# The Possible Molecular Effect of Lithium Carbonate on the Thyroid Gland Functions

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**Abstract**

For over a century, lithium carbonate has been an effective mental medicine. It is now a standard treatment for manic-depressive episodes, both bipolar and unipolar, as well as a preventative measure against these conditions. In rare cases, lithium salts can induce hyperthyroidism, hypothyroidism, or goitre. Little is known about how lithium carbonate affects the thyroid gland at the moment. Articles published up until February 2020 that discussed the effects of lithium treatment on thyroid gland function were sought after using the Pubmed and Google Scholar databases. Studies that concentrated on lithium effects on the thyroid gland and investigated its molecular mechanism of action, including pharmacokinetics, were included. The intricate mechanism of action of lithium as a mood stabiliser is quite remarkable. Despite a concentration gradient, the thyroid gland accumulates three to four times as much lithium as the plasma does due to the active transit of Na+/I-ions. It has the potential to alter thyroglobulin structure, weaken tyrosine iodination, and disrupt their coupling, as well as limit colloid formation in thyrocytes. Moreover, it decreases the elimination of free thyroxine from the blood, which in turn decreases the activity of 5-deiodinase type 1 and 2 and the deiodination of these hormones in the liver. This review suggests ways to follow up patients' thyroid glands when they're receving lithium for an extended period of time. It is recommended to do a thyroid ultrasound and evaluate the levels of thyroid hormones (fT3 and fT4), TSH, antithyroid peroxidase, and antithyroglobulin antibodies before starting lithium therapy. It is recommended to measure the TSH level and conduct thyroid ultrasounds every 6 to 12 months for patients with normal thyroid function. These tests should be continued over the long term.

**Keywords:** lithium carbonate, bipolar affective disorder, adjuvant therapy, thyroid hormones, hypercalcemia, goiter, hypothyroidism, hyperthyroidism

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**Introduction** John Frederick Joseph Cade, an Australian psychiatrist, first used lithium to treat patients with manic episodes of bipolar disorder (BD) in 1949 (1). Interestingly, the Danish physician Eric Lange used it as early as the 19th century in patients with recurrent depressive

disorders (2). To date, lithium carbonicum (as the first-generation normothymic drug) is one of the main drugs used in psychiatry, and it is still successfully administered to patients with manic episodes of BD, to prevent the recurrence of BD, to reduce the severity and incidence of subsequent episodes of mania in patients with a history of maniacal conditions, and to prevent the occurrence of depressive episodes in patients with recurrent depressive disorders (3, 4). Furthermore, a recent study by Tondo *et al.* revealed substantial reduction of the risk of suicide during long-term lithium treatment (5).

Lithium carbonicum has a complex and yet unclear mechanism of action, leading to many side effects, particularly disorders of the thyroid gland, the most frequent of which include hypothyroidism and goiter (6-8). Because of the occurrence of thyroid disorders, some psychiatrists have doubts about the use of lithium in clinical practice. Therefore, our present article aimed to review the current state of knowledge on the action of lithium, including the treatment protocol in cases of goiter, hypothyroidism, and very rarely, hyperthyroidism.

We used the PubMed database and Google Scholar to search articles related to lithium therapy and thyroid diseases published up to February 2020. The following search key words were used: lithium therapy, thyroid dysfunction, goiter, hypothyroidism, hyperthyroidism, thyrotoxicosis, autoimmune thyroid disease, lithium treatment plus BD plus depression, and thyroid abnormalities plus lithium therapy.

## Pharmacokinetics

Lithium carbonate is easily absorbed from the gastrointestinal tract after oral administration. It reaches its maximum concentration in the serum after approximately 2 – 4 hours; its half-life is 10 – 42 hours. It is almost completely excreted by the kidneys (95 – 98%); hence, the status of the kidney, the amount of sodium consumed, and age significantly affect its concentration in the blood (9). Lithium can enter cellular and extracellular fluids as well as breast milk. Its therapeutic concentration ranges from 0.4 to 1.2 mEq/L (9-11). The mechanism of action of lithium is not fully understood; however, similar to other psychotropic drugs, lithium ions have been proven to interfere with the metabolism of phosphatidylinositol.

