Pharmacological Reports 70 (2018) 1168–1172

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original article

Lithium disturbs homeostasis of essential microelements in erythrocytes of rats: Selenium as a protective agent?

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ARTICLE INFO

Article history:
Received 6 December 2017
Received in revised form 9 April 2018
Accepted 9 May 2018
Available online 17 May 2018

Keywords:
Lithium
Selenium
Elements
Erythrocytes
Rats

ABSTRACT

Background: Selenium is an essential element which shows protective properties against diverse harmful factors. Lithium compounds are widely used in medicine, but, in spite of undoubted beneficial effects, treatment with these compounds may lead to severe side effects, including renal, gastrointestinal, neurological, endocrine and metabolic disorders. This study was aimed at evaluating the influence of selenium and/or lithium on lithium, iron, zinc and copper content in rats' erythrocytes as well as estimate the action of additional selenium on lithium exposure effects.
Methods: The experiment was performed on four groups of rats (six animals each): control – received saline; Li – received 2.7 mg Li/kg b.w. as lithium carbonate; Se – received 0.5 mg Se/kg b.w. as sodium selenite; Se + Li – received simultaneously 0.5 mg Se/kg b.w. and 2.7 mg Li/kg b.w. (sodium selenite and lithium carbonate). The administration was performed for three weeks, once a day by stomach tube, in form of water solutions. In erythrocytes the content of lithium, iron, zinc and copper was determined using flame atomic absorption spectroscopy.
Results: Lithium treatment insignificantly disturbed iron and zinc homeostasis as well as markedly increased lithium accumulation and copper content in rat erythrocytes. Selenium coadministration reversed those effects.
Conclusions: The beneficial effect of selenium on disturbances of studied microelements homeostasis as well as on preventing lithium accumulation in erythrocytes in Li receiving animals allows suggesting that further research on selenium application as an adjuvant in lithium therapy is worth carrying on.

Introduction

Selenium belongs to bioelements whose metabolic role, despite their small content in organism, cannot be underrated. The importance of this element results from its presence in selenoproteins playing an essential role for organisms, first of all in an antioxidant enzyme glutathione peroxidase (GPx). Being a component of the active site of GPx selenium is considered as an antioxidant [1]. Oxidative stress interval – the upset balance between generation of reactive oxygen species and the functioning of antioxidative defense interval – is believed to be involved in pathogenesis of numerous disorders, *e.g.* metabolic ones like obesity or type 2 diabetes [2] as well as in mechanism of toxicity of diverse harmful factors like heavy metals [3,4] or mycotoxins [5] and side effects of different drugs including lithium [6]. For this reason, a lot of research studying the possibility of using selenium, alone or in cotreatment with other substances, as a protective agent has been done. The obtained results of animal studies confirmed selenium's protective properties in case of exposure to harmful substances like mycotoxins [5], heavy metals [4,7,8] or carcinogens [9]. Selenium compounds have also shown to present protective properties against physical factors and cancer in humans [10,11]. Considering the presented beneficial properties of selenium, the growing concern in its supplementation is being observed, although the necessity of the taking proper precautions is still emphasized [12]. Lithium has been used in medicine for almost seventy years. It remains a drug of first choice in cases of bipolar disorder and additionally its long-term cure lowers suicide and suicide attempts rate [13–15]. Apart from psychiatry, studies have revealed the possibility of its application in other fields *e.g.*: in therapy of thyroid diseases, neurodegenerative disorders or preventing nephrolithiasis [16–18]. Furthermore, the possibility

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https://doi.org/10.1016/j.pharep.2018.05.003
1734-1140/

