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The Protective Influence of Selenium on Oxidant Disturbances in Brain of Rats Exposed to Lithium

M. KIEŁCZYKOWSKA[1], J. KOCOT[1], A. LEWANDOWSKA[1], R. ŻELAZOWSKA[1], I. MUSIK[1]

[1]Chair and Department of Medical Chemistry, Medical University of Lublin, Lublin, Poland

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Summary

For more than sixty years lithium carbonate has been used in medicine. However, during its administration different side effects including oxidative stress can occur. Selenium belongs to essential elements possessing antioxidant properties. This study aimed at evaluating if selenium could be used as a protective adjuvant in lithium therapy. The experiment was performed on four groups of Wistar rats: I (control), II (Li), III (Se), IV (Li + Se) treated with saline, lithium carbonate (2.7 mg Li/kg b.w.), sodium selenite (0.5 mg Se/kg b.w.) and lithium carbonate (2.7 mg Li/kg b.w.) + sodium selenite (0.5 mg Se/kg b.w.), respectively. All substances were administered as water solutions by stomach tube for 3 or 6 weeks. Catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) as well as malonyldialdehyde (MDA) were determined in brain homogenates. Lithium slightly enhanced MDA and depressed CAT and SOD after 6 weeks as well as GPx after 3 weeks. Selenium co-administration showed tendency to restore the disturbed parameters. Selenium alone and given with lithium significantly increased GPx vs. Li-treated group after 3 weeks. Having regarded the outcomes of this study, the research on application of selenium during lithium treatment seems to be worth continuation.

Key words

Selenium • Lithium • Oxidative stress • Brain • Rats

Corresponding author

J. Kocot, Chair and Department of Medical Chemistry, Medical University of Lublin, Chodźki 4a, 20-093 Lublin, Poland. Fax: 81 535 7390. E-mail: joanna.kocot@umlub.pl

Introduction

For more than sixty years lithium salts have been widely used in different fields of medicine, first of all in psychiatry (Scheuch *et al.* 2010, Ahmad *et al.* 2011, Banerjee *et al.* 2012, Albayrak *et al.* 2013, Bauer *et al.* 2014). However, the promising outcomes concerning the possibility of its application in neurology (Camins *et al.* 2009, Ozkul *et al.* 2014) or in patients with thyroid diseases undergoing radioiodine therapy (Bogazzi *et al.* 2010) have also been reported. As lithium shows its beneficial action only within a strongly determined range (Vijaimohan *et al.* 2010, Singh *et al.* 2013, Smith *et al.* 2014) its administration must be applied taking appropriate precautions. An overrun of the safe threshold can result in different side effects including disturbances of nervous and alimentary system as well as disorders of kidneys, eyes and glands (Oktem *et al.* 2005, Saunders *et al.* 2009, Ahmad *et al.* 2011, Broberg *et al.* 2011, Eskandari *et al.* 2012). Our previous studies have shown changes of antioxidant activity in rats exposed to lithium (Kiełczykowska *et al.* 2008). Other scientists have also found the influence of lithium administration on oxidant processes (Bhalla *et al.* 2007, Malhotra and Dhawan 2008, Nciri *et al.* 2008, Eskandari *et al.* 2012, Ozkul *et al.* 2014). These observations provoked research on the use of essential metals or natural substances possessing antioxidant properties as protective agents against lithium toxicity (Chadha *et al.* 2008, Malhotra and Dhawan 2008, Vijaimohan *et al.* 2010). The contamination of the environment with lithium resulting from disposing of spent lithium batteries (Aral and Vecchio-Sadus 2008) as well as the fact that potential supplementation of drinking

water with lithium has been considered (Giotakos *et al.* 2013) suggest that such investigations could be worth undertaking.

Selenium belongs to essential microelements. Being a constituent of one of the main antioxidant enzymes – glutathione peroxidase - it is considered to be an antioxidant (Brüning *et al.* 2012, El-Demerdash and Nasr 2014, El-Boshy *et al.* 2015). Its possible application as a protective agent against toxic metals and compounds as well as against oxidative stress have already been studied and the outcomes have seemed to be encouraging (El-Demerdash 2004, Selamoglu Talas *et al.* 2009, El-Demerdash and Nasr 2014, Jebur *et al.* 2014, El-Boshy *et al.* 2015). Selenium alone or in combination with vitamin E has already been found to prevent oxidative stress in brain of animals exposed to cigarette smoke (Ozkan *et al*. 2007), chromium (Soudani *et al.* 2012) and mercury (Glaser *et al.* 2013).

Having regarded the presented facts we formulated a hypothesis that selenium could be administered to patients undergoing lithium therapy to alleviate side effects, particularly those related to oxidant stress. Relationships between selenium intake and functions of nervous system have already been reported (Benton 2002). In the current study the inorganic sodium selenite was chosen as it is still used in animal studies (Sreekala and Indira 2009, Loeschner *et al.* 2014) as well as in clinical practice (Savory *et al.* 2012, Beuth *et al.* 2013).

