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# Relationships between silicon content and glutathione peroxidase activity in tissues of rats receiving lithium in drinking water

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**Abstract** Lithium salts are widely used in psychiatry, but their presence in organism can result in both beneficial and adverse effects. Silicon, the third most abundant trace element in humans as well as antioxidant enzyme glutathione peroxidase (GPx) play important roles in organism. The disturbance of their level can cause severe disorders. The aim of our work was to evaluate the influence of $Li_2CO_3$ administration in drinking water for a period of 4 weeks on Si content and GPx activity in the tissues of liver, kidney, brain and femoral muscle in rats. The concentrations of provided solutions were 0.7, 1.4, 2.6, 3.6, 7.1 and 10.7 mmol $Li^+ \cdot dm^{-3}$. GPx activity was decreased versus control as a consequence of Li treatment, particularly in kidney and brain. This effect could be suggested to contribute to renal abnormalities which could occur during Li therapy. Si tissue level was significantly enhanced versus control in liver and femoral muscle in groups receiving high Li doses. In brain no well-marked changes were observed, whereas in kidney we observed the depletion in low-Li-groups, restoration of Si level in higher-Li-groups and unexpected decrease in the highest-Li-group. Positive correlations between Si content and GPx activity in the tissues of kidney ($r = 0.677$) and brain ($r = 0.790$) as well as negative correlation ($r = -0.819$) in femoral muscle were found. We consider that our results give some reason for suggesting that monitoring of silicon level in patients undergoing Li therapy could be recommended. However, more investigations should be performed, particularly regarding the relationships between Si and GPx in blood and urine Si excretion during lithium administration.

**Keywords** Silicon · Lithium · Glutathione peroxidase · Male rats

**Abbreviations**
GPx Glutathione peroxidase
ROS Reactive oxygen species

## Introduction

Lithium is an element which, not being included into the essential bioelements, can influence numerous metabolic processes. It affects the activity of antioxidant enzymes (de Vasconcellos et al. 2006), ''arachidonic acid cascade'' enzymes (Bosetti et al. 2002) as well as phosphatases (Yenush et al. 2000). Lithium ion influences serotoninergic (Subhash et al. 1999), dopaminergic

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(Al Banchaabouchi et al. 2004) and glutamate (Shaldubina et al. 2001) neuronal transmission. Li administration can affect functions of thyroid and parathyroid glands causing hypothyroidism (Engin et al. 2005) and hyperparathyroidism (Livingstone and Rampes 2006). Mutual relationships between lithium and both macro- and micro-elements homeostasis have already been reported (Carney and Jackson 1998; Tandon et al. 1999; Sharma and Iqbal 2005). Studies concerning different cytokines have displayed its complicated effect, resulting from the increase in both proinflammatory and negative immunoregulatory ones production (Maes et al. 1999; Szuster-Ciesielska et al. 2003). For almost 60 years lithium salts have been widely used in different fields of medicine. Their beneficial properties observed in cases of psychiatric disorders are known best of all (Fawcett 2003), however, recent years have brought reports revealing new possibilities of Li therapy application. Suppression of thyroid hormones caused by lithium made scientists study the efficacy of Li treatment as an adjuvant in patients suffering from thyroid diseases, undergoing radioiodine therapy (Vannucchi et al. 2005). Other authors have found the positive action of lithium in neurological disorders (Pardo et al. 2003). Topic application of lithium compounds have also been reported to show effectiveness in dermatological illnesses (Dreno et al. 2003). However, its presence in organism can also result in plenty of adverse effects, including renal and cardiovascular abnormalities, disturbances of cholesterol and glucose metabolism as well as abnormalities of erythropoiesis and leucopoiesis (Chmielnicka and Nasiadek 2003; Sharma and Iqbal 2005). It should be underlined that despite numerous works aiming at clearing of lithium's mechanism of action this question still remains unclear (Pardo et al. 2003).

Silicon is not so known as the other microelements however, after iron and zinc, it is the third most abundant trace element in human organism (Sripanyakorn et al. 2005). Si affects mainly the forming of connective tissues (Fauteux et al. 2005) but its presence has also been noted in blood and different organs (Bissé et al. 2005). It has been suggested to be requisite for lymphocyte proliferation in mammals (Seaborn et al. 2002). Relationships between renal disturbances and silica exposure have been described (Governa et al. 2005).