of using lithium in leukemia therapy has been suggested [19]. However, the lithium therapy may be burdened with severe side effects including renal, neurological, endocrine and metabolic disorders as well as disturbances of gastrointestinal tract, and dermatological complications [20–23], which can influence both the results of cure as well as a patient's compliance. An additional complication is the fact that lithium exhibits beneficial action only within a strongly determined range [24]. For these reasons the searching for protective agents against lithium's negative actions has seemed to be worth carrying out, particularly in view of the fact that its application in psychiatric patients is commonly long-term [25]. The research performed to date has revealed the beneficial influence of different substances of antioxidant properties, *e.g.*: zinc – an element rated among microelements of antioxidant properties [26] or antioxidant substances of natural origin [6]. The aim of the current study was to investigate the influence of lithium and selenium given alone and in cotreatment on lithium accumulation and homeostasis of chosen bioelements in rat erythrocytes as well as to estimate the action of additional selenium on lithium exposure effects. The choice of selenium was dictated by its antioxidant properties as well as the reports concerning some lithium-mimetic properties shown by an organic selenocompound ebselen which made the authors take into account the possible effectiveness of ebselen in bipolar disorder cases [27]. Having considered the issue of bioavailability, we chose an acknowledged inorganic supplement sodium selenite which is still used in scientific research [3,5,7,10] as well as in clinical practice [28]. Erythrocytes (red blood cells, RBC) play a crucial role in proper functioning of organism and lithium treatment was found to cause their damage [29,30]. Additionally, in an animal study it was shown to influence osmolitic fragility of erythrocytes [22]. Copper, zinc and iron belong to the most important microelements affecting cellular growth, immune system and antioxidant defence [31–33]. Considering these facts, the current experiment aimed at evaluating the influence of lithium treatment alone and in cotreatment with selenium on lithium, iron, zinc and copper content in rats' erythrocytes.

Materials and methods

Chemicals and drugs

Lithium carbonate (Li_2CO_3; 99.997%) was obtained from Aldrich Chemical Company, Inc. Milwaukee, Wisconsin, USA. Sodium selenite ($Na_2SeO_3 \cdot 5H_2O$; Analytical Reagent) was obtained from Riedel-de Haën, Seelze, Germany. Nitric acid (HNO_3, Suprapur®) and hydrochloric acid (HCl, Suprapur®), as well as standard solutions for iron, copper, and zinc (Certipur®, 1000 mg/L) and Lithium Standard Solution TITRISOL® were purchased from Merck, Darmstadt, Germany.

The solutions administered to rats were prepared as follows:

- the solution containing lithium by dissolving 8.4 g of Li_2CO_3 in dm^3 of water;
- the solution containing selenium by dissolving 1.5 g of $Na_2SeO_3 \cdot 5H_2O$ in dm^3 of water.
- the solution containing selenium and lithium by dissolving 1.0 g of $Na_2SeO_3 \cdot 5H_2O$ and 8.4 g of Li_2CO_3 in dm^3 of water.

Animals

The study was carried out on adolescent male Wistar rats (4-week-old, 130–160 g body weight) supplied by the firm Zbigniew Lipiec, Hodowla Zwierząt Laboratoryjnych, Brwinów, Poland. The housing conditions were as follows: temperature $22 \pm 2\,^{\circ}C$, 12 h light-dark cycle. The adolescent rats were chosen with the aim of the potential comparison of the results with those obtained previously in the cycle of studies concerning selenium. The animals had free access to standard feed (LSM produced by AGROPOL S.J., without lithium and selenium supplementation, the composition presented in Table 1) and drinking water. The study was performed according to statutory bioethical standards and approved by I Local Ethical Commission of Medical University of Lublin, acceptance no. 1/2013.

Experimental design

Rats were treated with lithium, selenium and the combination of these two elements as presented in Fig. 1. The time of experiment was comparable with some studies concerning lithium effect on animal organisms [6,22]. It was also chosen with the aim of making the comparison of the current experiment with our previous studies where Li was given for 4 weeks [34] and Se for 10 days [35].

Basing on the obtained values of body mass of each animal which were measured every time before administration, the appropriate amounts of administered solutions were calculated.

Erythrocytes were separated by centrifugation at 3000 rotations/min for 10 min at 4 °C and washed three times with phosphate saline buffer (PBS), pH 7.4. Supernatant and buffy coat were carefully removed by aspiration after each wash. The obtained RBC samples were then stored at −20 °C for further determinations.

Determination of content of lithium, iron, zinc, and copper in erythrocytes

Samples of erythrocytes were placed into quartz crucibles and dried at temperature of 105 °C. Then they underwent dry mineralisation over a gas burner and subsequently in a muffle furnace at a temperature of 450 °C. The ashes were sprinkled with a 15% water solution of HNO_3 with the aim of accelerating the burning. Then the ash was dissolved in a 10% water solution of HCl. Subsequently, the content of the crucibles was moved quantitatively into measuring flasks and the volumes were made up to 10 cm^3 using deionised water. In the obtained solutions the concentrations of lithium, iron, zinc and copper were all determined. The measurements were carried out using flame atomic absorption spectroscopy (FAAS) with help of a SOLAAR M5 apparatus (Thermo Elemental Ltd., United Kingdom). The wavelengths for the studied elements were as follows: 670.7, 248.3, 213.9, 324.8 nm, for lithium, iron, zinc and copper, respectively. The results were expressed in $\mu g \cdot g^{-1}$ of RBC.

