J. Elem. s. 1167–1178 DOI: 10.5601/jelem.2014.19.3.736

REVIEW PAPERS

LIHIUM AND THE APPLICATION OF ITS COMPOUNDS IN DIFFERENT FIELDS OF MEDICINE

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Abstract

Although lithium has not been classified as an essential element for humans, it can influence numerous metabolic processes and exert diverse effects in the human body, both positive and negative ones. Its actions enable the use of lithium compounds in therapy of different illnesses. It is mostly used for cure of psychiatric disorders: as a mood stabilizer and for intensifying the action of antidepressants. However, its compounds have been also tried in other fields of medicine: as an adjuvant in patients with thyroid diseases undergoing radioiodine therapy, in dermatology, in cure of neurodegenerative and ophthalmic illnesses as well as in tumour therapy. Lithium displays beneficial action only within a determined range of its serum concentration and an overrun of the safe threshold can cause side effects. Due to this fact, the Li serum level as well as many other factors, e.g.: body weight, creatinine, renal and thyroid functions should be monitored during the whole therapy. Many studies were undertaken to clarify the mechanism by which lithium affects organisms but the results still remain unsatisfactory. Nevertheless, some interesting aspects of lithium action have been revealed, including its effect on the enzymatic activity, neurodegenerative processes, apoptosis, formation of cytokines as well as neurotransmission and oxidant balance.

Key words: lithium, psychiatric disorders, neurodegenerative and ophthalmic illnesses, thyroid diseases, dermatology, side effects and precautions in lithium therapy, mechanism of lithium action.

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LIT I ZASTOSOWANIE ZWIĄZKÓW TEGO PIERWIASTKA W RÓŻNYCH DZIEDZINACH MEDYCYNY

Abstrakt

Obecność litu w organizmie może wywierać różnorodny wpływ zarówno korzystny, jak i negatywny na liczne procesy metaboliczne, jednakże nie został on jeszcze zaliczony do pierwiastków niezbędnych dla człowieka. Działanie litu umożliwiło zastosowanie jego związków w terapii różnych chorób. Jest on głównie stosowany w przypadkach zaburzeń psychicznych jako stabilizator nastroju oraz środek potencjalizujący działanie leków przeciwdepresyjnych. Przeprowadzono również próby zastosowania jego związków w innych dziedzinach medycyny: do wspomagania terapii radiojodem stosowanej w chorobach tarczycy, w dermatologii, w leczeniu schorzeń neurodegeneracyjnych i chorób oczu oraz w leczeniu nowotworów. Lit wywiera działanie terapeutyczne jedynie wtedy, gdy jego stężenie w surowicy mieści się w określonym zakresie, a przekroczenie dopuszczalnej wartości może spowodować działania uboczne. Z tego powodu stężenie litu w surowicy, podobnie jak wiele innych czynników, takich jak: masa ciała, poziom kreatyniny oraz funkcje tarczycy i nerek, musi być monitorowane podczas całej terapii. W celu wyjaśnienia mechanizmu oddziaływania litu na organizm przeprowadzono wiele badań, ale rezultaty są wciąż niezadowalające, niemniej jednak odkryto liczne, interesujące aspekty działania litu, m.in. wpływ na aktywność enzymatyczną, procesy neurodegeneracyjne i neurotransmisyjne, apoptozę, produkcję cytokin oraz na procesy pro- i antyoksydacyjne.

Słowa kluczowe: lit, schorzenia psychiatryczne, choroby neurodegeneracyjne, choroby oczu, schorzenia tarczycy, dermatologia, efekty uboczne i środki ostrożności w terapii litem, mechanizm działania litu.

Lithium belongs to the first group in the periodic table of elements. Chemists are not very much concerned with lithium compounds as it is not widespread in the Earth's crust and its properties can be predicted from its place in the periodic table (Aral, Vecchio-Sadus 2008). In contrast, Li compounds are widely applied in medicine and the physiological aspects of the effect of lithium on organisms have been studied for the last sixty years. Research has revealed that lithium is necessary for the correct functions of animal organisms (Zarse et al. 2011). As for the humans, it has not been classified as an essential element (Aral, Vecchio-Sadus 2008). However, a cohort study performed by Japanese scientists showed an inverse correlation between the Li concentration in drinking water and the mortality in 18 Japanese municipalities (Zarse et al. 2011).

