Oral administration of lithium increases tissue magnesium contents but not plasma magnesium level in rats

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Abstract:
The aim of this work was to determine the influence of different doses of lithium on magnesium concentration in plasma and tissues of rats. For a period of eight weeks rats had been provided with aqueous solutions of Li\textsubscript{2}CO\textsubscript{3} whose concentrations were established as follows: 0.7; 1.4; 2.6; 3.6; 7.1; 10.7 mmol Li\textsubscript{2}l\textsuperscript{1}. Magnesium concentration was determined in plasma and tissue supernatants. Lithium caused no changes in magnesium concentration in plasma, whereas Mg concentration in tissues was found to be enhanced, although the degree of the increment depended on the studied tissue. In the liver, brain and heart muscle, the increase was statistically insignificant vs. control. In the kidney, the higher Li doses were required to result in the significant Mg enhancement, whereas in femoral muscle all the used doses caused well-marked Mg increase vs. control. Positive correlations between average daily Li intake and tissue Mg concentration in the kidney ($r = 0.650$) and femoral muscle ($r = 0.696$) were found. In conclusion, the present study indicates that the different Li doses disturbed tissue homeostasis of magnesium. The increase in Mg tissue concentration, observed in groups receiving higher Li doses can influence nervous-muscular excitability.

Key words:
magnesium, lithium, male rats, plasma, tissues

Introduction

Lithium (Li) has been applied in different fields of medicine for half a century [7, 32, 33]. However, despite numerous works performed with the aim of explaining lithium influence on organisms, the mechanism of its action has not been clarified yet [23, 33]. Li influences plenty of metabolic processes. Experiments performed both \textit{in vivo} and \textit{in vitro} revealed its effect on activities of: phosphatases [37], copper-containing amine oxidase [21], NO synthase [35], enzymes of “arachidonic acid cascade” [5] and protein kinase C [34]. Li treatment exerts complex influence on serotonergic [24, 29], glutaminergic [26] and dopaminergic [3] neurotransmission. Li effect on the elements of antioxidant barrier [14] as well as on metabolism of bioelements was also reported [27, 31]. Magnesium (Mg) belongs to the most essential bioelements [16] and is regarded to be the most important intracellular divalent cation for organism [19]. It has anticonvulsant properties [10], and can protect against iron-induced lipid peroxidation [15]. Research performed on animals revealed its neuroprotective ef-
fect in oxidative stress caused by radiation [22]. Mutual relationships between Li and Mg action have been found [1, 8]. Our previous research has revealed that a high, toxic Li dose administered orally to rats may affect magnesium homeostasis [13]. The purpose of this work was to precisely define the influence of different doses of lithium administered orally on magnesium concentration in plasma and tissues of rats. The lower doses corresponded with those applied during long-term Li therapy in psychiatric patients [30] and during short-term administration of Li₂CO₃ as an adjuvant in radioiodine therapy in subjects suffering from thyroid diseases [2, 4]. The higher ones were comparable with the overdosing but without any evident symptoms of Li poisoning.

**Materials and Methods**

**Animals**

The experiment was carried out on two-month-old male Wistar rats (180–220 g), divided into seven groups (ten animals each). Six tested groups were provided with aqueous solutions of lithium carbonate (Li₂CO₃) as the only drinking fluid. 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⁺/l. Control group received re-distilled water. Rats had free access to standard LSM feed and drinking fluids. Each animal was kept in a separate cage and the consumption of the provided fluid as well as body weight were monitored every day.

Based on the obtained data, the daily lithium intake was calculated for each rat:

\[
\text{daily Li intake [mg Li⁺/kg b.w.] = V \cdot c / m}
\]

\(V\) – consumption of the provided fluid [ml]; \(c\) – concentration of the provided fluid [mg Li⁺/ml]; \(m\) – body weight [kg].

After the end of the experiment the average value was estimated for each rat and the mean of the daily Li intake in each group was calculated. Animals were sacrificed under ketamine narcosis after eight weeks and the blood from the heart as well as tissues of liver, kidney, brain, femoral muscle and heart muscle were collected. Plasma was separated. Tissue homogenates (10% w/v) were prepared in 0.1 mol/l Tris-HCl buffer pH = 7.4 and supernatants were obtained by centrifugation at 5000 \(\times\) g for 30 min. The prepared material was stored at the temperature of \(-20^\circ\text{C}\).

Magnesium concentration was measured in plasma and supernatants by the reaction with xylidyl blue (diagnostic set Liquick Cor-MG 60), using colorimetric method. Wavelength was 520 nm. The assays were carried out using SPECORD M40 (Zeiss Jena) spectrophotometer. Comparisons between control and tested groups were made using the Cochran-Cox test. Values were considered significant with \(p < 0.05\). The correlations between average daily lithium intake and tissue Mg concentration were estimated by Pearson test.

The study was performed according to statutory bioethical standards and was approved by I Local Ethical Commission of Feliks Skubiszewski Medical University of Lublin, acceptance 435/2003.

**Results**

Body weight gain as well as the consumption of the provided fluids were not different from the values observed in control group (Tab. 1).

Lithium administration did not cause any changes in magnesium concentration in plasma. On the contrary, in all studied tissues Mg concentration was found to be enhanced, although the degree of this effect was dependent on the tissue. In the liver, brain and heart muscle, the increase did not show statistical significance vs. control. In the kidney the higher Li doses were required to cause the significant Mg enhancement, whereas in femoral muscle all the used doses resulted in well-marked Mg increase vs. control (Tab. 2).