Table 1
Composition of Standard LSM feed.

Substance	Unit	Content
Protein min.	[%]	16.00
Raw fats min.	[%]	2.80
Raw ash max.	[%]	7.00
Raw fiber max.	[%]	5.00
L-Lysine min.	[%]	0.80
DL-Methionine min.	[%]	0.50
Calcium min.	[%]	1.10
Phosphorus min.	[%]	0.60
Sodium max.	[%]	0.20
Vitamin A (retinol) E 672	[jm/kg]	10 000
Vitamin D3 E 671	[jm/kg]	1500
Vitamin E (α-tocopherol 50%)	[mg/kg]	25
Copper (copper sulphate 24.5%) E 4	[mg/kg]	5

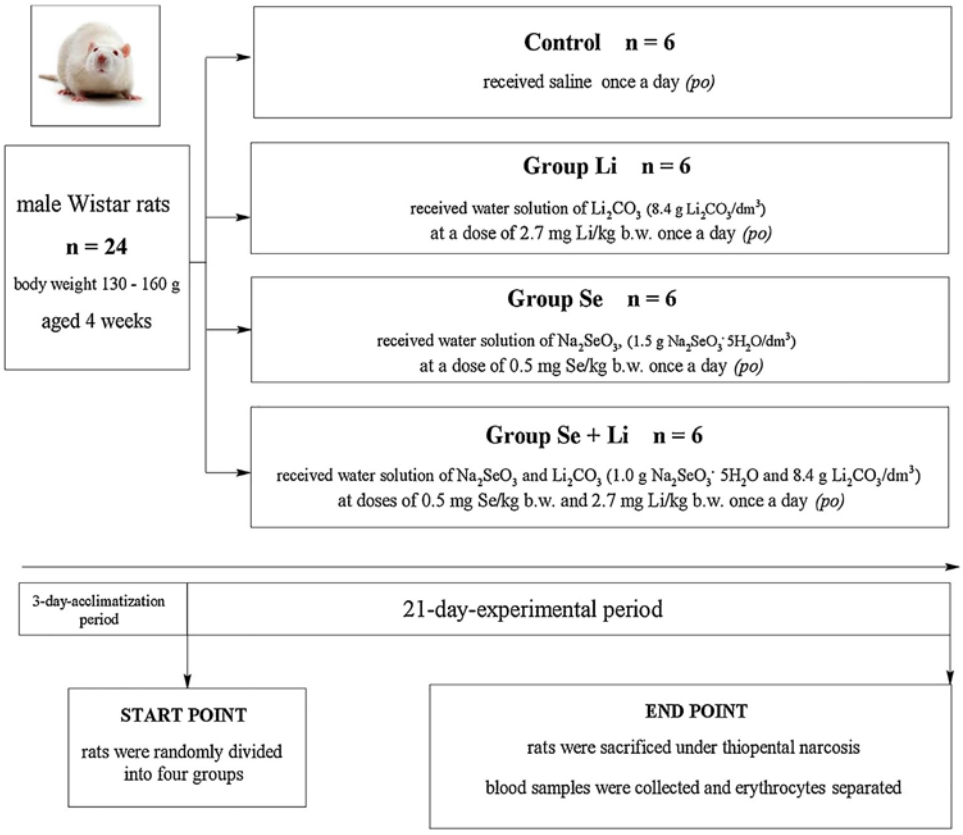

Fig. 1. Experimental design.

Statistics

The statistical analysis was performed using STATISTICA program (version 10.0). The normality of data distribution was verified using Shapiro-Wilk test. The differences among the studied groups were analyzed using a one-way analysis of variance (ANOVA), followed by Tukey test for normally distributed variables. Otherwise Kruskal-Wallis test followed by Dunn's *post hoc* test was used. Values with $p < 0.05$ were considered significant. The results were presented as mean ± SD.

Results

Lithium administration significantly increased the content of this element in RBC of rats *vs.* all other groups ($p < 0.001$ in all cases). However, selenium administered along with lithium inhibited the Li increase, resulting in the maintaining of Li level comparable to the control group.

No treatment used in the current study affected in distinct way iron content in RBC of rats receiving selenium and/or lithium. However, the lowest iron content was found in RBC of rats receiving lithium. The iron in Se + Li and Se groups was comparable with control. The obtained differences did not reach statistical significance.