As lithium salts occur in mineral waters (Aral, Vecchio-Sadus 2008), this element had been applied in medicine long before it was discovered. In ancient times, people suffering from nervous disorders were recommended to drink mineral waters (Gorgotas, Gershon 1981). In the 1940s, the beneficial effect of lithium in manic states was found and since then lithium in the form of its carbonate (Li_2CO_3) has been used for therapy of affective disorders (Pietruczuk, Witkowski 2008). This drug is regarded as the first choice one in therapy of affective disorders (Zhong, Lee 2007, Woźniak 2008, Rybakowski 2010) and one third of patients subjected to Li therapy display total remission of recurrences without any adjuvant (Rybakowski, Suwalska

2010). Among mood-stabilizers, lithium is best documented considering prevention of suicidal behaviours (Kliwicki, Rybakowski 2009). Furthermore, lithium can be used as an adjuvant to augment the pharmacological effect of antidepressants drugs (Hanson et al. 2011). Interestingly, bipolar disorders belong to hereditary illnesses (Möller 2003) and a clinical course of disease also seems to be inherited (Duffy et al. 2002). Considering these facts, the usefulness of genetic research for predicting the effectiveness of therapy and predisposition to psychiatric disorders has been studied (Szczepankiewicz et al. 2009, Remlinger-Molenda, Rybakowski 2010).

Lithium is absorbed from the gastrointestinal tract and excreted mainly in urine (Collins et al. 2010). After oral administration, it reaches the maximum serum concentration in about 30 minutes and the plateau occurs after 14 - 24 hours (Aral, Vecchio-Sadus 2008). As kidneys are practically the only way of lithium excretion, this element cannot be used in patients with renal insufficiency (Strzelecki 2006). Markers of renal disturbances such as proteinuria, increased N-acetyl-β-glucoaminidase activity in urine and enhanced Cu excretion, were suggested to be useful indicators of nephrotoxicity of lithium (Chmielnicka, Nasiadek 2003).

Lithium therapy can show high efficacy but it is necessary to take appropriate precautions. The reason is that lithium displays beneficial action only within a strictly determined range of its serum concentration (Mišak 2005, NG et al. 2006). If the safe threshold is overrun, side effects can occur (Chiu et al. 2007). Another problem is the lack of correlation between the applied Li dose and its serum level (Ng et al. 2006). Moreover, scientists from India found that the plasma lithium level underwent seasonal variations (Medhi et al. 2008). The same observations were reported by Dutch researchers, who also stated that the Li level was influenced by the ambient temperature, although these effects were therapeutically irrelevant (Wilting et al. 2007). Lithium therapy is usually long-term, therefore the serum or plasma Li concentration must be monitored during the whole administration period (Wilkowska et al. 2006, Medhi et al. 2008). It is recommended to be within the range of 0.6-1.2 mmol L^{-1} (Chiu et al. 2007). In India, the effective maintenance plasma level in manic-depressive patients was established to range from 0.35 to 1.0 mmol L^{-1} (Medhi et al. 2008). Similar values were reported by British authors (Collins et al. 2010). Besides, considering side effects of lithium, it is recommended to monitor creatinine, thyrotrophin and thyroid hormones in plasma, particularly in women, as well as renal functions (Mišak 2005). Strzelecki (2006) reported that at the onset of a therapy the lithium concentration should be controlled twice a week and parathormone and antithyroperoxidase antibodies ought to be measured before Li administration. In 2009, according the UK guidelines regarding Li therapy, renal and thyroid functions tests before administration and every 6 months during the Li treatment are advised; it is also recommended to measure the serum Li every 3 months (Collins et al. 2010). The symptoms of adverse effects of lithium could be disturbances of the central nervous, cardiovascular

and alimentary systems (Ng et al. 2006, Chiu et al. 2007), renal disorders (Hwang et al. 2010), hyperparathyroidism (Strzelecki 2006), disturbances of carbohydrate and lipid metabolism (Olszewska, Rybakowski 2007, Vijaimohan et al. 2010) as well as alterations of the thyroid volume, enhancement of the thyroid stimulating hormone level and depression of the secretion of thyroid hormones (Ozsoy et al. 2010). Animal studies also revealed that subcutaneous administration of lithium resulted in depleted thymus mass (Levine, Saltzman 2006). The teratogenic effects of lithium were also described (Nguyen et al. 2009) although a more recent article stated that the teratogenic risk resulting from Li therapy should be softened (Gentile 2011). However, a lithium treatment was found to raise the risk of cardiovascular malformation in pregnancy and perinatal complications (Galbally et al. 2010), thus it is still recommended that lithium ought to be avoided during gestation (Howland 2009). Several methods for lithium dosage prediction have been described. These *a priori* calculations are based on different data, including: the patient's age, gender, body weight, blood urea level, creatinine and lithium clearance, and concurrent administration of tricyclic antidepressants. However, the use of these methods is connected with the risk of under- or overdosing, hence the claim that nothing can replace monitoring of the Li serum level (Chiu et al. 2007).

