ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN—POLONIA
VOL. XXXVIII, 46 SECTIO D 1983

Zakład Farmakologii. Instytut Patologii Klinicznej. Akademia Medyczna w Lublinie
Kierownik: prof. dr hab. n. med. Zdzisław Kleinrok
Instytut Żywienia Zwierząt i Higieny. Akademia Rolnicza w Lublinie
Kierownik: prof. dr hab. Stanisław Wójcik

Zdzisław KLEINROK, Barbara CHMIELEWSKA,
Stanisław WÓJCIK

Influence of Lithium Salts on the Concentration of Some Elements in the Tissues of Rats and Chickens

Wpływ soli litu na zawartość niektórych pierwiastków w tkankach szczurów i kurcząt

Влияние солей лития на содержание некоторых химических элементов в тканях крыс и цыплят

Lithium, as a monovalent cation in the first group of periodic table, is similar to sodium and potassium in its essential chemical features. Also some common properties exist between lithium and bivalent cations from the second group of Mendeleev's table, especially calcium and magnesium (21).

The introduction of lithium salts to treatment (3, 26) and prophylaxis (24) of unipolar and bipolar mania and depression gave the impulse to numerous investigations aimed to elucidate the biological role and mechanism of the therapeutic action of lithium. Up to now the exact mechanism underlying the effectiveness of lithium has not been known. Substantial evidence suggests that lithium influenced neurotransmitters, especially, monoaminergic systems in CNS. Another interesting aspect of the lithium mode of action results from the fact that this element influences the activity of biologically important ions. There are still few data concerning this problem.

The present study was undertaken to find out the effect of prolonged administration of lithium salts on sodium, potassium, calcium, magnesium, copper, zinc and manganese concentration in the serum, brain, kidney and liver of chickens and rats.

MATERIALS AND METHODS

Male Wistar rats, weighing initally 204—224 g and Cornish-Whiterock chickens (approximately 950 g) were used. Body weight was controlled each day. The rats, randomly divided into four groups (10 animals in each group), were injected i.p.

once daily for 10 days with 25, 50 or 100 mg/kg LiCl (Chemapol, Praha, Czechoslovakia). Control group received vehicle only. The drug was given in the volume of 5 ml/kg of body weight. The animals had free access to water and food (standard pellets "Murigran", Poland).

The chickens, divided also into four groups of 8 birds each, were fed on standard diet DKA (ZPP, Poland) containing 2800 kcal/kg and had access to water *ad libitum*. During 28 days three experimental groups received respectively an addition of 0.1 g Li_2CO_3 (ZPF „Polfa", Poland), 0.5 g NaCl or 0.1 g Li_2CO_3+0.5 g NaCl in each 100 g standard food. Control group was similarly fed on diet without addition of salts.

On the last day of experiment samples of blood were taken from chicken-wing vein and the obtained serum was stored at —20°C. All animals were decapitated. Brains, kidneys and livers (in rats) were immediately removed, frozen at —20°C and subsequently homogenized in glass Potter homogenizer. A sample of 1 ml of homogenate or serum was joined with 6 ml of concentrated HNO_3 and 3 ml of 10% $HClO_4$ in Kjeldahl bulb. Bulbs were heated (approximately 2 hrs), up to clear solution.

Appropriate dilutions of the obtained mineralized liquids were prepared in bidistilled water and the concentration of sodium, potassium, calcium, magnesium, copper, zinc and manganese was determined using atomic spectrophotometry absorption method in Pye Unicam Fi-1009 apparatus. Student's *t*-test was used for the statistical evaluation of the results.

RESULTS

Prolonged administration of lithium chloride in a dose of 100 mg/kg lasting for ten consecutive days resulted in a marked diminution of increase of the rats' body weight. Smaller doses of this salt produced no marked differences in comparison to control (Table 1).

In the experiment performed on chickens a considerably lesser increase of body weight was noted after addition of 0.1% of Li_2CO_3 to the standard diet. Treatment with food containing 0.5% of NaCl had no significant effect on body mass as compared with control. Furthermore, sodium chloride when administered in combination with lithium carbonate seemed to block the effect produced by the latter. Simultaneous treatment with both salts led to an increase of body gain however lesser in comparison to control. Considerable differences of body gain were observed only in the group given lithium carbonate and the one treated with lithium carbonate in combination with sodium chloride (Table 2).