## Lithium And Secondary Messengers

By competing with magnesium ions for binding sites in intracellular transmission systems, lithium blocks the formation of secondary messenger systems (cAMP, cyclic adenosine monophosphate; PI, phosphoinositol; Ca, calcium ion) (12).

Lithium affects the phosphatidylinositol pathway by inhibiting inositol polyphosphate-1-phosphatase and inositol monophosphate phosphatase, thereby providing protection against the detachment of the last phosphate residue from the inositol molecule. Consequently, the levels of IP3 (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol) are reduced, resulting in the inhibition of intracellular transmission (13).

Lithium acts on the adenylate cyclase (AC) pathway probably through the interaction of its ions with G proteins (stimulating Gs protein and blocking Gi protein). Lithium has been shown to inhibit the formation of the cAMP secondary messenger when AC is associated with Gs, but the

basic production of cAMP increases under the influence of lithium ions (AC forms a complex with Gi protein and lithium stabilizes it, thereby reducing the activity of this protein) (14).

### *Participation of lithium in apoptosis*

According to Li and El-Mallah, lithium inhibits the pathway of caspase-3, which is involved in the activation of apoptosis (14). Interestingly, Dwivedi and Zhang demonstrated that lithium in a dose-dependent manner increased the expression of the antiapoptotic genes Bcl2 and Bcl-XL (20). On the other hand, lithium reduced the expression of the proapoptotic genes Bad, Bax, and caspase-3. Both doses were effective in lowering the levels of Bad and caspase-3; however, the lower dose was ineffective for inhibiting the Bax gene itself. Recent studies have shown that patients with BD who respond to lithium show an increased ratio of antiapoptotic to proapoptotic genes (15).

## Lithium Activity At The Molecular Level

The molecular-genetic basis of the mechanism of action of lithium is laid on the stimulation of gene expression through activation protein-1 (AP-1), which is one of the most important transcription factors, to the site of its binding to DNA (16). Lithium salts are likely to affect the creatine phosphokinase complex and mitogen-activated protein kinase (PKC-MAPK), wherein the latter probably affects the expression of AP-1 (16). The GSK-3β enzyme is encoded by the *GSK3B* gene in humans (17). Abnormal regulation and expression of GSK3β are associated with an increased susceptibility to BD (18). Most likely, by inhibiting the GSK-3β enzyme, lithium inhibits the activation of the transcription factor c-Jun. Consequently, there is no breaking of the bonds between the transcription factors and the DNA promoter region. Because of these mechanisms, lithium ions are likely to regulate the expression of the tyrosine hydroxylase gene, which is one of the major genes responsible for BD, and increase the stability of tyrosine hydroxylase mRNA.

## Effects Of Lithium on The Thyroid Gland

The primary function of the thyroid gland is the production of iodine containing hormones, tri-iodothyronine (T3) and thyroxine (T4). The synthesis of thyroid hormones involves several essential steps that occur in the thyroid gland. The sodium-iodine symporter (NIS) transports iodide into the thyroid cell, where iodide is oxidized by thyroid peroxidase (TPO). The iodine molecules then bind to the amino acid tyrosine residues within the protein thyroglobulin (Tg), which is secreted by the follicular cells into the colloid. Iodination of tyrosine forms monoiodotyrosine (MIT) (one iodine molecule attached) and diiodotyrosine (DIT) (two iodine molecules attached). The TPO enzyme catalyzes the coupling of MIT and DIT. Two DIT molecules combine to form T4 (thyroxine), and one MIT and one DIT combine to form T3 (triiodothyronine). The thyroglobulin-bound T3 and T4 are stored in the colloid until the thyroid gland is stimulated to release them. When needed, thyroglobulin is taken back into the follicular cells by endocytosis, and the protein is degraded by lysosomes to release free T3 and T4 into the bloodstream. In the bloodstream, T4 is the more abundant hormone, but T3 is more biologically active. T4 is often converted to T3 in peripheral tissues by deiodinase enzymes, particularly in the liver, kidney, and other tissues. This process is tightly regulated by thyroid-stimulating hormone (TSH) from the anterior pituitary gland. TSH stimulates iodide uptake, thyroid hormone synthesis, and release (19).