Lithium may exert beneficial effects not only in cases of psychiatric disorders. Studies revealed that lithium could show action against the herpes virus (Remlinger-Molenda, Rybakowski 2010). Lithium succinate and gluconate were suggested to be effective as topical drugs in seborrhoeic dermatitis. The local application was found to decrease the risk of side effects and might be used even in renal insufficiency, although not in the third trimester of pregnancy (Sparsa, Bonnetblanc 2004).

Owing to its ability to inhibit secretion of thyroid hormones, lithium has been studied as a possible adjuvant in patients with thyroid diseases subjected to radioiodine therapy (Bal et al. 2002, Liu et al. 2006, Bogazzi et al. 2010, Oszukowska et al. 2010). Lithium was found to inhibit hyperthyroidism resulting from radioiodine treatment (Vannucchi et al. 2005). It was emphasized that Li enhanced radioiodine retention in the thyroid without increasing its uptake. Thus, a risk of side effects was lower because the Li treatment was shorter and the serum Li concentrations lower than used in psychiatric diseases (Vannucchi et al. 2005, Bogazzi et al. 2010).

Numerous studies showed possible applications of lithium to cure neurodegenerative illnesses, although it was still recommended that the proper precautions should be taken to avoid side effects (Zhong, Lee 2007). These studies were based on the evidence of a broad range of effects of lithium on processes involved into the pathogenesis of neurodegenerative disorders e.g. Alzheimer's disease (Nakashima et al. 2005, Kessing et al. 2008). Lithium inhibits the activity of glycogen synthase kinase (GSK) (Bielecka, Obuchowicz 2008, Camins et al. 2009), whose isoform GSK3 β stimulates τ protein phos-

phorylation (Leroy et al. 2010). Inhibition of GSK-3β activity may also decrease *β*-catenin degradation (Bielecka, Obuchowicz 2008, Chiu, Chuang 2010). Lithium may inhibit *β*-amyloid formation (Nakashima et al. 2005) although contradictory observations were also described (Feyt et al. 2005). Lithium treatment, both *in vivo* and *in vitro*, was found to cause significant increase in the neuroprotective protein Bcl-2 level (Camins et al. 2009). Animal studies revealed that lithium administration significantly enhanced anti-apoptotic protein Bcl-2 and decreased pro-apoptotic Bax in testes of cadmium-exposed rats (Al Azemi et al. 2010). Another study performed on aluminium-treated rats revealed that lithium administration could display a neuroprotective action by improving the histoarchitecture of the cerebrum and cerebellum, which confirmed the potential use of Li against neurotoxicity (Bhalla, Dhawan 2009). All the evidence of lithium being able to alleviate neurodegenerative processes encourage research on its administration in cases of disorders of the nervous system such as Alzheimer's, Parkinson's and Huntington's diseases as well as ethanol-induced neurotoxicity (Luo 2010). Other perspectives of Li application were connected with its possible efficacy in therapy of Canavan's disease (Janson et al. 2005, Assadi et al. 2010). The results of animal studies revealed that lithium used in the same doses as those applied in cases of bipolar disorders may be useful for prevention and cure of neonatal brain injury (Li et al. 2010). Continued lithium treatment was believed to reduce the rate of dementia (Kessing et al. 2008) although observations contradicting this conclusion were also reported (Dunn et al. 2005). Nonetheless, lithium was considered as an adjuvant in cases of dementia resulting from HIV infection (Dou et al. 2005).

Another possible application of lithium in cases of some ophthalmic diseases is connected with its action on the nervous system. Studies revealed that lithium could sustain the survival and regeneration of retinal ganglion cells. Bcl-2 protein was believed to be involved into the mechanism of this effect. The authors suggested that lithium therapy could be beneficial in cure of glaucoma, neuritis of optic nerve and degeneration of retinal ganglion cells (Huang et al. 2003).

Studies concerning the possibility of Li application in cases of tumour have been performed on mice. Inhibition of the tumour growth by lithium carbonate has been shown. Moreover, additional positive effects were observed as white blood cells were unaffected, superoxide dismutase activity was enhanced and lipid peroxidation was inhibited (Zhang et al. 1998). Moreover, a recent animal study pointed to a possible application of lithium for protection against side effects of the anti-neoplastic agent doxorubicin (Rahimi Balaei et al. 2010). On the contrary, Johnson et al. (2001) reported that lithium gamolenate should not to be recommended in cases of the pancreatic cancer.

