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The influence of different doses of lithium administered to rats in drinking water on calcium homeostasis

Although lithium has been applied in medicine for half a century (1, 2) the mechanism of its action still remains unclear (3). Studies revealed lithium's influence on plenty of metabolic processes (4–6). Among other things it was found out that lithium may affect bioelements' metabolism (7–10). Most of all lithium compounds are used in cases of psychiatric diseases. Disturbances of macro- and microelements homeostasis in psychiatric patients were reported (11–13).

Calcium belongs to essential bioelements and its homeostasis can be influenced by the content of diet (10) or drugs' administration (2, 7). Mutual relationships between Li and Ca were reported (3, 13).

Our previous studies showed that lithium administration may influence calcium storage in rats (8). This work was performed with the aim of specifying the influence of different doses of lithium administered in drinking water on calcium concentration in plasma and chosen tissues of rats. The low and middle doses were established in the way corresponding with those used in medicine, whereas the higher ones were comparable with the overdosing.

MATERIAL AND METHODS

The experiment was carried out on two-month-old male Wistar rats (180–220 g), divided into seven groups (six animals each). Six tested groups were given water solutions of lithium carbonate (Li_2CO_3) as the only drinking fluids. Concentrations were established as follows: group I – 0.7; group II – 1.4; group III – 2.6; group IV – 3.6; group V – 7.1 and group VI – 10.7 mmol $Li^+ \cdot dm^{-3}$. Control group received redistilled water. Rats had free access to standard feed LSM and drinking fluids. After eight weeks the animals were sacrificed under ketamine narcosis and the blood from the heart as well as tissues of liver, kidney, brain, femoral muscle and heart muscle was collected. Plasma was separated. Tissue homogenates (10% w/v) were prepared in 0.1 mol $\cdot dm^{-3}$ Tris - HCl buffer, pH = 7.4 and supernatants were obtained by centrifugation at 5000 x g for 30 min. The prepared material was stored at the temperature –20°C.

In plasma and supernatants calcium concentration was measured by the reaction with o-cresolophtalein (diagnostic set Liquick Cor-CALCIUM 120), using colorimetric method. Wave length was 575 nm. The assays were carried out with the help of SPECORD M40 (Zeiss Jena) spectrophotometer. Comparisons between control and tested groups were made using the Cochran-Cox test. Values were considered significant at $p < 0.05$. The correlations between Li concentration

in administered solutions and Ca tissue concentration were estimated with the help of the Pearson test.

The study was approved by I Local Ethical Commission of the Medical University of Lublin, acceptance 435/2003.

RESULTS

Lithium administration caused no significant changes of calcium concentration in plasma. On the contrary, in all the studied tissues Ca content was found to be decreased. In liver, brain and femoral muscle the decrease was significant. In kidney only the high doses caused a significant Ca decrement, whereas in heart muscle the observed changes were insignificant (Table 1).

Analysis of correlations between Li concentration in provided solutions and tissue Ca concentration displayed the existence of negative correlations in kidney r = –0.588 (Fig. 1) and in femoral muscle r = – 0.538 (Fig. 2).

Table 1. Calcium concentration in plasma and tissues of rats provided with lithium in drinking water

Group	Ca (mmol · dm^{-3})	Ca (μmol · g^{-1} of wet tissue)				
	plasma	liver	kidney	brain	femoral muscle	heart muscle
	$\overline{x}$ ± SD	$\overline{x}$ ± SD	$\overline{x}$ ± SD	$\overline{x}$ ± SD	$\overline{x}$ ± SD	$\overline{x}$ ± SD
K	2.11 ± 0.29	5.2 ± 0.9	3.4 ± 0.6	3.2 ± 0.5	2.6 ± 0.3	3.0 ± 0.5
I	2.37 ± 0.31	1.5 ± 0.8 *↓	2.9 ± 0.5	2.0 ± 0.4 *↓	2.0 ± 0.2 *↓	2.9 ± 0.6
II	2.20 ± 0.30	1.4 ± 0.4 *↓	2.8 ± 0.6	2.1 ± 0.4 *↓	1.8 ± 0.3 *↓	2.9 ± 0.4
III	2.08 ± 0.24	1.4 ± 0.5 *↓	2.5 ± 0.4	2.0 ± 0.4 *↓	1.8 ± 0.3 *↓	2.6 ± 0.7
IV	2.10 ± 0.25	1.1 ± 0.4 *↓	2.3 ± 0.7	1.8 ± 0.7 *↓	1.7 ± 0.2 *↓	2.4 ± 0.3
V	2.19 ± 0.31	1.1 ± 0.6 *↓	2.2 ± 0.3 *↓	1.9 ± 0.6 *↓	1.7 ± 0.4 *↓	2.1 ± 0.4
VI	2.01 ± 0.28	1.2 ± 0.5 *↓	2.0 ± 0.4 *↓	1.6 ± 0.4 *↓	1.5 ± 0.4 *↓	2.0 ± 0.6