Reactive oxygen species (ROS) are the products of uncompleted reduction of $O_2$ molecule (Drewa et al. 2002). They are formed in organisms during metabolic processes and can cause damage of proteins, membranes and DNA resulting in severe disturbances (Kuzniar et al. 2003; de Vasconcellos et al. 2006). ROS generation has been found to be involved into pathogenesis of the most dangerous diseases including cardiovascular abnormalities, Down syndrome and epilepsy (Gaeta et al. 2002; Kozlovski et al. 2006). Organisms have developed a complex defence system containing of high- and low-molecule substances which counteract ROS activity (Skibska et al. 2006). One of the most important antioxidant substances is glutathione peroxidase (GPx), an enzyme catalyzing the conversion of hydrogen peroxide into water. The correct action of antioxidant barrier is a question of great importance and depends on plenty of different factors. Alterations of antioxidants' level caused by abnormal elementary content of diet (Kuzniar et al. 2003) or by administration of different elements both under physiological and pathological conditions have been observed (Najda et al. 1994; Panneerselvam and Govindasamy 2004).

Having regarded the presented facts and aiming at contributing to knowledge of lithium's mechanism of action we tried to evaluate the influence of Li administration in drinking water on Si content and GPx activity in chosen tissues of rats.

## Materials and methods

Our study was performed on 2-month-old male Wistar rats (180–220 g). The animals were divided into seven groups (six animals each): control group (C) received redistilled water, while six tested groups were given water solutions of $Li_2CO_3$ as the only drinking fluids. The concentrations were established as follows: 0.7, 1.4, 2.6, 3.6, 7.1 and 10.7 mmol $Li^{+} \cdot dm^{-3}$. The animals had free access to standard feed LSM and drinking fluids. After four weeks rats were sacrificed under

ketamine narcosis. The tissues of liver, kidney, brain and femoral muscle were collected. 10% (w/v) tissue homogenates were prepared in Tris–HCl buffer (0.1 mol·dm$^{-3}$, pH = 7.4). Supernatants were obtained by centrifugation at 5000×*g* for 30 min. GPx activity was determined using RANSEL kit produced by RANDOX, according to Paglia and Valentine method (Paglia and Valentine 1967) and expressed in U·g$^{-1}$ of protein. Protein was measured using method of Bradford (Bradford 1976). The concentration of silicon was measured using the spectrophotometric method (Wielkoszyński 2000). The assays were carried out with the help of SPECORD M40 (Zeiss Jena) spectrophotometer. Comparisons between control and tested groups were made using c-Cochran-Cox test. Values were considered significant with $P < 0.05$. The correlations between Si concentration and GPx activity were estimated with the help of the Pearson test.

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

## Results

The outcomes of the present experiment (Table 1) indicate that the influence of lithium administration on Si content and GPx activity depends strongly on the applied dose as well as on the tissue.

In liver and femoral muscle lower Li doses did not significantly alter silicon content. Higher Li doses markedly increased Si versus control in both tissues. GPx activity was not significantly changed in both tissues versus control, except for liver in the group receiving the highest Li dose, where the statistically significant depletion was observed.

In brain Si content did not display well-marked changes versus control in all tested groups. GPx activity was decreased in dose-dependent way. In the group provided with the lowest dose the depletion was not statistically significant, while in the others the decrease showed statistical significance versus control.

The results concerning silicon content in kidney were unexpected. The administration of lower doses caused well-marked depression versus control. Higher ones caused the restoration of Si level to values observed in control group, whereas in the group receiving the highest dose of lithium the significant decrease versus control was obtained. GPx activity was markedly depressed versus control, without regard to the used dose.

The analysis of correlations between Si content and GPx activity displayed the existence of positive correlations in the tissues of kidney ($r = 0.677$) (Fig. 1) and brain ($r = 0.790$) (Fig. 2) as well as negative correlation ($r = -0.819$) in femoral muscle (Fig. 3).

