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Department of General Chemistry, Medical University of Lublin
Medicine of Work Centre, Gniezno

MAŁGORZATA KIEŁCZYKOWSKA, ANNA HORDYJEWSKA, ANNA LEWANDOWSKA, MAŁGORZATA SZTANKE, KAZIMIERZ PASTERNAK, WŁODZIMIERZ BULIKOWSKI

The influence of different doses of lithium administered in drinking water and exposure time on concentrations of chosen bioelements in rats' skin

Lithium, the lightest of the metals has been known from the beginning of the 19th century. It occurs in rocks, soils, mineral and salt waters (8). For more then fifty years it has been used in medicine (7, 8, 9, 15). However, lithium treatment can also exert a negative influence (4, 8, 15). Studies demonstrate very diverse metabolic effects of lithium administration. The protective influence of Li supplementation on insulin-secreting pancreatic islet cells and on the action of antioxidant barrier in diabetic rats was displayed. It was accompanied by the restoration of lithium content in the tissues of liver and muscle (6). Lithium plus pilocarpine treatment results in the status epilepticus, which causes biochemical changes in brain, particularly in frontal cortex (5) The maintenance of the correct level of essential bioelements is very important for organisms. The disturbances in macro- and microelements homeostasis lead to very severe disorders (1, 11). What is more, the changes of bioelements' concentration can influence other elements' level through mutual interactions (14). Lithium presence affects the transport of Ca^{2+} and Mg^{2+} ions through membranes (8) and the concentrations of these elements in serum and tissues of rats (7). Serum is most often used in diagnostic investigations; however, it should be noticed that bioelements' concentration in serum does not always reflect their content in tissues. The AAS method has made it possible to determine the tissue level of elements (13). The skin is the tissue which separates the organism from the environment but some substances can be exchanged through its mediation. All the displayed facts and a wider and wider application of lithium in medicine urged us to undertake the investigations on the influence of lithium administration in drinking water on the calcium, magnesium, copper and zinc concentration in rats' skin.

MATERIAL AND METHODS

The investigation was carried out on two-months-old male Wistar rats, divided into seven groups of twelve animals each. Six groups were given the lithium carbonate water solutions as the only drinking fluids at the doses of 0.7, 1.4, 2.6, 3.6, 7.1 and 10.7 mmol of Li^{+}/dm^{-3}. The seventh group was the control group and received redistilled water. The LSM food and administered fluids were offered ad libitum. A half of animals of each group were killed after four weeks and the rest after eight weeks. The animals were killed under ketamine narcosis and the skins with fur were collected together with blood and tissues. The skins were kept at the temperature of 0–4°C and then dried at the temperature of 22°C with relative humidity of 56% for 24 h (2). Next the skins were rinsed in Wacker drums in redistilled water at the temperature of 25° and dried for 24h at the temperature of 25°C against air flow 0.2–0.8 m/s. After drying, the skins were cut into pieces and incinerated at the temperature of 550°C for 2h. The obtained white ash was dissolved in 25 ml of 2M HCl and the chosen bioelements were assayed by AAS method with the help of atomic absorption spectrophotometer AAS-3 (10). Magnesium and calcium were measured in the presence of strontium chloride correction buffer. The wave lengths were 285.2 nm and 422.7 nm, whereas the slit widths were 0.2 mm and 0.5 mm, respectively. For Zn and Cu wave lengths were 213.9 nm and 324.8 nm, whereas the slit widths were 0.2 mm and 0.3 mm, respectively. Comparisons between control and tested groups were made using t-Student tests. Values were considered significant at $p < 0.05$.

RESULTS

The lithium treatment resulted in changed essential bioelements' concentration in skin of rats provided with different doses of lithium.

In the case of copper we obtained the dose-dependent increment of Cu level vs. control. The lengthening of time exposure caused the decrease of Cu concentration in all tested groups and the control one, although this depletion was less in Li administered groups (Table 1, Fig. 1). The changes of zinc concentration vs. control were more diverse but it should be noticed that the Zn level increased during the experiment in the control group and in those receiving lower doses of Li, whereas in the case of animals treated with higher doses the tendency to stabilization was observed (Table 1, Fig. 2).