Values are mean ± standard deviation

* Statistical significance vs. control $p < 0.05$

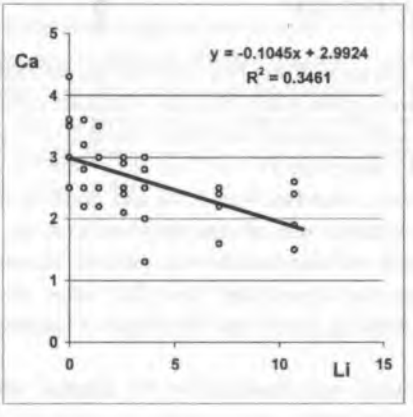

Fig. 1. The negative correlation between Li concentration in administered fluids and Ca concentration in kidney

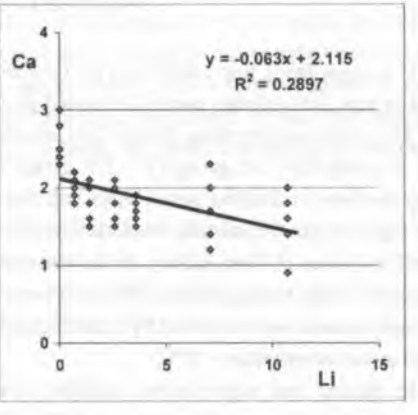

Fig. 2. The negative correlation between Li concentration in administered fluids and Ca concentration in femoral muscle

DISCUSSION

Our experiments reveal that the influence of lithium on Ca homeostasis in rats depends on the applied dose. The high concentration (21.4 mmol $Li^+ \cdot dm^{-3}$), administered during three or six weeks resulted in a significant increase of serum Ca, although the degree of this effect decreased with the lengthening of the time of exposure. In most tissues Ca content was not markedly altered, except for kidney and brain (8). The present study revealed that administration of lower lithium concentrations caused the depletion of tissue Ca accompanied by no changes of calcium concentration in plasma. It should be underlined that while in the present work the animals displayed no morbid symptoms, those given 21.4 mmol $Li^+ \cdot dm^{-3}$ showed symptoms of lithium toxicity.

Such outcomes are partially consistent with other scientists' results. Carney and Jackson found out that acute lithium intoxication caused no changes in calcium plasma concentration in rats accompanied with increased urine excretion of this element (4). Chaudhuri-Sengupta et al. in turn revealed that lithium's effect on serum Ca depended on the time of exposure and the age of animals. Juvenile (30-day-old) and aged (3-year-old) rats showed increased serum Ca after long-term treatment and unchanged after short-term intoxication. Adult (100-day-old) rats showed enhanced calcium concentration in serum irrespectively of the time of administration (5). Lithium nitrate given to rats caused a significant increase of calcium concentration in serum (9). Tandon et al. observed a statistically significant depletion of hepatic Ca content in rats receiving lithium in diet (10).

Hyperparathyroidism associated with hypercalcaemia is known to be the possible consequence of lithium therapy (2, 6). A case of a patient treated with lithium, showing hypercalcaemia and normal urine Ca^{2+} excretion was described (7). Other authors described in turn the case of a patient who showed hyperparathyroidism associated with low urinary calcium excretion (10). Studies carried out on rats revealed that acute lithium administration inhibited PTH-mediated reabsorption of Ca^{2+} in kidney and this effect was noticed when Li plasma concentration was high (4). Having regarded the presented observations we suggest that monitoring of plasma Ca^{2+} does not seem to be an efficient method to evaluate the effects of lithium treatment.

CONCLUSIONS

1. Lithium administered in drinking water caused a decrease in calcium content in rats' tissues associated with no changes of plasma Ca.
2. The existence of negative correlations between lithium concentration in administered fluids and calcium concentration in kidney and femoral muscle was shown.
3. The monitoring of plasma calcium in patients undergoing lithium therapy does not seem to be an efficient method to evaluate the effects of lithium treatment.

REFERENCES

1. Engin A. et al.: Erythrocyte glutathione levels in lithium-induced hypothyroidism. Drugs R D, 6, 35, 2005.
2. Pieri-Balandraud N. et al.: Hyperparathyroidism and lithium therapy. A new case. Rev. Med. Interne, 22, 460, 2001.
3. Corbella B., Vieta E.: Molecular targets of lithium action. Acta Neuropsychiatrica, 15, 316, 2003.