Analysis of correlations between average daily lithium intake and tissue Mg concentration displayed the existence of positive correlations in the kidney (\(r = 0.650\)) (Fig. 1) and femoral muscle (\(r = 0.696\)) (Fig. 2).

**Discussion**

Lithium is mainly used in the treatment of psychiatric diseases [17, 28]. It has been suggested that the enhancement of cellular magnesium plays an important
Lithium administration increases tissue Mg but not plasma Mg in rats

**Tab. 1.** Average daily lithium intake and body weight gain during the experiment

<table>
<thead>
<tr>
<th>Li concentration in provided fluids (mmol Li/L)</th>
<th>Average daily Li intake (mg Li/kg b.w.)</th>
<th>4 days before the beginning of intoxication</th>
<th>Body weight during the experiment (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 4</td>
<td>Day 21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 36</td>
<td>Day 44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
</tr>
<tr>
<td>Control</td>
<td>–</td>
<td>210 ± 15</td>
<td>280 ± 30</td>
</tr>
<tr>
<td>0.7</td>
<td>0.6 ± 0.1</td>
<td>200 ± 14</td>
<td>292 ± 31</td>
</tr>
<tr>
<td>1.4</td>
<td>1.1 ± 0.2</td>
<td>219 ± 10</td>
<td>295 ± 16</td>
</tr>
<tr>
<td>2.6</td>
<td>2.2 ± 0.6</td>
<td>199 ± 8</td>
<td>305 ± 25</td>
</tr>
<tr>
<td>3.6</td>
<td>3.1 ± 0.6</td>
<td>212 ± 11</td>
<td>276 ± 26</td>
</tr>
<tr>
<td>7.1</td>
<td>5.1 ± 1.2</td>
<td>209 ± 15</td>
<td>273 ± 15</td>
</tr>
<tr>
<td>10.7</td>
<td>6.9 ± 0.6</td>
<td>209 ± 13</td>
<td>267 ± 24</td>
</tr>
</tbody>
</table>

Values are the mean of ten animals; X ± SD = mean ± standard deviation

**Tab. 2.** Magnesium concentration in plasma and tissues of rats receiving lithium in drinking water

<table>
<thead>
<tr>
<th>Li concentration in provided fluids (mmol Li/L)</th>
<th>Mg (mmol/L)</th>
<th>Mg (µmol/g of wet tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
</tr>
<tr>
<td>Control</td>
<td>1.06 ± 0.14</td>
<td>6.3 ± 1.1</td>
</tr>
<tr>
<td>0.7</td>
<td>0.98 ± 0.12</td>
<td>6.8 ± 0.7</td>
</tr>
<tr>
<td>1.4</td>
<td>0.88 ± 0.11</td>
<td>6.7 ± 1.2</td>
</tr>
<tr>
<td>2.6</td>
<td>1.01 ± 0.13</td>
<td>7.0 ± 0.7</td>
</tr>
<tr>
<td>3.6</td>
<td>0.90 ± 0.15</td>
<td>6.9 ± 0.6</td>
</tr>
<tr>
<td>7.1</td>
<td>0.74 ± 0.19</td>
<td>6.7 ± 1.2</td>
</tr>
<tr>
<td>10.7</td>
<td>1.06 ± 0.17</td>
<td>6.4 ± 0.8</td>
</tr>
</tbody>
</table>

Values are the mean of ten animals; X ± SD = mean ± standard deviation; *↑ the statistically significant difference in comparison with the control group – *p < 0.05

**Fig. 1.** The positive correlation between average daily lithium intake and magnesium concentration in the tissue of kidney

**Fig. 2.** The positive correlation between average daily lithium intake and magnesium concentration in the tissue of femoral muscle
role in some psychiatric drugs’ action through the inhibition of presynaptic release of excitatory neurotransmitters and reactive oxygen species generation as well as by preventing anxiety states and hallucinations [20]. Disturbances of magnesium homeostasis in psychiatric patients were reported, but the obtained results are not consistent [11, 18, 20]. However, research concerning Mg was suggested to be very useful in mood disorders [36]. Decreased Mg$^{2+}$ erythrocytic concentration was documented in subjects suffering from schizophrenia [20]. Other authors noticed that patients with mood disorders, both medicated and unmedicated, showed increased Mg serum concentration in comparison with healthy control persons [11]. The case of a patient with bipolar disorder treated with Li for several years who displayed normal Mg level in serum was also reported [9]. Some authors observed the increased mean Mg content in both erythrocytes and plasma of patients with major depression [36], whereas in another study patients with major depression, irrespective of the phase of disease showed no differences in erythrocytic magnesium concentration in comparison with control [12].

The experiments carried out on Li-treated rats also resulted in divergent outcomes. Carney and Jackson [6] in “acute” experiment noticed that Li administration to rats did not change concentration of magnesium in plasma although the evidence of disturbances of Mg homeostasis was found. In another work, the increase in Mg plasma level was displayed by rats treated with Li [25].

The comparison of the present data with those obtained during our previous study has revealed the strong dependence between Li dose and its influence on Mg homeostasis. The research regarding the effect of much higher concentration (21.4 mmol Li$^+/l$) [13], administered to rats during three or six weeks resulted in significant increase in plasma Mg, whereas in tissues both decrease and increase were observed, pointing to tissue replacements.

The results of the present experiment make us conclude that the different Li doses disturbed tissue homeostasis of Mg. The increase in Mg tissue concentration, observed in groups receiving higher Li doses can influence nervous-muscular excitability.

References:


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