Table 1. Cooper and zinc concentrations in skin of rats exposured to different doses of lithium

Lithium dose (mmol/l)	Cu (µg/g of skin)		Zn (µg/g of skin)	
	after 4 w. x ± SD	after 8 w. x ± SD	after 4 w. x ± SD	after 8 w. x ± SD
control	6.5 ± 1.2	3.7 ± 0.9	155.0 ± 15.7	358.0 ± 36.8
0.7	7.0 ± 0.9	5.3 ± 0.8	171.2 ± 13.3	205.7 ± 24.7*
1.4	7.5 ± 0.8	6.4 ± 1.1*	128.4 ± 14.9	302.5 ± 36.5
2.6	7.9 ± 0.6	6.9 ± 0.8*	254.8 ± 27.1*	449.5 ±40.7*
3.6	9.0 ± 0.9*	7.6 ± 0.5*	225.5 ± 24.3*	237.5 ± 35.8*
7.1	10.5 ± 1.2*	7.9 ± 0.8*	182.1 ± 13.4	266.4 ± 17.2*
10.7	10.8 ± 0.7*	8.4 ± 1.1*	223.6 ± 25.6*	213.4 ± 14.8*

x – arithmetic mean, SD – standard deviation; values are mean ± SD of six rats

* Statistical significance vs. control $p < 0.05$

With regard to macroelements a dose-dependent increase of Mg concentration vs. control and a decrease of Ca concentration vs. control were observed. The lengthening of time exposure resulted in Mg increment and Ca depletion in all the groups. It agrees with the fact that these two elements are antagonists (Table 2, Fig. 3 and 4).

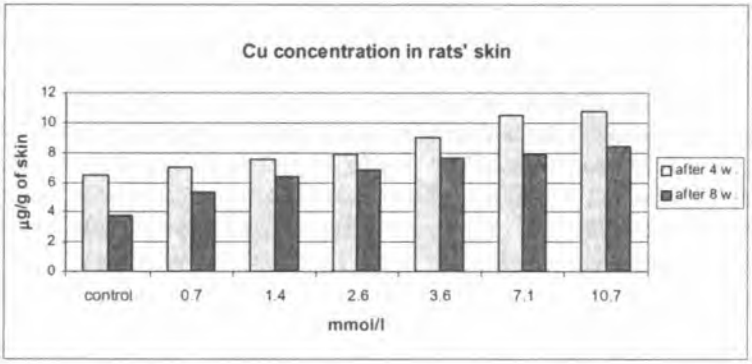

Fig. 1. Copper concentration in skin of rats exposured to different doses of lithium

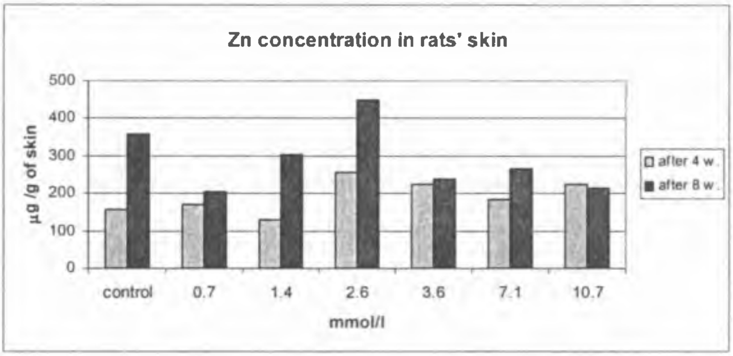

Fig. 2. Zinc concentration in skin of rats exposured to different doses of lithium

Table 2. Magnesium and calcium concentrations in skin of rats exposured to different doses of lithium

