithium is toxic. From the origin of life, lithium was in the environment, interacting with all of the biological molecules that life created. Lithium demonstrates a broad range of inhibitory effects from the cell to the behavioral level. We have been suggested that even natural lithium level intake can influence *impulsivity*, a possible core factor that mediate to the manifestation of both suicidality and aggressiveness, or even criminality. Moreover, a lithium deficiency state may precipitate these situations **[107, 108, 116].** Also, other mechanisms acting in parallel, like the initial lithium induced hypothyroidism may help to rearrange and normalize thyroid hormone secretion in the long-term therapy, acting possibly through an adaptive thyroid system resetting, which may results in a correction of an isolated CNS hypothyroidism **[35].**

What we know about the effects of lithium is likely only a small fraction of what there is to know. The bulk of evidence suggests that the optimum level of lithium intake from food and drinking water is more than most people get. Weighing the benefits and the potential risks, we can pose the question of whether the prospect of adding lithium to drinking water is realistic. In general, lithium seems to operate like a universal inhibitor, helping the organism to readjust balances, through the development of new compensatory mechanisms. Biological evolution had to accommodate to the presence of lithium to survive, since, those entities that best minimized lithium toxicity and maximized the benefits of lithium action had an edge in the competition to survive and reproduce **[107].**

Signaling pathways
lithium inhibits more than ten cellular targets and displacing magnesium ions
inhibits enzymes which have essential cofactor cations, such as Ca2+, Mg2+, Na+, K+, and Zn2+ by displacement of these cations from the enzymes **[17]**
inhibits many magnesium–dependent phosphomonoesterases
competes for a magnesium binding site in glycogen synthase kinase-3, inositol polyphosphate 1-phosphatase, fructose 1,6-bisphosphatase, bisphosphate nucleotidase, and phosphoglucomutase **[18].**
modulates cell function via inhibitory effects on adenosine triphosphatase activity, cyclic adenosine monophosphate, and intracellular enzymes **[19]**
inhibitory effect on the G proteins, inhibitory effect on parts of various signaling pathways, such as cyclic GMP and cyclic AMP formation **[20]**.
by inhibiting inositol monophosphatase, lithium obstructs the enzymatic degradation of inositol trisphosphate (IP3), resulting in reduced availability of the second messengers IP3 and DAG, the derivatives of the PIP cycle.
decreases the turnover of arachidonicacid (AA) in several brain phospholipids, which is correlated with a significantly decrease of phospholipase A2 (PLA2) activity **[23, 24]**.
inhibitor of the enzyme glycogen synthase kinase-3
reduces TGFBIp expression and blocks indirectly the GSK-3 activity through the phosphorylation of GSK-3α at ser21 and of GSK-3β at ser9 [**59]**

Thyroid system
anti-thyroid effects, inhibition of thyroid hormone release
inhibits thyroidal iodine uptake and iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion.
at the peripheral level, lithium decreases deiodination of tetraiodothyronine (T4) or thyroxine, by decreasing the activity of type I 5′ de-iodinase enzyme **[31]**
rearrange and normalize thyroid hormone secretion in the long-term therapy, acting possibly through an adaptive thyroid system resetting, which may result in a correction of an isolated CNS hypothyroidism **[35].**
cancer cell
reverts apoptosis models, inhibition of the GSK-3 has revealed anti-apoptotic effects **[46]**
reduced overall cancer risk in lithium treated patients with bipolar **[113]**
suppress leukopenia in patients undergoing radiotherapy or chemotherapy **[61]**
reduce melanoma risk **[66]**
reduce ovarian cancer cell metabolism **[69]**
decrease the proliferative potential of colorectal [**72]**
neurotransmission
inhibition of the countertransport mechanism (interfere with transporting systems for sodium and potassium in the plasma membranes of neurons)
induced inhibition of inositol monophosphatase may lead to Ins1P accumulation and inositol depletion **[20]**
lithium antidepressant action may be linked with reduced phosphoinositide cycle-coupled 5-HT_2 receptor function **[80**
reduces 5-HT_2 receptor function **[81]**
inhibits the glycogen synthase kinase-3 (GSK3) β isoenzyme, which in turn act as a mediator of serotonergic function **[92].**
impulsive behavior
mood stabilizing, prophylaxis of bipolar disorders and treatment of acute mania **[8]**
reduces the risk of suicide in people with mood disorders and superior antisuicidal effects, in relation to other mood stabilizers **[93-94]**
decreases impulsivity levels in bipolar patients and in other impulse control disorders **[85-89]**
low lithium intakes reduce suicide, as well as homicide rate **[99-105, 116]**
readjusting balances
neuroprotective effect: neurological (epilepsy, Huntington chorea, Parkinson diseases, and headaches)
also, endocrinological effects (hyperthyreosis, diabetes mellitus, and the inappropriate secretion of the antidiuretic hormone), haematological (neutropenia, and trombocytopenia), alergological (asthma), **[11, 12],** in oncology (thyroid carcinoma) **[13],** infectious diseases (AIDS related dementia) **[14],** and dermatology, in seborrhoeic dermatitis, with topically application
"unlike other pharmaceuticals that are far more specific and inhibit or activate one gene or a small number of genes, the model for lithium action is that it alters the balance between a large number of interacting processes and pathways" **[115]**

Table 1. *A broad range of lithium inhibitory effects and readjusting balances*

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