Similarly, no statistical differences were obtained in case of zinc. However, in Li group a trend towards enhancement *vs.* all other groups was observed, particularly compared to control ($p = 0.06$ *vs.* control; $p \leq 0.1$ *vs.* Se and Se + Li groups). Administration of selenium, both alone and together with lithium, did not alter zinc content *vs.* control ($p > 0.1$ in both cases).

Lithium treatment markedly increased the RBC copper content *vs.* control and Se group ($p = 0.006$, $p = 0.04$ *vs.* control and Se group, respectively). Selenium, provided both alone and in coadministration with lithium, did not change copper content compared to control in a significant way.

All the results are collected in Table 2.

Discussion

As mentioned in Introduction, lithium treatment can cause diverse negative effects. Among other things, the possibility of causing damage to erythrocytes has been reported. An *ex vivo*

Table 2
Lithium, iron, zinc and copper content in erythrocytes of rats receiving selenium and/or lithium.

Group	Lithium [μg· g^{-1}] mean ± SD	Iron [μg· g^{-1}] mean ± SD	Zinc [μg· g^{-1}] mean ± SD	Copper [μg· g^{-1}] mean ± SD
Control (C)	0.0389 ± 0.0196	901.93 ± 210.19	13.203 ± 4.041	1.0017 ± 0.0991
Li group	0.1639 ± 0.0657[b]	815.78 ± 188.07	26.843 ± 6.642	2.3300 ± 1.0833[a]
Se group	0.0308 ± 0.0189[d]	926.71 ± 113.89	15.712± 9.872	1.3367 ± 0.3725[c]
Se + Li group	0.0276 ± 0.0129[d]	909.04 ± 116.64	13.328 ± 3.605	1.4967 ± 0.3691

[a] $p < 0.01$ *vs.* control.
[b] $p < 0.001$ *vs.* control.
[c] $p < 0.05$ *vs.* Li group.
[d] $p < 0.001$ *vs.* Li group.

research has revealed that lithium ion exposure can lead to RBC suicidal death [29] or echinocytes generation [30]. In an experiment performed on an animal model lithium carbonate administered in drinking water to rats was found to increase osmolitic fragility of erythrocytes [22].

In the current study lithium administration significantly increased its RBC content, whereas selenium cotreatment prevented its accumulation in erythrocytes. This might be an issue of great importance considering the fact that in patients with acute-on-chronic poisoning (previously treated with lithium who take an overdose) RBC to plasma lithium concentration ratio was found to be considerably higher than in those subjected to regular treatment. Moreover, in a hemodialysed patient this ratio was found to be insignificantly higher after dialysis [24]. The latter should be emphasized as dialysis is a common treatment in lithium poisoning [36]. Additionally, the accumulation of lithium in erythrocytes has been suggested to contribute to a rebound of plasma Li^+ concentration observed after hemodialysis [25]. The animal study, performed recently on rats, confirmed the observations mentioned above. In acute-on-chronic poisoning model (28-day-exposure to 800 mg/L Li_2CO_3 in drinking water and then an intraperitoneal treatment with 185 mg/kg Li_2CO_3), RBC Li/plasma Li ratio was found to be higher than in acute poisoning (an intraperitoneal treatment with 185 mg/kg Li_2CO_3), starting from 24 h after intraperitoneal administration and reaching statistical significance at 54 and 72 h [37].

Furthermore, Dashti-Khavidaki et al. studied the renal parameters in bipolar disorder patients treated with lithium and found that lower urine specific gravity was accompanied by higher lithium content in erythrocytes. Additionally, patients showing higher Li in RBC displayed significantly decreased sodium and potassium in urine as well as enhanced serum sodium. Those results made the authors suggest the possibility of existence of relationships between RBC lithium and kidney impairments [38].

In the available literature, there are few studies concerning the relationships among the studied elements in erythrocytes. The ones performed to date revealed observations confirming in some part the outcomes of the present experiment.