Lithium is accumulated in the thyroid at a concentration 3 – 4 times higher than that in the plasma due to the active transport of Na+/I– ions, lithium, contrary to the concentration gradient (20). Lithium carbonate influences the thyroid gland function by affecting the level of synthesis and release of thyroid hormones (TH). The inhibitory effect of lithium on the secreted TH is a result of changes in tubulin polymerization and the inhibitory effect of TSH on cAMP (34, 37). Dysfunction of the thyroid gland during lithium carbonate therapy occurs more frequently in patients with pre-existing goiter or elevated titer of thyroid autoantibodies in the serum (43, 44). It is believed that patients with BD are particularly susceptible to thyroid diseases with frequent cycle change (rapid cyclers). During lithium treatment, the development of goiter, hypothyroidism, and even thyrotoxicosis has been observed (20).

*Lithium-induced hypothyroidism*

Hypothyrodism is a common complication of lithium thrapy. One-fourth of Lithium-treated patients developed hypothyroidism. It may appear in the first few months after the therapy and even after 15 years of therapy . Several factors can contribute to its development as gender (women suffer five times more often than men), geographical zone (areas with iodine insufficiency or proper iodine supplementation), and pre-existing autoimmune diseases (especially in patients with positive thyroid antibodies) (21).

Li inhibits the synthesis of thyroid hormones by reducing iodine uptake through sodium-iodide symporter interference, disrupting tyrosine iodination, and changing thyroglobulin structure with subsequent iodotyrosine coupling defects. Li also reduces the release of thyroid hormones through a variation in tubulin polymerization as well as inhibition of the action of TSH on cyclic adenosine monophosphate (cAMP). Moreover, at the peripheral level, lithium inhibits the hepatic T4 to T3 conversion. If LiI-Hypo occurs, levothyroxine supplementation is recommended (25 – 75 μg/day), and lithium therapy can be continued

*Goiter*

The occurrence of goiter during lithium therapy may result from two mechanisms: first, it can occur due to the inhibition of the synthesis and release of TH, leading to an increase in the serum TSH concentration and thus causing an enlargement of the gland; second, the proliferation of thyrocytes occurs through the activation of tyrosine kinase by lithium ions and its effect on the intracellular signaling associated with the adenylate cycle and Wnt/beta-catenine (22).

In 1968, it was reported goiter in patients with bipolar disorder treated with lithium carbonate. He examined 330 patients, 12 of whom (five women and seven men) aged 18 to 51 years had goiter. Lee *et al.* described goiter during lithium therapy in 50% of patients when they examined Chinese patients from Hong Kong. Perrild H *et al.* studied 100 Danish patients with BD and demonstrated that goiter occurred in 44% of those treated by lithium for 1 – 5 years and in 50% of those treated for more than 10 years, as compared to 16% in the control group (22).

Goiter in lithium-treated patients remains a controversial issue even among clinicians; the question remains whether to use TSH-suppressive therapy with levothyroxine as soon as goiter has been diagnosed even in the absence of hypothyroidism (23).

According to Martino *et al*., prophylaxis with levothyroxine in patients treated with lithium is essential, particularly in goiter-endemic areas (24). However, Lazarus presents a completely different view and claims that this type of treatment can lead to lithium-associated thyrotoxicosis; moreover, TSH-suppressive treatment can lead to osteoporosis or cardiovascular complications (25).

Long-term stimulation of the thyroid gland through TSH promotes the formation of nodules and may lead to the development of malignancy (prevalence of nodular goiter is 2 – 4% of the population, and prevalence of thyroid cancer is 0.0025% of the population) (26).