Lithium dose (mmol/l)	Mg (µg/g of skin)		Ca (µg/g of skin)	
	after 4 w. x ± SD	after 8 w. x ± SD	after 4 w. x ± SD	after 8 w. x ± SD
control	160.6 ± 19.0	200.5 ± 21.0	174.1 ± 14.2	110.1 ± 12.4
0.7	171.4 ± 15.7	245.8 ± 28.6	167.0 ± 12.4	89.2 ± 10.6
1.4	180.2 ± 19.4	271.5 ± 19.6*	146.3 ± 19.2	82.9 ± 9.3*
2.6	184.5 ± 11.3	282.8 ± 24.7*	128,1 ± 10.6*	68.7 ± 8.2*
3.6	202.3 ± 14.4*	312.6 ± 28.9*	94.9 ± 9.6*	61.3 ± 9.4*
7.1	219.9 ± 29.6*	341.9 ± 25.9*	78.7 ± 8.2*	52.8 ± 7.8*
10.7	240.5 ± 18.0*	357.4 ± 29.8*	71.6 ± 11.8*	40.9 ± 8.8*

x – arithmetic mean, SD – standard deviation; values are mean ± SD of six rats

* Statistical significance vs. control $p < 0.05$

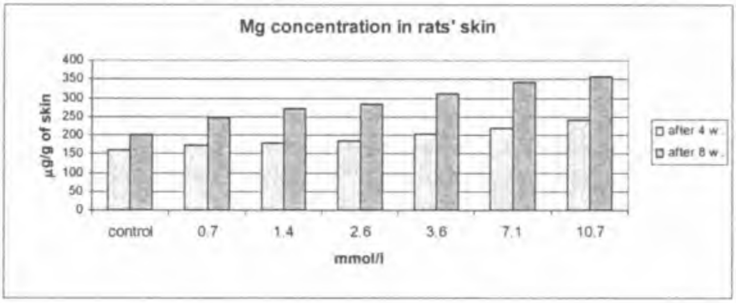

Fig. 3. Magnesium concentration in skin of rats exposured to different doses of lithium

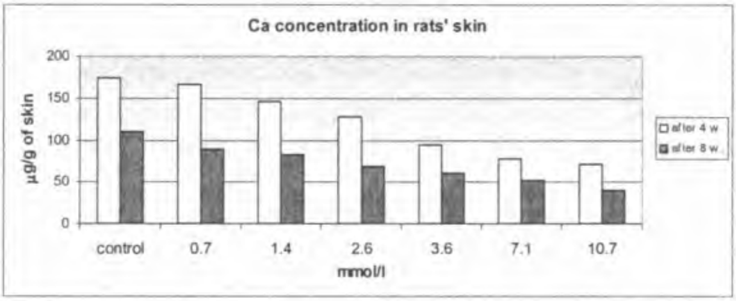

Fig. 4. Calcium concentration in skin of rats exposured to different doses of lithium

DISCUSSION

There are not many studies on the concentration of essential bioelements in skin of animals exposured to different metals. Bulikowski et al. revealed the protective effect of magnesium supplementation on chromium concentration in skin of rats receiving intraperitoneally $K_2Cr_2O_7$ (3). Pasternak et al. investigated the influence of zinc and copper administration in food on macro- and microelements' concentration in rats' skin. The Cu supplementation resulted in dose-dependent depletion of Ca and Zn level. In the case of Mg the decrease was also observed, but it did not depend on the dose. Cu skin deposit showed a dose-dependent increase. The zinc supplementation caused no changes in Mg and Cu concentrations, the decrease of Ca level and dose-dependent increase of Zn deposit (14).

The same authors studied the impact of lead intoxication on the concentrations of bioelements in rats' skin. As a consequence of Pb administration in drinking water the unchanged skin Mg and dose-dependent decrease of skin Ca were displayed. Zn content was diminished in a dose-dependent way, whereas Cu was enhanced in the group receiving the lower dose (100 pm) and it was unchanged in the one provided with the higher dose (300 ppm) (12).

