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Lithium in medicine – new aspects and attempts at application

Lithium, the lightest metal, known since 1817 is widely used in psychiatry (3, 5, 6, 7, 12, 14). The first attempts towards its medical application were made still in the 19th century but the great "career" of this element began in the middle of the 20th century (12) – the time when its positive effect in the cases of manic states was reported. From that time lithium has entered the pantheon of drugs.

In patients with affective disorders Li therapy exerts normothymic effect and significantly decreases the risk of suicide. In this group of subjects the suicide rate is higher than in general population. Li diminishes it 2.5–7 times. What's more, Li withdrawal is combined with the enhanced risk of suicide (3).

The beneficial impact of lithium in psychiatric subjects is known best of all, however, the new fields of its influence on organisms are still displayed, resulting in the growing interest of the possibilities of its other medical application, although in some parts the scientists' opinions are divergent (2, 4).

Lithium administration can cause different adverse effects, among other things the disturbances of digestive and cardiovascular system, kidneys, liver and thyroid as well as neurological and ECG abnormalities (3, 4, 5, 7). It can also exert teratogenic influence (3). The influence of Li on thyroid hormones' secretion was used in therapy of thyroid illnesses: metastatic carcinoma and Graves' disease. It was studied if Li could serve as an adjuvant to radioiodine (RAI) therapy (2, 4, 10). Lithium treatment was found to have a beneficial effect resulting from impeding the increase of thyroid hormone concentrations in serum observed after RAI treatment and enhancing RAI retention in thyroid gland (4). Bal et al. (2) undermined this conclusion, ascertaining that their works showed no positive effect of Li addition to RAI therapy in patients with hyperthyroidism. Li was also used in the cases of subjects suffering from metastatic thyroid carcinoma. Li_2CO_3 treatment to patients after near-total thyroidectomy, showing metastatic lesions, enhanced ^{131}I retention and accumulation in lesions. The beneficial influence was more significant in metastases displaying poor iodine retention (10).

Another study concerning the possibility of Li application in tumour therapy was performed on mice. The growth of two kinds of tumour (hepatoma H22 and sarcoma S180) was inhibited by Li_2CO_3 administration. The additional positive effect was no influence on white blood cells, the increment of superoxide dismutase activity and the decrease of lipid peroxidation (16). The trials towards administration of lithium gamolenate to patients with inoperable pancreatic cancer were performed. However, this compound occurred to be inefficient in such cases (9).

Lithium has a complicated insulin mimetic impact resulting from changes in activities of key enzymes in the glucose metabolism, affecting the intracellular glucose transport and from the influence on insulin receptors (8). In addition to the described observations the improving impact on impaired antioxidant barrier was shown (14).

Because of different side-effects of Li treatment the searching of the markers of its toxicity was conducted. The increases of urinary N-acetyl-β-glucoaminidase activity as well as Cu and protein levels were suggested to serve as indicators of Li-induced nephrotoxicity (5). Lithium level in serum cannot exceed the "safe" range. Because of no correlation between the dose and serum concentration

of this element the searching of early predictors of over-range Li level was performed. ECG abnormalities were shown to occur in this case so that ECG check-up was suggested to be useful in the monitoring of Li-therapy (7).

One of the newest advances is the application of lithium compounds in dermatology as topical drugs in the case of seborrhoeic dermatitis. Such treatment is safer due to limited Li percutaneous penetration which does not result in the increase of its plasma level. It lets this element be used even in renal insufficiency. However, such therapy during pregnancy is not recommended. It should be noticed that in psychiatry lithium is commonly administered in the form of carbonate, sulphate and citrate, whereas in dermatology succinate and gluconate were employed (13).

Another "new target" of lithium's action was discovered – it was shown to inhibit the activities of phosphatases. This effect results in the storage of toxic 3'-phosphadenosine 5'-phosphate (PAP) and is suggested to be responsible for Li-induced side-effects (15).