*Antithyroid antibody titers (Tg-Ab and TPO-Ab)*

Lithium carbonate affects cellular and humoral immune responses, both *in vitro* and *in vivo*. Lithium treatment in patients with BD is associated with elevated antithyroid antibodies (from 8% to 49%, average 10%), especially when such elevated levels are already present at the beginning of treatment and are significantly higher than that in the general population (27). However, another study reported that despite long-term administration of lithium, no autoimmunization occurred (28). According to these authors, the autoimmunization process was obviously associated with the dysfunction of the thyroid gland; however, it was not associated with lithium therapy, age, gender, and mood state, because autoantibodies were present in 64 of 226 (28%) patients who had never been subjected to lithium therapy. Similar results were obtained by Baethge *et al.* who showed no significant difference in the incidence of autoantibodies between the group of BD patients receiving lithium and the control group. In contrast, Wilson *et al.* demonstrated that a much larger group of patients treated with lithium had antithyroid autoantibodies as compared to untreated patients (20% versus 7.5%) (29). These authors proved that long-term lithium therapy induces B-cell activation and decreases the ratio of suppressor T cells to cytotoxic lymphocytes, which could be a possible mechanism for the immunogenic properties of lithium. Bocchetta *et al.* conducted a 15-year long retrospective analysis which unequivocally proved that the percentage of new cases with disputed autoantibody titer was 1.7% per year and that hypothyroidism was a significant risk factor for the development of the autoimmunization process (65). A positive titer of antithyroid autoantibodies can be stimulated with lithium therapy, but the antibody stimulation can also occur without the involvement of lithium.

Therefore, it is believed that there are no special indications for monitoring autoantibodies (Tg-Ab and TPO-Ab) during lithium therapy, as many patients with positive autoantibodies do not develop hyperthyroidism or hypothyroidism (7).

*Lithium-induced hyperthyroidism*

Lithium-induced hyperthyroidism (LiI-Hyper) is rarely reported in the literature, and its incidence ranges from 0.1% to 1.7%. The mechanism of LiI-Hyper development is not fully understood. According to Carmaciu *et al*., it is probably the result of the participation of antithyroid autoantibodies, disturbance of iodine kinetics, Jod-Basedow effect, co-occurrence of Graves' disease (GD) before the therapy, or direct destruction of thyrocytes by lithium (direct cytotoxic activity) that release Tg into the bloodstream (30).

LiI-Hyper can occur in the form of asymptomatic (silent) thyroiditis, GD or toxic nodular goiter (31). The pathogenesis of painless thyroiditis is unclear; however, various studies suggest a possible

direct, toxic effect of lithium on the thyroid gland. In patients treated with lithium, an increased titer of positive antithyroid peroxidase antibodies has been demonstrated, which is most likely due to an increased B-cell lymphocyte activity and reduced ratios of suppressor to cytotoxic T-cell lymphocytes.

Although the incidence of LiI-Hyper is rare, it occurs more often in lithium-treated patients than in the general population, and its incidence is significantly different in multiple studies, for example, Kirov *et al.* showed the occurrence of hyperthyroidism in only 2 of 209 patients with BD who were treated with lithium for a long time (31). After 7 years, the same group of researchers conducted an 8-year long retrospective analysis, where Lil-Hyper was found in 1.8% of 109 men and 3.9% of 152 women. Bocchetta *et al.* studied patients treated with lithium, and during a 10-year long observation period, they found no case of thyrotoxicosis; only after 15 years, they observed only one case among 150 patients (31). Barclay *et al.* obtained different results (68). During an 18-year long follow-up period, they detected Lil-Hyper in 14 patients, which was three times higher than the incidence of thyrotoxicosis in the population of New Zealand. Later, during a 12-year research period (1995 – 2006), they recorded 23 cases (20 women and 3 men), 9 of whom were diagnosed to have painless thyroiditis (69). There are other interesting observations regarding the occurrence of ophthalmopathy. Ozpoyraz *et al.* detected ophthalmopathy in 25% of 73 patients treated with lithium, while according to Byrne and Delaney, exophthalmus resolved after the discontinuation of lithium therapy (32).