A marked enhancement of potassium and decrease of manganese level was observed in the rats' brains following prolonged administration of lithium chloride in a dose of 50 and 100 mg/kg. Calcium level was not characteristically altered.

Lithium chloride in all doses used, considerably decreased sodium concentration in the rat kidney. In the case of calcium the same effect was

Table 1. The influence of 10-days administration of lithium chloride on the body weight in rats ($N=10$)

Group	Treatment mg/kg i.p.	Mean body weight in g		Increase of body weight /x ±SE/
		before treatment	after 10-days	
C	placebo	207.5	246.5	39.0 ±2.7
I	LiCl 25	224.0	266.5	42.5 ±1.7
II	LiCl 50	204.5	237.5	33.0 ±2.6
III	LiCl 100	222.5	228.5	5.5 ±2.8*

* $p<0.05$ comp. with C.

Table 2. The influence of 28-days administration of lithium carbonate or sodium chloride on the body weight in chicken ($N=7$)

Group	Treatment	Mean body weight in g		Increase of body weight /x ±SE/
		before treatment	after 28-days	
C	standard diet	993	1556	563 ±42.5
I	standard diet with 0.1% Li_2CO_2	933	1241	308 ±58.0*
II	standard diet with 0.5% NaCl	966	1535	569 ±40.0
III	standard diet with 0.1% Li_2CO_3 and 0.5% NaCl	1046	1532	482 ±37.3**

* $p<0.05$ comp. with C. ** $p<0.05$ comp. with I.

significant when the highest dose of lithium salt was administred. An enhancement of manganese content was noted in the liver and higher doses of lithium chloride also produced an increase of potassium and copper level (Table 3).

In the experiment on birds fed on diet containing lithium carbonate an enhancement of potassium in the brain, a decrease of magnesium and copper in the kidney and an increase of calcium and magnesium concentrations in serum was observed.

Administration of the enhanced amount of sodium chloride led to an increase of sodium and depletion of copper and manganese in the kidney. A significantly higher level of calcium was simultaneously noted in serum. When the chickens were treated with diet containing lithium carbonate in combination with sodium chloride, smaller concentrations of sodium and potassium and higher of manganese were measured in the animal brains. Moreover, these salts given together produced an increase

Table 3. The influence of 10-days administration of lithium chloride on the tissue concentration of some elements in rats

	Group	Treatment	Concentration in μg/g fresh tissue /$\bar{x}$ ±SE/						
			Na	K	Ca	Mg	Cu	Zn	Mn
brain	C	placebo	1841.1 ± 50.2	2745.2 ±165.2	130.42 ±6.52	270.0 ±10.1	4.25 ±0.10	16.32 ±0.52	0.79 ±0.012
	I	LiCl 25	1772.4 ± 30.9	2589.4 ± 73.5	109.86 ±5.40	240.0 ±11.2	4.37 ±0.09	16.32 ±0.24	0.80 ±0.023
	II	LiCl 50	1826.4 ± 39.1	3252.6 ±168.3*	142.10 ±4.10	257.1 ±11.9	4.45 ±0.24	15.86 ±0.24	0.74 ±0.018*
	III	LiCl 100	1892.2 ± 59.3	3378.2 ±169.2*	152.62 ±8.86	248.5 ± 6.5	4.24 ±0.10	15.71 ±0.19	0.68 ±0.016*
kidney	C	placebo	2744.2 ±209.0	2463.2 ±279.3	97.60 ±1.74	295.3 ±11.6	1.15 ±0.04	24.10 ±0.67	1.24 ±0.041
	I	LiCl 25	2178.1 ± 57.6*	1938.4 ± 45.8	95.60 ±4.60	264.3 ± 8.1	1.12 ±0.05	24.66 ±0.34	1.18 ±0.041
	II	LiCl 50	2127.4 ± 52.1*	2064.2 ± 97.2	87.72 ±4.28	282.3 ±10.2	1.10 ±0.06	25.53 ±0.59	1.22 ±0.042
	III	LiCl 100	2067.2 ± 49.8*	2004.2 ±101.2	76.82 ±4.50**	277.5 ± 8.6	1.16 ±0.11	25.70 ±0.82	1.14 ±0.031*
liver	C	placebo	2708.2 ±184.0	1520.8 ± 88.0	28.02 ±1.82	176.3 ± 5.6	4.63 ±0.14	22.50 ±0.52	1.74 ±0.070
	I	LiCl 25	2392.2 ± 42.0	1775.4 ±193.5	24.06 ±1.88	177.2 ± 5.5	5.32 ±0.30	25.62 ±2.29	1.96 ±0.062*
	II	LiCl 50	2452.4 ± 62.2	1900.5 ± 93.0**	32.40 ±2.88	186.3 ± 7.1	5.28 ±0.17**	23.80 ±0.88	1.98 ±0.060*
	III	LiCl 100	2376.8 ± 58.2	1955.6 ± 35.0**	24.20 ±2.62	178.4 ± 9.5	5.25 ±0.20*	22.24 ±0.18	1.98 ±0.059*