It is known that Alzheimer's disease has lately become a problem of great importance. In the neurodegeneration processes occurring in this disorder phosphorylated τ-protein and β-catenin play a significant role. Lithium was displayed to inhibit glycogen synthase kinase 3β which regulates the amounts of these substances. What's more, Li enhanced the level of neuroprotective protein Bcl-2. It is suggested that such outcomes could point to new possibilities of medical application of lithium (12). Not only τ-hiperphosphorylation but also the storage of β-amyloid peptide (Aβ) is characteristic of Alzheimer's disease. Li exerts a protective influence against neurons' death caused by Ab. It confirms the conclusions that Li therapy could be efficient in Alzheimer's disease (1). Other investigations also corroborate the neuroprotective and neurotrophic impact of lithium treatment. It results from many diverse actions, among other things up regulation of anti-apoptotic Bcl-2, reducing of brain infarction in an animal model of stroke, expressing of brain-derived neurotrophic factor as well as the depletion of both DNA damage and loss of neurons in Huntington's disease. It is interesting that in some part the similar effect is exerted by another mood stabilizer – valproate (6). Due to the presented observations Li-therapy is regarded as useful in the cases of brain diseases or acute injuries.

Studies displayed the existence of sodium-lithium counter transport (SLC) – the mechanism of ions' transport which causes the Na^+ penetration into the cell and Li^+ excretion outside. The erythrocyte SLC activity is suggested to be useful as a marker of genetic predisposition to nephropathy present in diabetes (11).

All studies reported above reveal that lithium is still the element of scientists' greater and greater interest and that future investigations can bring to light completely unexpected discoveries considering the mechanism of its action on organisms.

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SUMMARY

Lithium, an element discovered in 1817, has been used in medicine for more than fifty years. Its normothymic effect is known best of all and employed in affective disorders. However, the last years have brought the new outcomes, which have resulted in the attempts towards the application of Li compounds in other fields of medicine. The inhibiting lithium's influence on thyroid hormones' secretion made scientists try to use Li treatment as an adjuvant in the cases of thyroid gland diseases, although their opinions on the efficacy of such coadministration are divergent. Lithium exerts insulin-mimetic impact connected with restoring influence on antioxidant enzymes' level, which is usually decreased in diabetes. The new advance is also the application of lithium compounds as topic drugs in dermatology. This way of treatment reduces Li penetration into blood and the possibility of adverse effects. Li therapy can also influence the levels of τ-protein and β-catenin – two substances subserving the neurodegeneration in Alzheimer's disease. Li treatment can increase neuroprotective protein Bcl-2 level, diminish brain infarction in stroke as well as DNA damage and loss of neurons in Huntington's disease. For these reasons Li compounds could be effective in neurodegenerative diseases and acute brain injuries. The reported studies reveal that lithium is still the element of great interest and that future investigations on its impact on organisms could discover completely unexpected findings.

Lit w medycynie – nowe aspekty i próby zastosowania

Lit, pierwiastek odkryty w 1817 roku, od ponad 50 lat jest stosowany w medycynie. Najbardziej znane jest jego działanie normotymiczne wykorzystywane w terapii chorób afektywnych. Jednakże ostatnie lata przyniosły nowe odkrycia, które zainspirowały próby wykorzystania związków litu także w innych dziedzinach medycyny. Hamujący wpływ tego pierwiastka na sekrecję hormonów tarczycy skłonił do prób podawania go jako środka wspomagającego w terapii jodem radioaktywnym w przypadkach schorzeń gruczołu tarczowego, chociaż opinie na temat skuteczności takiej skojarzonej kuracji są podzielone. Lit wywierać może działanie insulinopodobne, tym korzystniejsze, że połączone z normującym wpływem na poziom enzymów antyoksydacyjnych, zwykle w przypadku cukrzycy obniżony. Do nowych osiągnięć zaliczyć należy miejscowe zastosowanie związków litu w dermatologii. Taka kuracja redukuje przenikanie Li do krwi, a co za tym idzie możliwość wystąpienia skutków ubocznych. Podawanie związków litu może także wpływać na poziom β-kateniny i białka τ - substancji, odgrywających rolę w procesach neurodegeneracyjnych występujących u pacjentów z chorobą Alzheimera. Terapia litem może także podwyższać poziom białka neuroochronnego Bcl-2, zmniejszać obszar mózgowej martwicy niedokrwiennej w przypadkach apopleksji, a także redukować uszkodzenia DNA i utratę neuronów w chorobie Huntingtona. Pozwala to na stwierdzenie, że związki Li mogłyby być skuteczne w przypadkach chorób neurodegeneracyjnych oraz ostrych urazów mózgu. Przedstawione wyniki badań wskazują na to, że lit znajduje się wciąż w kręgu zainteresowania, a przyszłość może przynieść zupełnie nieoczekiwane odkrycia, dotyczące mechanizmu jego działania na organizmy.