4. Carney S., Jackson P.: Acute lithium administration impairs the action of parathyroid hormone on rat renal calcium, magnesium and phosphate transport. Clin. Exp. Pharmacol. Physiol., 25, 795, 1998.
5. Chaudhuri-Sengupta S. et al.: Lithium action on adrenomedullary and adrenocortical functions and serum ionic balance in different age-groups of albino rats. Arch. Physiol. Biochem., 111, 246, 2003.
6. Hundley J. C. et al.: Revisiting lithium-associated hyperparathyroidism in the era of intraoperative parathyroid hormone monitoring. Surgery, 138, 1027, 2005.
7. Khandwala H. M., Van Uum S.: Reversible hypercalcemia and hyperparathyroidism associated with lithium therapy: case report and review of literature. Endocr. Pract., 12, 54, 2006.
8. Kiełczykowska M. et al.: The influence of lithium on calcium and magnesium homeostasis in serum and tissues of rats. Annales UMCS, Sectio D, 58, 281, 2003.
9. Sharma S. D., Iqbal M.: Lithium induced toxicity in rats: a hematological, biochemical and histopathological study. Biol. Pharm. Bull., 28, 834, 2005.
10. Tandon A. et al.: Effect of lithium on hepatic and serum elemental status under different dietary protein regiments. Biol. Trace Elem. Res., 68, 51, 1999.
11. Nechifor M.: Involvement of some cations in major depression. Metal Ions in Biology and Medicine. John Libbey Eurotext, 8, 518, Paris 2004.
12. Nechifor M. et al.: The influence of some antipsychotics on erythrocyte magnesium and plasma magnesium, calcium, copper and zinc in patients with paranoid schizophrenia. J. Am. Coll. Nutr., 23, 549S, 2004.
13. Suzuki K. et al.: Effects of lithium and valproate on agonist-induced platelet intracellular calcium mobilization: relevance to myosin light chain kinase. Prog. Neuropsychopharmacol. Biol. Psychiatry, 28, 67, 2004.
14. Vannucchi G. et al.: Radioiodine treatment of non-toxic multinodular goitre: effects of combination with lithium. Eur. J. Nucl. Med. Mol. Imaging, 32, 1081, 2005.
15. Ulrich M. L et al.: Effects of dextroamphetamine, lithium chloride, sodium valproate and carbamazepine on intraplatelet Ca^{2+} levels. J. Psychiatry Neurosci., 28, 115, 2003.

SUMMARY

The experiment was performed with the aim of determining the effect of different doses of lithium administered in drinking water on calcium concentration in plasma and tissues of rats. For a period of eight weeks rats received water solutions of Li_2CO_3. The concentrations were established as follows: 0.7; 1.4; 2.6; 3.6; 7.1; 10.7 mmol $Li^+ \cdot dm^{-3}$. In plasma and tissue supernatants calcium concentration was measured using the colorimetric method. Lithium treatment resulted in no changes of calcium concentration in plasma, whereas in tissues Ca content was found to be decreased. In liver, brain and femoral muscle the decrease was statistically significant. In kidney the administration of higher doses resulted in a significant Ca depletion, whereas in heart muscle none of the used doses exerted a significant influence. Negative correlations between Li dose and tissue Ca concentration in kidney ($r = -0.588$) and in femoral muscle ($r = -0.558$) were found. The lack of changes of Ca concentration in plasma does not correspond with lithium's influence on Ca content in tissues. For this reason we suggest that monitoring of plasma calcium does not seem to be an efficient method to evaluate the effects of lithium treatment.

Wpływ różnych dawek litu podawanego szczurom w wodzie pitnej na homeostazę wapnia

Doświadczenie zostało przeprowadzone w celu określenia wpływu różnych dawek litu podawanego w wodzie pitnej na stężenie wapnia w osoczu i tkankach szczurów. Przez okres ośmiu tygodni szczurom podawano wodne roztwory Li_2CO_3, których stężenia wynosiły: 0.7; 1.4; 2.6; 3.6; 7.1; 10.7 mmol $Li^+ \cdot dm^{-3}$. W osoczu i homogenatach tkankowych oznaczono metodą kolorymetryczną stężenie wapnia. Podawanie litu nie spowodowało zmian stężenia wapnia w osoczu, natomiast w tkankach zaobserwowano obniżenie zawartości wapnia. W wątrobie, mózgu i mięśniu uda obniżenie było znaczące statystycznie. W tkance nerki jedynie wyższe dawki spowodowały znaczące obniżenie, natomiast w mięśniu sercowym nie zanotowano istotnych zmian. Zaobserwowano ujemne korelacje pomiędzy stężeniem litu w podawanych roztworach a tkankowym stężeniem wapnia w nerce ($r = -0.588$) i w mięśniu uda ($r = -0.558$). Brak zmian stężenia wapnia w osoczu nie odzwierciedla wpływu litu na zawartość wapnia w tkankach. Pozwala to wnioskować, że monitorowanie stężenia wapnia w osoczu u pacjentów przyjmujących lit nie jest wystarczająco dobrą metodą pozwalającą na ocenę efektów terapii litowej.