The therapy of patients with LiI-Hyper depends on the etiology; in cases of GD or toxic nodular goiter, the best therapeutic effects are obtained using antithyroid drugs and heterocyclic thiourea derivatives (thioamides) such as thiouracil derivatives (propylthiouracil) or thioimidazole derivatives (thiamazole) (6). If ophthalmopathy occurred in the course of GD, thyrostatic agents in combination with glucocorticoids may be used. For toxic nodular goiter with compression symptoms in the neck, treatment with radioiodine is indicated (33). Thus, in cases of LiI-Hyper, there is no need to abruptly discontinue lithium treatment.

*Lithium and radioiodine uptake by the thyroid gland*

In the literature, there are divergent data on the effect of lithium carbonate on radioiodine uptake (RAIU) by the thyroid gland. An increase in RAIU after the administration of lithium carbonate was reported by Sedvalla *et al.* who showed an increase in uptake from 26% to 36.7% after 24 h of treatment. Similar results were observed in animals by Berens *et al.* These authors also found that the thyroid shows an increased ability to accumulate iodine during lithium carbonate treatment regardless of the degree of prolonged iodine retention in the thyroid gland. Temple *et al.* and Turner *et al.*, however, presented different results (34). They investigated the effect of lithium carbonate on RAIU in 11 patients with GD. The initial RAIU in this group was 33 – 88% and did not change during the administration of 900 – 1500 mg of lithium carbonate per day for 10 days. Turner *et al.* administered a dose of 400 mg of lithium carbonate per day for 1 week before radioactive iodine (131I) administration and continued for 1 week after the administration of a standard therapeutic activity of 131I (5 mCi) (35). The baseline value of RAIU in this group was ca. 70%, and after the administration of lithium carbonate, it decreased to 67%. Summarizing their results, these authors emphasize that lithium carbonate only affects the effective half-life of iodine, but does not affect iodine uptake. The basic difference between the groups studied by

Sedvalla *et al.*, Turner *et al.*, and Temple *et al.* lies in the initial iodine uptake (36) As mentioned above, the initial iodine uptake was 26% in the study of Sedvalla *et al.*, while it was 70% in the study of Turner *et al.* (37). Currently, it is believed that lithium carbonate has a beneficial effect on the increase in RAIU, especially in patients after treatment with amiodarone, contrasting agents, or preparations containing iodine (38).

*Adjuvant lithium therapy before radioactive iodine treatment*

The 131I treatment is the first-line effective treatment for hyperthyroidism in most cases. The aim of the treatment is to destroy thyroid tissue in order to yield euthyroid or ultimately hypothyroidism (38). In this context, lithium is used prior to the administration of 131I in patients with hyperthyroidism (GD, *e.g.*, after contrast media or amiodarone administration) who show low iodine uptake (80). Moreover, lithium strengthens the retention of 131I in the thyroid gland, which effectively prevents transient exacerbation of hyperthyroidism (due to the discontinuation of antithyroid medications and the administration of 131I). Hence, the use of lithium adjuvant therapy enables to obtain the most satisfactory effects in 131I therapy and potentially facilitates the treatment of thyrotoxicosis (131I therapy) (39).

## MONITORING OF LITHIUM CONCENTRATION IN THE SERUM

It is crucial to strictly monitor lithium levels in the blood because of its narrow therapeutic index. Lithium concentration in the serum should be measured 1 week after the beginning of treatment as well as after dose adjustment, followed by weekly check-ups until the therapeutic level is stable. Serum lithium level is influenced by renal clearance (from 10 to 40 ml/min), distribution volume (from 20% to 120% of body weight), and the absorption rate and solubility of lithium salt. Serum lithium concentration of up to 1.2 mEq/L is recommended, and patients in remission need lower levels than those treated for acute mania (40).