The distinct, although insignificant changes of RBC iron and zinc, observed in the current study, point to a possibility of the existence of tendency to an adverse influence of zinc on iron homeostasis in erythrocytes. It is consistent with the results of an animal study performed by Kaluza and Madej who found that under conditions of dietary iron deficit the supplementation with iron alone was more beneficial than combined supplementation with both iron and zinc, considering amelioration of Fe status [39]. Yanagisawa et al. also reported a negative effect of high zinc in diet on haematological parameters *i.e.*: decrease in haemoglobin, haematocrit, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and mean corpuscular volume as well as the depletion of serum iron concentration. An increase in serum erythropoietin, observed in animals fed with high Zn diet, was regarded as another proof of the harmful influence of zinc overdose on the process of erythropoiesis and made the authors suggest some role of erythropoietin enhancement in the mechanism aiming at preventing the development of anaemia [40]. On the other hand, Eze et al. found that dietary zinc could prevent haemoglobin decrease caused by *Trypanosoma brucei* infection in rats [31]. However, the latter study was performed on infected animals and the Zn dose was considerably lower (2, 4 or 8 ppm *vs.* 412 mg/kg in Kaluza and Madej study). The effects of administration of zinc in drinking water (227 mg/L) to rats was also studied by Malhotra and Dhawan who found no distinct influence of Zn on haemoglobin in animals subjected to zinc alone or in cotreatment with dietary lithium carbonate (1.1 g/kg) [26]. Comparing the mention studies, it must be noted that while Eze et al. as well as Malhotra and Dhawan measured only haemoglobin, Kaluza and Madej studied more parameters of iron status, *i.e.*: haemoglobin, transferrin saturation and ferritin.

The current study proved a significant enhancement of RBC copper and lithium in rats receiving lithium compared to control, which allows taking into account a possibility of occurrence of any connections between these two elements. Additional support for such an assumption might be the results reported by Kędzierska et al. who found negative correlation between plasma copper and erythrocyte Na^+/Li^+ exchanger in patients with hypertension [32].

Although in the current experiment lithium exposure caused a tendency to an increase in RBC zinc and copper, it was not reflected by any enhancement of SOD (an enzyme whose one isoform contains Cu and Zn) in whole blood according to Musik et al. The same authors also found a significant depression of an-iron-containing enzyme CAT in plasma of rats receiving lithium [41]. The present experiment revealed a slight depletion of RBC iron. These two facts could point to the decrease in whole blood content of iron, but this issue needs further research.

In the present experiment neither selenium alone nor combined with lithium altered any studied element in rats' erythrocytes *vs.* control in a significant way. These results seem to be worth emphasizing as the maintaining of the proper level of these elements is an issue of great importance for RBC functioning. In rats fed with Zn-deficit diet the impairment of antioxidant defense as well as increase in oxidant stress were found [42]. An additional reason for considering this effect as being beneficial can be the results obtained by Messaoudi et al. who found simultaneous supplementation with both selenium and zinc to be more effective than either of these elements alone in reversing cadmium-induced effects in rats [4]. Similar results were observed by Banni et al. in regard of lipid peroxidation in chosen organs of zebrafish – Se and Zn administered together were more effective than either of the studied elements given alone [3].

Furthermore, a positive effect of selenium on erythrocytes subjected to any harmful factor has already been reported. Selamoglu Talas et al. found the protective influence of selenoorganic compounds against oxidative stress caused by a carcinogenic hydrocarbon in rat RBC [9]. According to Soudani et al. selenium was proved to prevent harmful oxidative effects, observed in erythrocytes of rats, being the consequence of exposure to chromium(VI) [8]. Tariba et al., in turn, performed an *in vitro* experiment and found that selenium treatment alleviated decrease in activity of one of the antioxidant enzymes – Cu,Zn-superoxide dismutase in RBC subjected to simultaneous exposure to platinum and cadmium [43]. However, the research considering selenium protective properties included only oxidative stress and there is the lack of studies regarding the microelements.

The relationships among different microelements, in turn, were studied by Türkan et al. who determined RBC concentrations of zinc, copper and selenium in patients subjected to anaesthesia with halothane, enflurane or isoflurane. Cu, Zn and Se measured 1 h, 1 day and 3 days after anaesthesia induction were significantly decreased compared to the values observed before anaesthesia, pointing to the possibility of the existence of any positive correlation among zinc, copper and selenium in erythrocytes [44]. Similarly, in the present study such a relationship was observed between Zn and Cu.

Conclusions

The results of the current study reveal that cotreatment with selenium prevents lithium accumulation in RBC of animals receiving this element orally. Such an effect could prevent its release into plasma after applying dialysis in case of poisoning as well as protect from subsequent prolongation of occurring the

excess Li plasma concentration. The lack of any changes of other studied microelements in Se + Li given animals also seems to be significant considering their physiological importance. Concluding, the obtained results may contribute to the knowledge of the relationships among microelements in RBC under conditions of lithium treatment or selenium supplementation as well as support the further research on the possibility of selenium introduction into lithium therapy as a beneficial adjuvant.

Funding

This study was funded by the Medical University of Lublin.

Declaration of interest

None.

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