* $p<0.05$ comp. with C. ** $p<0.01$ comp. with C.

Table 4. The influence of 28-days administration of lithium carbonate and natrium chloride on the tissue concentration of some elements in chickens

	Group	Treatment	Concentration in μg/g fresh tissue /$\bar{x}$ ±SE/						
			NA	K	Ca	Mg	Cu	Zn	Mn
brain	C	standard diet	1964.2 ±318.0	1790.4 ± 89.5	71.16 ±7.92	175.2 ± 6.2	3.11 ±0.26	10.64 ±0.24	0.47 ±0.016
	I	standard diet with 0.1% Li_2CO_3	1770.5 ±386.0	2375.8 ±134.0**	71.64 ±8.22	177.7 ± 5.4	2.80 ±0.25	10.60 ±0.59	0.44 ±0.038
	II	standard diet with 0.5% NaCl	1920.6 ±379.2	1790.4 ±101.0	59.74 ±4.82	151.8 ±16.2	2.33 ±0.22	10.54 ±0.54	0.45 ±0.007
	III	standard diet with 0.1% Li_2CO_3 and 0.5% NaCl	1144.4 ±154.0**	1495.2 ± 60.0**	71.76 ±6.18	163.8 ± 7.3	2.85 ±0.37	10.04 ±0.19	0.52 ±0.012**
kidney	C	standard diet	3440.2 ±230.0	1996.5 ± 82.0	82.05 ±4.35	229.5 ± 6.7	1.59 ±0.06	28.8 ±0.87	2.84 ±0.012
	I	standard diet with 0.1% Li_2CO_3	3800.4 ±370.0	2124.2 ± 66.0	87.90 ±2.76	188.4 ±12.7**	1.41 ±0.03*	27.6 ±1.10	2.56 ±0.080*
	II	standard diet with 0.5% NaCl	9760.2 ±1196.0**	1848.2 ± 80.8	78.90 ±3.63	220.7 ± 6.3	1.40 ±0.04*	25.7 ±1.15	2.37 ±0.020*
	III	standard diet with 0.1% Li_2CO_3 and 0.5% NaCl	5420.6 ±602.0**	1916.0 ±206.8	91.56 ±9.27	196.4 ±13.2*	1.37 ±0.07**	24.1 ±1.41*	2.43 ±0.018*
serum	C	standard diet	3265.2 ±375.7		81.0 ±6.02	12.60 ±0.9		1.66 ±0.22	
	I	standard diet with 0.1% Li_2CO_3	3130.1 ±338.3		118.5 ±8.16*	17.81 ±1.7*		1.54 ±0.30	
	II	standard diet with 0.5% NaCl	2730.2 ±184.2		119.2 ±4.20	13.92 ±0.7		1.24 ±0.17	
	III	standard diet with 0.1% Li_2CO_3 and 0.5% NaCl	2620.6 ±172.1*		119.6 ±5.3*	19.96 ±1.1**		1.31 ±0.01	

* $p<0.05$. ** $p<0.01$ comp. with C.

of sodium and diminution of manganese, copper and zincum contents in the kidney. In addition, decreased sodium level ad enhanced concentration of calcium and magnesium was estimated in the chicken serum (Table 4).