## SIDE EFFECTS OF LITHIUM

The symptoms of lithium toxicity can be mild, moderate, or severe (86). Nausea, vomiting, diarrhea, hand tremor, and drowsiness are the mild symptoms of lithium toxicity with lithium levels of up to 1.5 – 2 mEq/L. The symptoms of moderate lithium toxicity with lithium levels in the range of 2 – 2.5 mEq/L are myoclonic contractions, nystagmus, dysarthria, and ataxia. For serious toxicity where lithium levels exceed > 2.5 mEq/L, the symptoms include renal impairment, disturbances in consciousness, convulsions, coma, and death. The toxicity of lithium may be increased due to the following factors: dehydration (as a major factor); increase in lithium dose; decrease in renal function, particularly in older patients, and the effect of other medications such as nonsteroidal anti-inflammatory drugs, thiazides, and angiotensin-converting enzyme inhibitors. These drugs increase the reabsorption of lithium by the kidneys, resulting in an increased concentration of lithium in the serum. According to Timmer *et al.*, toxic symptoms may occur even in the therapeutic range of lithium (41).

*Lithium-associated hypercalcemia*

Lithium carbonate affects the parathyroid gland, which leads to increased calcium levels in the blood- lithium-associated hypercalcemia (LAH). Its incidence is higher in patients with pre-existing renal failure. The mechanism of LAH probably involves: 1) the action of the drug on the

receptors for calcium ions found in the parathyroid gland, resulting in continuous secretion of parathyroid hormone (PTH) despite hypercalcemia; 2) lithium in therapeutic doses leads to an increase in calcium reabsorption in renal tubules, resulting in reduction in the excretion of calcium and magnesium through the kidneys; and 3) by inhibiting the GSK-3β enzyme activity, lithium directly stimulates the main parathyroid cells to synthesize PTH (43). Cinacalcet (allosteric activator of the calcium sensitive receptor (CaSR)), a calcimimetic that directly reduces the concentration of PTH and increases the sensitivity of the calcium receptor in the parathyroid gland to extracellular calcium, is used in the treatment of LAH (44).

*Conclusions*

In summary, lithium as a mood-stabilizing drug demonstrates a complex mechanism. Goiter, hypothyroidism, or thyrotoxicosis could develop during lithium treatment. In addition, by causing the induction of TSH, lithium increases the expression of autoantigens on the surface of thyrocytes, thereby contributing to the intensification of the existing autoimmune processes. Because of the high incidence of thyroid dysfunction, patients should undergo a careful physical and visual examination of the thyroid gland; furthermore, the levels of thyroid hormones (fT3 and fT4), TSH, antithyroid peroxidase antibodies, and thyroglobulin should be tested prior to lithium treatment. Patients with a normal thyroid function should be re-evaluated (TSH level measurement and thyroid ultrasonography) every 6 to 12 months for long term. The development of both hyperthyroidism and hypothyroidism usually does not require discontinuation of lithium treatment. An additional benefit is the use of adjuvant lithium therapy to increase the iodine uptake of the thyroid gland, which allows to obtain satisfactory results in treatment with radioactive iodine and potentially facilitates the treatment of thyrotoxicosis. In addition, because of the numerous side effects of lithium and its narrow therapeutic index, its concentration in the blood must be constantly monitored.

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**References:**

1. Cade JF. Lithium salts in the treatment of psychotic excitement. Med J Austr 1949; 2: 349-352.
2. Lange C, Amdisen A. Om periodiske depressionstilstande of deres patogenese: foredrag holdt i Medicinsk Selskab den 19. Januar 1886: Duo; 1886.
3. Mutschler E, Geisslinger G, Kroemer H, Ruth P, Schaefer-Korting M. Farmakologia i Toksykologia. Wroclaw, MedPharm Polska, 2010.
4. Mueller-Oerlinghausen B, Lewitzka U. Lithium reduces pathological aggression and suicidality: a mini-review. Neuropsychobiology 2010; 62: 43-49.
5. Tondo L, Baldessarini RJ. Antisuicidal effects in mood disorders: are they unique to lithium? Pharmacopsychiatry 2018; 51: 177-188.
6. Jastrzebska H. Lithium therapy and thyroid disorders. Post Nauk Med 2017; 12: 694-698.
7. Kraszewska A, Abramowicz M, Chlopocka-Wozniak M, Sowinski J, Rybakowski J. The effect of lithium on thyroid gland function in patients with bipolar disorder [in Polish]. Psychiatria Pol 2014; 48: 694-698.
8. Lazarus JH. Endocrine and Metabolic Effects of Lithium. Springer Science & Business Media, 1986.