## Discussion

The present experiment revealed the deleterious impact of lithium administration on GPx activity,

**Table 1** Silicon concentration and glutathione peroxidase activity in tissues of rats receiving lithium in drinking water

| Li concentration (mmol dm$^{-3}$) | Liver | | Kidney | | Brain | | Femoral muscle | |
|---|---|---|---|---|---|---|---|---|
| | Si μmol g$^{-1}$ of fresh tissue $\bar{x} \pm SD$ | GPx U g$^{-1}$ of protein $\bar{x} \pm SD$ | Si μmol g$^{-1}$ of fresh tissue $\bar{x} \pm SD$ | GPx U g$^{-1}$ of protein $\bar{x} \pm SD$ | Si μmol g$^{-1}$ of fresh tissue $\bar{x} \pm SD$ | GPx U g$^{-1}$ of protein $\bar{x} \pm SD$ | Si μmol g$^{-1}$ of fresh tissue $\bar{x} \pm SD$ | GPx U g$^{-1}$ of protein $\bar{x} \pm SD$ |
| C | 2.2 ± 0.5 | 1500 ± 424 | 3.5 ± 0.3 | 1300 ± 205 | 1.6 ± 0.4 | 172 ± 38 | 1.5 ± 0.7 | 77 ± 21 |
| 0.7 | 1.8 ± 0.6 | 1250 ± 278 | 1.9 ± 0.2[a] | 800 ± 182[a] | 1.4 ± 0.3 | 157 ± 34 | 2.3 ± 0.9 | 72 ± 26 |
| 1.4 | 1.9 ± 0.6 | 1300 ± 302 | 1.9 ± 0.4[a] | 674 ± 175[a] | 1.0 ± 0.4 | 87 ± 30[a] | 2.2 ± 0.7 | 67 ± 19 |
| 2.6 | 1.8 ± 0.6 | 1041 ± 215 | 2.0 ± 0.3[a] | 700 ± 164[a] | 1.1 ± 0.4 | 98 ± 24[a] | 2.8 ± 0.6 | 63 ± 20 |
| 3.6 | 3.5 ± 0.5[a] | 1066 ± 273 | 3.1 ± 0.9 | 754 ± 180[a] | 1.1 ± 0.4 | 90 ± 28[a] | 2.9 ± 0.9[a] | 61 ± 25 |
| 7.1 | 3.3 ± 0.5[a] | 1090 ± 302 | 3.1 ± 1.1 | 750 ± 107[a] | 1.2 ± 0.6 | 97 ± 22[a] | 3.3 ± 0.6[a] | 61 ± 22 |
| 10.7 | 3.4 ± 0.7[a] | 924 ± 254[a] | 2.2 ± 0.2[a] | 800 ± 124[a] | 1.2 ± 0.6 | 72 ± 27[a] | 3.1 ± 0.8[a] | 59 ± 21 |