The present study was performed with the aim of evaluation if selenium in its inorganic form (sodium selenite) could exert beneficial influence on chosen oxidative parameters in brain of rats receiving lithium.

Materials and Methods

Animals

The experiment was carried out on adolescent male Wistar rats (48 animals, 130-160 g body weight). Rats had free access to standard feed and drinking water. The study was performed according to statutory bioethical standards and approved by Local Ethical Commission of Medical University of Lublin, acceptance no.1/2013.

Experimental design

After an acclimatization period of three days the animals were randomly divided into four groups (twelve animals each): group I (control) – treated with saline; group II (Li) – treated with lithium (as Li_2CO_3) at a dose of 2.7 mg Li/kg b.w.; group III (Se) – treated with selenium (as Na_2SeO_3) at a dose of 0.5 mg Se/kg b.w.; group IV (Li + Se) – treated simultaneously with lithium (Li_2CO_3) and selenium (Na_2SeO_3) at a dose of 2.7 mg Li/kg b.w. and of 0.5 mg Se/kg b.w., respectively. The administration was performed in form of water solutions by stomach tube. The compounds were given for a period of three or six weeks, once a day. Body mass of each animal was measured every day before administration and the appropriate amount of selenium and/or lithium solutions was calculated. After 3 weeks a half of rats of each group and after 6 weeks the rest of the animals were sacrificed under thiopental narcosis and samples of brain were collected. Ten per cent (w/v) tissue homogenates were prepared in 0.1 mol dm^{-3} Tris-HCl buffer, pH=7.4. Supernatants were obtained by centrifugation at 5000 x g for 30 min.

Biochemical investigations

The following oxidant parameters were determined in brain homogenates: activities of antioxidant enzymes – catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) as well as the concentration of a lipid peroxidation marker – malonyldialdehyde (MDA). CAT activity was measured using a spectrophotometric method described by Góth (1991) and expressed in U of CAT/mg of protein. SOD and GPx activities were determined using diagnostic kits RANSOD and RANSEL produced by RANDOX and expressed in U of SOD/mg of protein and U of GPx/g of protein, respectively. Malonyldialdehyde (MDA) concentration was determined using method of Ledwożyw *et al.* (1986) and expressed in mmol of MDA/g of protein. Protein was measured using method of Bradford (1976). The assays were performed with use of spectrophotometer SPECORD M40 (Zeiss Jena).

Statistics

All statistical analyses were 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) or Kruskal-Wallis one way analysis of variance (for non-normally distributed variables). Values were considered significant with $p<0.05$.