9. Grandjean EM, Aubry J-M. Lithium: updated human knowledge using an evidence-based approach. CNS Drugs 2009; 23: 397-418.
10. Nolen WA, Licht RW, Young AH, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord 2019; 21: 394-409.
11. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20: 97-170.
12. Layden B, Diven C, Minadeo N, Bryant FB, Mota de Freitas D. Li+/Mg2+ competition at therapeutic intracellular Li+ levels in human neuroblastoma SH-SY5Y cells. Bipolar Disord 2000; 2: 200-204.
13. Gill R, Mohammed F, Badyal R, et al. High-resolution structure of myo-inositol monophosphatase, the putative target of lithium therapy. Acta Crystallographica D Biol Crystallography 2005; 61: 545-555.
14. Schlecker C, Boehmerle W, Jeromin A, et al. Neuronal calcium sensor-1 enhancement of InsP 3 receptor activity is inhibited by therapeutic levels of lithium. J Clin Invest 2006; 116: 1668-1674.
15. Devaki R, Rao SS, Nadgir SM. The effect of lithium on the adrenoceptor-mediated second messenger system in the rat brain. J Psychiatry Neurosci 2006; 31: 246-252.
16. Assis GG, Sousa MB, Kozacz A, Murawska-Cialowicz E. Brain derived neutrophic factor, a link of aerobic metabolism to neuroplasticity. J Physiol Pharmacol 2018; 69: 351-358.
17. Gawlinska K, Gawlinski D, Przegalinski E, Filip M. Maternal high-fat diet during pregnancy and lactation provokes depressive-like behavior and influences the irisin/brain-derived neurotrophic factor axis and inflammatory factors in male and female offspring in rats. J Physiol Pharmacol 2019; 70: 407-417.
18. Li R, El-Mallahk RS. A novel evidence of different mechanisms of lithium and valproate neuroprotective action on human SY5Y neuroblastoma cells: caspase-3 dependency. Neurosci Lett 2000; 294: 147-150.
19. Rybakowski JK. Lithium in neuropsychiatry: a 2010 update. World J Biol Psychiatry 2011; 12: 340-348.
20. Dwivedi T, Zhang H. Lithium-induced neuroprotection is associated with epigenetic modification of specific BDNF gene promoter and altered expression of apoptotic-regulatory proteins. Front Neurosci 2015; 8: 457. doi: 10.3389/fnins.2014.00457
21. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Menji HK. Lithium-induced increase in human brain grey matter. Lancet 2000; 356: 1241-1242.
22. Moore GJ, Bebchuk JM, Hasanat K, et al. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of Bcl-2's neurotrophic effects? Biol Psychiatry 2000; 48: 1-8. doi: 10.1016/s0006-3223(00)00252-3
23. Gildengers AG, Butters MA, Aizenstein HJ, et al. Longer lithium exposure is associated with better white matter integrity in older adults with bipolar disorder. Bipolar Disord 2015; 17: 248-256.
24. De Ferrari G, Chacon M, Barria M, et al. Activation of Wnt signaling rescues neurodegeneration and behavioral impairments induced by β-amyloid fibrils. Mol Psychiatry 2003; 8: 195-208.