DISCUSSION

Numerous experimental studies confirmed the observations that duration and strength of drug action depends on reaction capacity with a specific receptor and the efficiency of effector (13). During binding reaction at receptor level, the competition of ionized amine group is observed between the electrostatically active drug and the identically charged electrolyte. If the reaction between the drug and receptor has an electrostatic nature, enhanced concentration of the surrounding electrolyte may be a factor limiting the binding. On the other hand, nonpolar connections between the drug and its receptor are facilitated at a high electrolyte concentration and attenuated at its low level. Another possibility is the reaction of drug with its receptor at the presence of nonorganic ion as a factor liberating binding process.

The foregoing considerations suggest the essential role of electrolytes in the mechanisms of the action of drugs. Studies in recent years have shown that the introduction of lithium salts into animal organism should alter receptor susceptibility and influence neuromediators (6, 8, 19, 20, 28, 29) and the effects of drugs (2, 4, 7, 9, 12, 25). Lithium has been also regarded as an essential substance in metabolic processes (23). One may connect the above effects with lithium ions activity per se, but the indirect influence of lithium on the balance of other cations should be also considered. One of the significant features of lithium activity seems to be its good penetration through biological membranes, using sodium canal (5, 14, 30). Therefore biological effects of lithium may be associated not only with its own activity but also with the influence on sodium (15, 18) and other cation (1, 30) contents. Interactions observed between other trace elements in animal tissues support such conception (11, 27).

The results of this study have shown that subchronic administration of lithium salts led to significant alterations in the content of some elements. Both in rats and in birds a considerable enhancement of potassium in the brain was measured, simultaneously with a diminution of manganese. In the kidney, a decrease of sodium and calcium was observed in rats while that of magnesium and copper in chickens. Higher concentrations of potassium, copper and manganese in samples of the rat liver, and calcium and magnesium in chicken serum were noted.

Several literature data suggest interactions between some trace elements, especially copper and zincum, zincum and cadmium, copper and molybdenum and also cadmium and copper (10, 27). Furthermore, investigations of Mellerup and Plenge (22) and Transbol et al. (30) produced considerable evidence for an increase of magnesium, copper and phosphate in the rat serum after lithium administration.

Alterations in the concentration of elements, indirectly influencing the activity of cells and tissues, should be taken into consideration as factors of the therapeutic and toxic mechanism of lithium action. It has been shown that isolated organs put into nutritive solution, in which lithium chloride or Tris buffer was introduced instead of sodium chloride or potassium chloride, revealed the altered susceptibility to acetylcholine, serotonine and noradrenaline (16, 17).

The results achieved in the experiment with birds very likely suggest that sodium salt given together with lithium attenuates the toxic effect of the latter. Moreover, considerable differences in cation content were revealed between the lithium group and the animals treated with both elements. These findings seem to indicate that not only lithium can displace other elements but it also can be displaced by other ions. Therefore, it is possible to consider sodium as an antidote in the case of lithium overdose.

It is suggested, on the basis of the obtained results, that in the mechanism of lithium action not only its direct influence on biological processes should be considered but also its indirect effects via alterations in electrolyte balance seems to play and essential role. This last effect is particularly important in the case of chronic treatment with lithium.