Although lithium compounds have been used in medicine for more than sixty years, different aspects of their influence on organisms are still being

studied. Numerous new "targets" of Li action have been displayed, but the mechanism of lithium action remains unclear (Aghdam, Barger 2007, Bielecka, Obuchowicz 2008, Chiu, Chuang 2010, Zarse et al. 2011).

The inositol depletion hypothesis was one of the theories regarding the mechanism of action of lithium cations on organisms. Lithium inhibits the activity of inositol monophosphatase, which leads to a decrease in the brain myo-inositol level and subsequently to the downregulation of the phosphatidylinositol cycle (Agam et al. 2002). It was regarded to be the explanation of the positive Li action in psychiatric diseases (Brandish et al. 2005). Some studies have undermined this hypothesis (Berry et al. 2004), although the inositol theory is still taken into account (Chiu, Chuang 2010).

Observations regarding the proinflammatory cytokines interleukins IL-1β and IL-6, which play an important role in the immune system's functions and also affect the brain and neuroendocrine system, can contribute to the clarification of the mechanism of Li action. In LPS-stimulated monocytes of non-lithium-treated patients suffering from bipolar disorder, production ratio of these interleukins was found to be changed, whereas lithium treatment resulted in restoration of the aberrant ratio (Knijff et al. 2007).

Studies on the influence of lithium on the organism also revealed its effect on enzymatic activity (Gould, Manji 2005, Martins et al. 2008). Lithium can affect the activity of arachidonic acid cascade enzymes (Rapoport, Bosetti 2002) as well as nitrogen oxide synthase (Wegener et al. 2004) and the mitochondrial respiratory chain enzymes (Maurer et al. 2009).

Lithium treatment influences the neuronal transmission in a complex way (Pietruczuk, Witkowski 2008, Permoda-Osip, Rybakowski 2009). It was found to affect the serotonin neurotransmission by modifying the serotonin release and turnover. This fact was supposed to be connected with the ability of lithium to intensify the action of antidepressants (Birkenhäger et al. 2007, Scheuch et al. 2010).

Animal studies revealed that lithium can also affect levels of selected amino acids, causing their decrease in the brain (O'donnell et al. 2003) and kidneys (Hwang et al. 2010).

Interactions between lithium and bioelements seem to be another aspect of Li action in organism. Lithium was shown to increase significantly the serum calcium and phosphorus in rats, which seemed to result from bone demineralization and renal impairment (Sharma, Iqbal 2005). Dietary lithium was found to prevent aluminium storage in the cerebrum and cerebellum of rats subjected to Al-exposure (Bhalla, Dhawan 2009). Increase in the intracellular sodium level was suggested to be involved into the pathogenesis of bipolar disorder, while *in vitro* research showed that lithium decreased the ouabain-induced enhancement of the intracellular Na in human glial cells. The authors believed that their research results could contribute to a better understanding of the action mechanism of lithium (Huang et al. 2007).

Lithium treatment was also found to influence pro- and antioxidant pro-

cesses, which are believed to be involved in the pathogenesis of numerous illnesses. The results are inconsistent, as some studies have revealed that Li administration can affect the activity of antioxidant enzymes (Bhalla, Dhawan 2009, Al-Azemi et al. 2010), whereas others observed no influence of lithium on the activity of superoxide dismutase (Engin et al. 2005). In the cerebrum and cerebellum of rats exposed to aluminium, lithium treatment resulted in a significant depression of the lipid peroxidation, level of reactive oxygen species as well as activities of antioxidant enzymes such as superoxide dismutase and catalase (Bhalla, Dhawan 2009). The serum activity of the superoxide dismutase isoform Zn-Cu SOD was increased in cadmium -exposed rats receiving lithium orally, whereas animals with no cadmium Li treatment showed no significant effect (Al-Azemi et al. 2010). Some authors also stated that Li can inhibit lipid peroxidation processes (Shao et al 2005, Bhalla, Dhawan 2009, Al-Azemi et al. 2010). Contrary to that, an animal study carried out on Li-treated mice displayed an enhanced lipid peroxidation level in the liver (Nciri et al. 2009). Moreover, the lithium salt of cysteine was found to produce an antioxidant effect (Ovsepian et al. 2010)

Lithium may affect the metabolism of carbohydrates (Wiernsperger, Rapin 2010), as it was reported to show an insulin-like effect (De Almeida Souza et al. 2010). The hormonal balance, e.g. availability of thyroxin (Constantinou et al. 2005) as well as levels of luteinizing hormone, follicle stimulating hormone, prolactin and testosterone (Al-Azemi et al. 2010) were also reported to be subjected to the influence of lithium.

All the findings described above show that lithium is an element of great potential and that future investigations may bring to light surprising and entirely unexpected facts which will contribute to the elucidation of lithium action and allow new medical applications.

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