Kiełczykowska et al. investigated the Mg and Ca concentrations in serum and tissues of rats receiving lithium at the dose of 21 mmol Li^+/dm^{-3} in drinking water for the periods of three or six weeks. Ca decreased in serum, brain and femoral muscle during the experiment. Ca concentration vs. control was diminished in brain after six weeks and in heart muscle after three and six weeks (7). Tandon et al. studied the concentrations of bioelements in liver of rats given Li_2CO_3 at the dose of 1.1 g/kg of diet. Li treatment resulted in the decrease of Zn, Cu and Ca concentration in rats' liver (15). In our experiment we observed the depletion of skin Zn concentration vs. control in the groups receiving

Li for the period of eight weeks. Skin Ca concentration was diminished in all the groups, both in dependence on the dose and on the time. After eight weeks we observed a significantly increased magnesium concentration in skin of rats provided with lithium. This fact agrees with the previous observations revealing that lithium causes magnesium retention in organism (9).

Concluding, we can ascertain that in some part our observations confirm the previous investigations on the lithium impact on bioelements' concentration in organism. Few studies on the essential metals' level in the skin of animals subjected to different metals' exposure make us suggest that it could be useful to continue the work concerning these problems.

CONCLUSIONS

1. Lithium carbonate treatment influenced essential bioelements' concentration in rats' skin.
2. In relation to microelements in the case of Cu skin concentration the dose dependent increase and the time dependent depletion were observed. In the case of Zn skin content changed in diverse way.
3. Macroelements' skin concentration showed time- and dose-dependent tendency to increment in the case of magnesium and to depletion with regard to calcium.

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SUMMARY

Lithium compounds occur in the environment and are used in medicine. Their administration may cause side effects, among other things disturbances in essential bioelements' homeostasis. The skin is the tissue which separates organisms from the environment but some substances are exchanged through its mediation. This is why we studied the influence of lithium carbonate administration in drinking water on concentrations of chosen microelements (Cu and Zn) and macroelements (Mg, Ca) in rats' skin. In the case of Cu and Mg we observed a dose-dependent increase vs. control. During the experiment Mg level in all the groups was enhanced, whereas Cu level diminished. The skin Ca showed time- and dose-dependent depletion. In the case of Zn the obtained changes were diverse but it should be noticed that the lenghtening of exposure time resulted in the increased skin Zn in control group and in groups receiving lower doses of Li. On the other hand, in the groups provided with higher Li doses a tendency to stabilization was observed.

Wpływ różnych dawek litu podawanego w wodzie pitnej oraz czasu ekspozycji na stężenie wybranych biopierwiastków w skórze szczurów

Związki litu występują w przyrodzie i są stosowane w medycynie. Ich przyjmowanie może powodować niekorzystne skutki uboczne, między innymi zaburzenia homeostazy podstawowych biopierwiastków. Skóra jest tkanką oddzielającą organizm od otoczenia, ale niektóre substancje mogą być wymieniane za jej pośrednictwem. Dlatego podjęliśmy badania nad wpływem podawania węglanu litu w wodzie pitnej na stężenie wybranych mikro- (Cu, Zn) i makropierwiastków (Mg, Ca) w skórze szczurów. W przypadku miedzi i magnezu obserwowaliśmy zależny od dawki wzrost stężenia w stosunku do grupy kontrolnej. Podczas eksperymentu poziom Mg we wszystkich grupach uległ podwyższeniu, a miedzi obniżeniu. Stężenie wapnia w skórze wykazało obniżenie, zależne zarówno od dawki, jak i od czasu ekspozycji. W przypadku cynku obserwowane zmiany były bardziej różnorodne, ale należy zauważyć, że przedłużanie czasu ekspozycji spowodowało podwyższenie stężenia Zn w grupach kontrolnej i otrzymujących niższe dawki Li. Natomiast w grupach narażonych na wyższe dawki Li zaobserwowano tendencję do stabilizacji.