REFERENCES

1. Baer L., Kassir S., Fieve R. R.: Lithium-induced Changes in Electrolyte Balance and Tissue Electrolyte Concentration. Psychopharmakologia (Berlin) **17**, 216, 1970.
2. Berggren U. et al.: The Effect of Lithium on Amphetamine-induced Locomotor Stimulation. Psychopharmacology **59**, 41, 1978.
3. Cade J. F. J.: Lithium Salts in the Treatment of Psychotic Excitement. Med. J. Austr. **2**, 349, 1949.
4. Chouinard G. et al.: Potentation of Lithium by Tryptophan in a Patient wirt Bipolar Depression. Am. J. Psychiatry **136**, 719, 1979.
5. Ehrlich B. E., Diamond J. M., Gosenfeld L.: Lithium-induced Changes in Sodium-lithium Countertransport. Behav. Pharmacol. **30**, 2539, 1981.
6. Eroglu L., Binyildiz P., Atamer-Simsek S.: Lithium-Induced Changes in the Brain Levels of Free Aminoacids in Stress-exposed Rats. Psychopharmacology **70**, 187, 1980.

7. Furukawa T., Ushizima I., Ono N.: Modifications by Lithium of Behavioral Responses to Metamphetamine and Tetrabenazine. Psychopharmakologia (Berlin) **42**, 243, 1975.
8. Gottesfeld Z.: Effect of Lithium and Other Alkali Metals on Brain Chemistry and Behavior. I Glutamic Acid and GABA in Brain Regions. Psychopharmakologie (Berlin) **45**, 239, 1976.
9. Hermoni M. et al.: Chronic Lithium Prevents Reserpine-induced Supersensitivity of Adenylate Cyclase. J. Pharm. Pharmacol. **32**, 510, 1980.
10. Hill C. H., Matrone G.: Chemical Parameters in the Study of *in vivo* and *in vitro* Interactions of Transition Elements. Fed. Proc. **29**, 1474, 1970.
11. Hill C. H. et al.: *In vivo* Interactions of Cadmium with Copper, Zinc and Iron. J. Nutr. **80**, 227, 1963.
12. Ho A. K. S., Ho C. C.: Potentiation of Lithium Toxicity by Ethanol in Rats and Mice. Alcoholism: Clin. Exp. Res. **2**, 386, 1978.
13. Holmes W. C., Klein R. L., Briggs A. H.: Molekuläre Pharmakologie. G. Thieme Verl., Stuttgart 1967.
14. Janka Z., Jones D. G.: Indirect Ultrastructural Evidence for Lithium Uptake by Cultured Rat Cerebral Cells Trough Sodium Channel. Brain Res. **237**, 261, 1982.
15. Kersten L., Bräunlich H.: Verteilungs- und Eliminationsverhalten von Lithium bei jungen und erwachsenen Ratten nach akuter Zufuhr verschiedener anorganischer Kationen und Anionen. Acta biol. med. germ. **41**, 365, 1982.
16. Kleinrok Z., Czajka R., Oleszczuk J.: Wpływ chlorku litu na wrażliwość wyosobnionego jelita cienkiego i serca szczura na acetylocholinę, 5-hydroksytryptaminę i noradrenalinę. Ann. Univ. M. Curie-Skłodowska, Lublin, Sectio D **28**, 189, 1973.
17. Kleinrok Z., Czajka R., Oleszczuk J.: Wpływ zamiany chlorku potasu przez chlorek litu lub Tris na wrażliwość izolowanego jelita cienkiego szczura na acetylocholinę i 5-hydroksytryptaminę oraz izolowanego serca szczura na noradrenalinę. Ann. Univ. M. Curie-Skłodowska, Lublin, Sectio D **30**, 255, 1975.
18. Kleinrok Z. et al.: Investigations of Subchronic Toxicity and Some Pharmacological Properties of Lithium Chloride. Dissert. Pharm. Pharmacol. **23**, 439, 1971.
19. Knapp S., Mandell A. J.: Effects of Lithium Chloride on Parameters of Biosynthetic Capacity for 5-HT in Rat Brain. J. Pharmacol. Exp. Ther. **193**, 812, 1975.
20. Maggi A., Enna S. J.: Regional Alterations in Rat Brain Neurotransmitter System Following Chronic Lithium Treatment. J. Neurochem. **34**, 888, 1980.
21. Mellerup E. T., Jörgensen O. S.: Basic Chemistry and Biological Effects of Lithium. [in:] Lithium Research and Therapy. Ed. Johnson, Academic Press, London 1975.
22. Mellerup E. T., Plenge P.: Lithium Effects on Magnesium, Calcium and Phosphate Metabolism in Rats. Int. Pharmacopsychiatr. **11**, 190, 1976.
23. Plenge P.: Lithium Effects on Rat Brain Glucose Metabolism in Long-term Lithium Treated Rats Studied *in vivo*. Psychopharmacology **59**, 317, 1978.
24. Prien R. J.: Lithium in the Prophylactic Treatment of Affective Disorders. Arch. Gen. Psychiatry **36**, 847, 1979.