25. Jope RS. Anti-bipolar therapy: mechanism of action of lithium. Mol Psychiatry 1999; 4: 117-128.
26. King TD, Jope RS. Inhibition of glycogen synthase kinase-3 protects cells from intrinsic but not extrinsic oxidative stress. Neuroreport 2005; 16: 597-601.
27. Lowthert L, Leffert J, Lin A, et al. Increased ratio of anti-apoptotic to pro-apoptotic Bcl-2 gene-family members in lithium-responders one month after treatment initiation. Biol Mood Anxiety Disord 2012; 2: 15. doi: 10.1186/2045-5380-2-15
28. Caykoylu A, Capoglu I, Unuvar N, Erdem F, Cetinkaya R. Thyroid abnormalities in lithium-treated patients with bipolar affective disorder. J Int Med Res 2002; 30: 80-84.
29. Lenox R, Wang L. Molecular basis of lithium action: integration of lithium-responsive signaling and gene expression networks. Mol Psychiatry 2003; 8: 135-144.
30. Yuan PX, Chen G, Huang L-D, Manji HK. Lithium stimulates gene expression through the AP-1 transcription factor pathway. Mol Brain Res 1998; 58: 225-230.
31. Chen G, Masana MI, Manji HK. Lithium regulates PKC-mediated intracellular cross-talk and gene expression in the CNS in vivo. Bipolar Disord 2000; 2: 217-236.
32. Lau KF, Miller CC, Anderton BH, Shaw PC. Molecular cloning and characterization of the human glycogen synthase kinase-3b promoter. Genomics 1999; 60: 121-128.
33. Stambolic V, Woodgett JR. Mitogen inactivation of glycogen synthase kinase-3b in intact cells via serine 9 phosphorylation. Biochem J 1994; 303: 701-704.
34. Mariotti S, Beck-Peccoz P. Physiology of the hypothalamic-pituitary-thyroid axis. In: Endotext Comprehensive Free Online Endocrinology Book. Feingold K, Anawalt B, Boyce A, et al. (eds.) South Dartmouth (MA, USA), 2000.
35. Segarra A, Prieto I, Martinez-Canamero M, et al. Cystinyl and pyroglutamyl-beta-naphthylamide hydrolyzing activities are modified coordinately between hypothalamus, liver and plasma depending on the thyroid status of adult male rats. J Physiol Pharmacol 2018; 69: 197-204.
36. Werner SC, Ingbar SH, Braverman LE, Utiger RD. Werner & Ingbar's the Thyroid: a Fundamental and Clinical Text. Lippincott Williams & Wilkins, 2005.
37. Spaulding S, Burrow G, Bermudez F, Himmelhoch J. The inhibitory effect of lithium on thyroid hormone release in both euthyroid and thyrotoxic patients. J Clin Endocrinol Metab 1972; 35: 905-911.
38. Bogazzi F, Tomisti L, Ceccarelli C, Martino E. Recombinant human TSH as an adjuvant to radioiodine for the treatment of type 1 amiodarone-induced thyrotoxicosis: a cautionary note. Clin Endocrinol 2010; 72: 133-134.
39. Nieuwlaat WA, Huysmans DA, van den Bosch HC, et al. Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 2003; 88: 3121-3129.
40. Mori M, Tajima K, Oda Y, Matsui I, Mashita K, Tarui S. Inhibitory effect of lithium on the release of thyroid hormones from thyrotropin-stimulated mouse thyroids in a perifusion system. Endocrinology 1989; 124: 1365-1369.
41. Williams J, Berens S, Wolff J. Thyroid secretion in vitro: inhibition of TSH and dibutyryl cyclic-AMP stimulated 131I release by Li+. Endocrinology 1971; 88: 1385-1388.
42. Hahn CG, Pawlyk AC, Whybrow PC, Gyulai L, Tejani-Butt SM. Lithium administration affects gene expression of thyroid hormone receptors in rat brain. Life Sci 1999; 64: 1793-1802.

43. Berens S, Bernstein R, Robbins J, Wolff J. Antithyroid effects of lithium. J Clin Invest 1970; 49: 1357-1367.
44. Lazarus JH, McGregor AM, Ludgate M, Darke C, Creagh FM, Kingswood CJ. Effect of lithium carbonate therapy on thyroid immune status in manic depressive patients: a prospective study. J Affective Disord 1986; 11: 155-160.