$\bar{x} \pm SD$, mean ± standard deviation

[a] Statistical significance $P < 0.05$

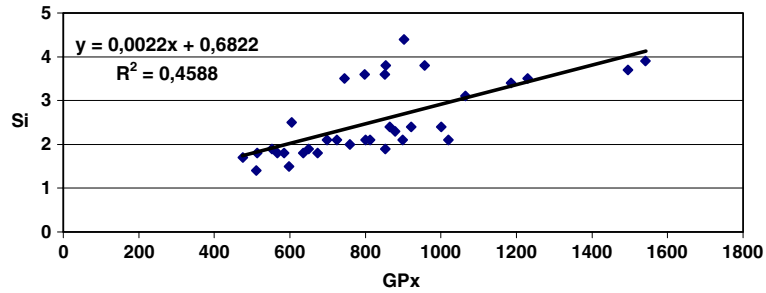


**Fig. 1** Positive correlation between GPx activity and Si content in the tissue of kidney

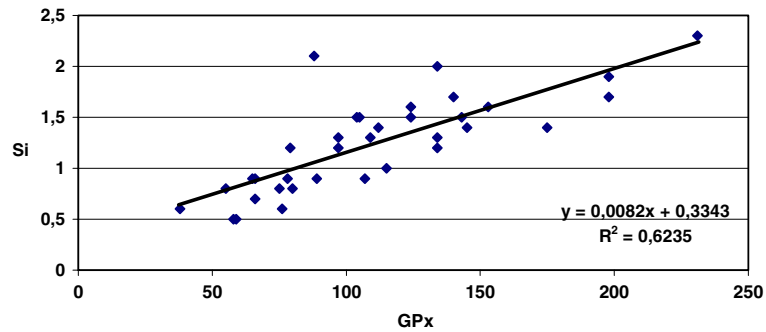


**Fig. 2** Positive correlation between GPx activity and Si content in the tissue of brain

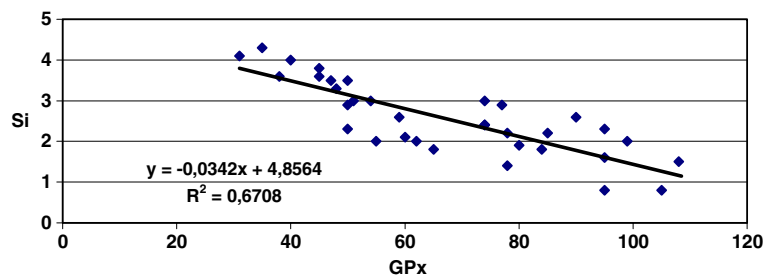


**Fig. 3** Negative correlation between GPx activity and Si content in the tissue of femoral muscle

particularly in the tissues of kidney and brain. Our previous study concerned the influence of longer, 8-week administration of lithium on antioxidant enzymes. We noted that in that case GPx activity was insignificantly decreased in liver and brain, whereas in kidney well-marked depression versus control was obtained in all tested groups (Kiełczykowska et al. 2006b). The comparison of those results with the present ones points, that Li influence on GPx in brain is at least partially transient and can be overcome by organism, whereas in kidney the effect of Li exposure has more permanent character. The later fact is consistent with the observed renal disturbances caused by lithium therapy (Chmielnicka and Nasiadek 2003; Livingstone and Rampes 2006). The outcomes obtained by other authors studying Li influence on GPx have been proved to be inconsistent and the differences between action of lithium under physiological and pathological conditions have been found out.

It has been reported that increased ROS generation which occurs during immune system stimulation in phagocytic leukocytes can cause their damages. It encouraged the scientists to study the functions of antioxidant barrier in these cells under different conditions. LiCl given to sham-operated rats decreased GPx activity in neutrophils, whereas in bulbectomised animals no significant effect was observed (Song et al. 1994).

Short-term administration of lithium carbonate to healthy rats resulted in no changes of GPx activity in erythrocytes and tissues of brain and liver (Abdalla and Bechara 1994).

Healthy rats provided orally with $Li_2CO_3$ for a period of 4 weeks showed a slight, insignificant GPx increase in liver, while in diabetic rats a very strong increase was displayed (Hu et al. 1999).

In rats undergoing LiCl + pilocarpine treatment inducing epilepticus status well-marked depletion of GPx in different regions of brain was reported (Eraković et al. 2000).

Lithium therapy is widely applied in patients suffering from different psychiatric diseases, exposed to stress. No significant influence of lithium on hippocampus GPx was observed in normal rats, whereas in animals submitted chronically to variate stress significant enhancement was shown (de Vasconcellos et al. 2006).

Kidney and liver were shown to belong to the main storage organs for silicon in rats (Almeida et al. 2002). Liver, kidney and brain functions could be influenced as a consequence of exposure to lithium (Chmielnicka and Nasiadek 2003). Relationships between Si and Li in pathological states were found (Bocca et al. 2005).

Lithium administration to rats resulted in divergent, dose-dependent influence on tissue silicon concentration. Our previous study, concerning the effect of longer, 8-week-exposure revealed different observations. The comparison of the outcomes point to the strong dependence between the time of exposure and the effect of lithium treatment. In liver in the first period of administration (4 weeks) higher doses of lithium caused significant increase, while after the longer exposure well-marked depression was obtained. In kidney after 8 weeks no significant influence was observed which suggests that in this organ lithium disturbs Si level transiently, at the beginning of treatment (Kiełczykowska et al. 2006a).

Our results provide some evidence for the existence of relationships between Si concentration and antioxidant defence in the chosen organs. The studies reveal links between oxidative processes and exogenous Si in plants (Liang et al. 2003) and animals (Kleczkowski et al. 2003). The addition of silicon alleviated oxidative stress in plants exposed to excess manganese (Shi et al. 2005). Exogenous silicon caused decrease of GPx activity in liver and kidney of rats (Najda et al. 1994). Antioxidants were found to have a preventive effect against silica-induced toxicity (Zhang et al. 2000). However, there are not too many works concerning this question, so further investigations should be performed to provide its solution.

As a conclusion, it has been found that lithium administration has deleterious impact on GPx activity in important organs and this influence could contribute to adverse effects of Li therapy. Silicon homeostasis can also show abnormalities resulting from Li administration, although this question has not been studied systematically and further studies seem to be advisable, particularly in view of correlations between GPx activity and tissue Si content. We consider that our results give some reason for suggesting that monitoring of silicon level in patients undergoing Li therapy could be recommended. However, more investigations should be performed, particularly regarding the relationships between Si and GPx in blood and urine Si excretion during lithium administration.

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