25. Rosenblatt J. E. et al.: The Effect of Imipramine and Lithium on α and β Receptor Binding in Rat Brain. Brain Res. **160**, 186, 1979.
26. Schou M. et al.: The Treatment of Manic Psychoses by the Administration of Lithium Salts. J. Neurol. Neurosurg. Psychiatry **17**, 250, 1954.
27. Schroeder H. A., Nasou A. P.: Interactions of Trace Metals in Rat Tissues. Cadmium and Nickel with Zinc, Chromium, Copper, Manganese. J. Nutr. **104**, 167, 1974.
28. Segawa T., Nakano M.: Brain Serotonin Metabolism in Lithium-treated Rats. Jap. J. Pharmacol. **24**, 319, 1974.
29. Stefanini E. et al.: Effect of Lithium on Dopamine Uptake by Brain Synaptosomes. J. Neurochem. **27**, 1237, 1976.
30. Transbol J. et al.: Endrocrine Effects of Lithium. III Hypermagnesaemia and Activation of the Renin-angiotensin System. Acta Endocrin. **88**, 619, 1978.

Otrzymano 12 II 1983.

STRESZCZENIE

W doświadczeniach prowadzonych na szczurach Wistar oraz kurczętach Cornish-Whiterock badano wpływ przewlekłego stosowania chlorku i węglanu litu na zawartość niektórych pierwiastków w wybranych tkankach. Metodą spektrofotometrii absorbcji atomowej stwierdzono istotne zmiany zawartości sodu, potasu i magnezu w mózgu, sodu, wapnia, magnezu, miedzi i manganu w nerce, potasu, miedzi i manganu w wątrobie oraz sodu, wapnia i magnezu w surowicy. Równocześnie obserwowano istotne zmniejszenie przyrostu masy ciała szczurów otrzymujących chlorek litu oraz kurcząt w następstwie stosowania węglanu litu. Łączne stosowanie z węglanem litu chlorku sodu powoduje istotne zmniejszenie efektu wywieranego przez lit.

РЕЗЮМЕ

В экспериментах проведенных на крысах Wistar и на цыплятах Cornish-Whiterock исследовано влияние хлористого и углекислого лития на содержание некоторых химических элементов в избранных тканях. Спектрофотометрическим методом атомной абсорбции доказано достоверные изменения содержания натрия, калия и магнезия в мозге; натрия, кальция, магнезия, меди и марганца в почке; калия, меди и марганца в печени и натрия, кальция и магнезия в сыворотке. Одновременно замечено достоверное уменьшение прибавки в весе крыс получавших хлористый литий и цыплят в наследствии применения углекислого лития. Совместное применение углекислого лития с хлористым натрием вызывало у цыплят достоверное уменьшение эффекта вызванного литием.

ANNALES UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA

Nakład 600 egz.+25 nadb., ark. wyd. 27, ark. druk. 23+56 str. wkl. kred. Papier druk. sat. kl. III, B1 80 g. Oddano do składania w styczniu 1984 r., podpisano do druku w grudniu 1986 r., wydrukowano w styczniu 1987 r. Cena zł 270,—

Tłoczono w Drukarni UMCS w Lublinie, zam. nr 1/84

ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN—POLONIA
VOL. XXXVII SECTIO D 1982

ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN—POLONIA
VOL. XXXVII SECTIO D 1982

Adresse:

UNIWERSYTET MARII CURIE-SKŁODOWSKIEJ
BIURO WYDAWNICTW
Plac Marii
Curie-Skłodowskiej 5 20-031 LUBLIN POLOGNE

Cena zł 270,—