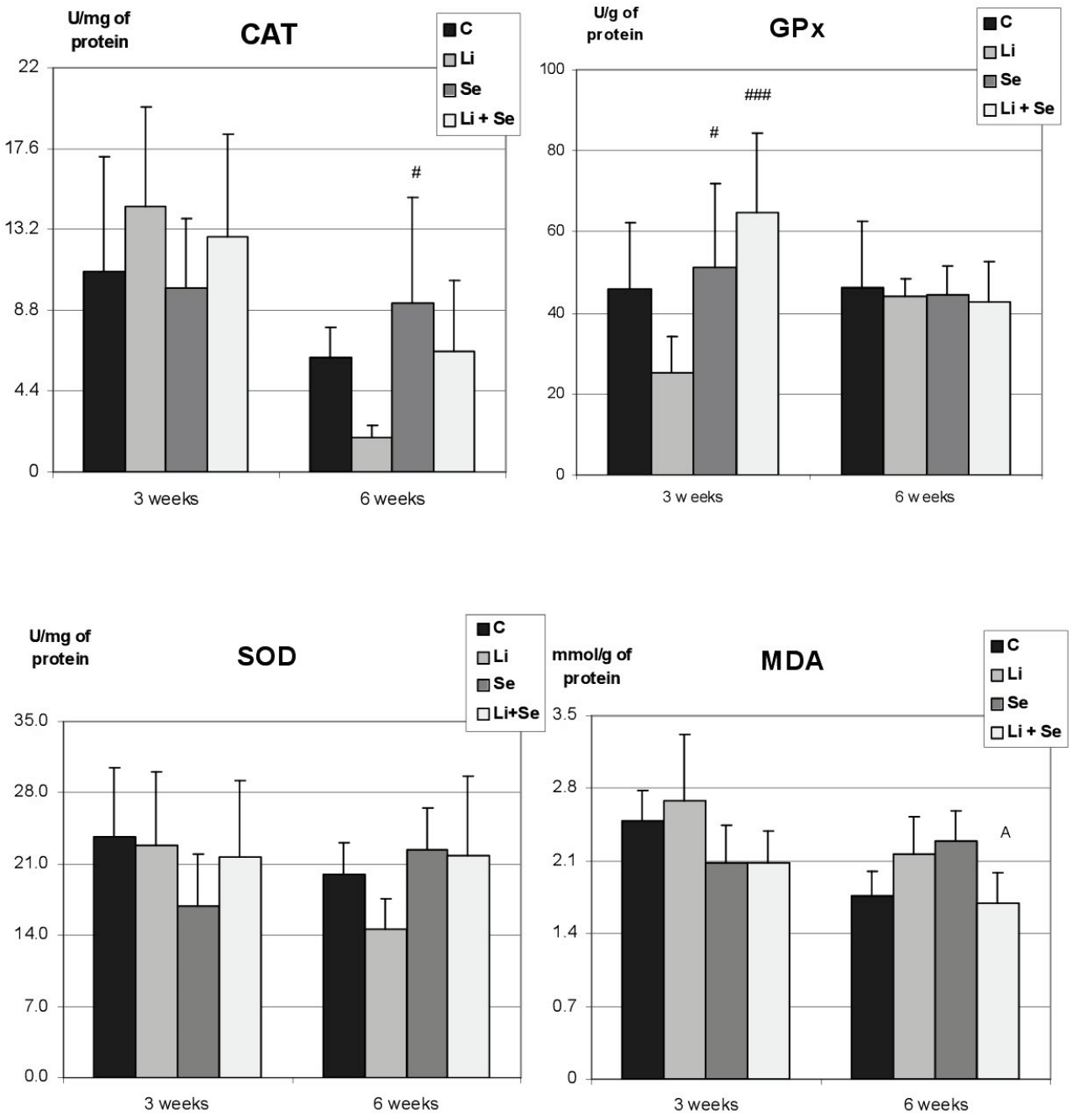

Fig. 1. CAT, GPx and SOD activity as well as MDA concentration in brain of rats receiving lithium and/or selenium. [A] significantly different vs. Se group $p<0.05$; [#] significantly different vs. Li group $p<0.05$; [###] significantly different vs. Li group $p<0.001$.

Results

After 3 weeks of experiment there were not distinct differences in CAT activity among the studied groups. After 6 weeks lithium slightly depressed CAT compared to control while selenium co-administration restored CAT activity. Selenium alone caused significant increase vs. Li-treated group ($p=0.0284$).

After 3 weeks in rats receiving lithium alone GPx was insignificantly depressed vs. control. Selenium alone and given with lithium significantly increased GPx vs. Li-treated group ($p=0.0351$ and $p=0.0008$, respectively). After 6 weeks the obtained values of GPx activity did not show any differences among all studied groups.

SOD activity did not markedly differ after both 3 and 6 weeks. However, a slight tendency to depletion in Li-treated rats vs. control, accompanied by restoration

tendency in Li + Se group was observed after 6 weeks.

MDA concentration after 3 weeks did not display significant differences. However selenium alone and given with lithium slightly depressed MDA in comparison with control and Li-treated group. After 6 weeks selenium given with lithium caused significant decrease when compared with Se-group ($p=0.0235$).

All the presented results are collected in Figure 1.

Discussion

Oxidative and nitrosative processes have been found to be involved into pathogenesis of diverse illnesses, including psychiatric ones (Savory *et al.* 2012, de Sousa *et al.* 2014a, b). Due to this fact the growing concern in possible application of antioxidant substances in preventing disorders of organism is being observed (Oktem *et al.* 2005, Chadha *et al.* 2008, El-Boshy *et al.* 2015).

The research on the effect of lithium on oxidant balance has revealed quite divergent results. Some authors have stated that lithium may exert antioxidant action (Banerjee *et al.* 2012, Albayrak *et al.* 2013, de Sousa *et al.* 2014b), whereas other scientists have reported contradicting results (Oktem *et al.* 2005, Ahmad *et al.* 2011, Eskandari *et al.* 2012). Furthermore, Nciri *et al.* (2008) showed that pro-oxidative action of lithium can differ, depending on the studied organ.

The attempts towards the application of bioelements and substances of natural origin possessing antioxidant properties as protective agents against lithium toxicity have already been made and the obtained results seem to be promising (Oktem *et al.* 2005, Bhalla *et al.* 2007, Chadha *et al.* 2008, Malhotra and Dhawan 2008, Vijaimohan *et al.* 2010).

In the current study lithium caused depletion of CAT and SOD after 6 weeks as well as GPx after 3 weeks. MDA was slightly increased. The obtained results are partially consistent with those reported by other authors.

Similarly as in the present experiment, GPx, SOD and CAT were not significantly altered in brain of mice receiving lithium carbonate in diet during 1- and 3-month-experiment (Riadh *et al.* 2011). In mice receiving lithium intraperitoneally no significant effect on brain CAT and GPx was observed (Nciri *et al.* 2008). No significant effect of dietary lithium on GPx and SOD was observed in hypothalamus and hippocampus of rats under normal condition, whereas in stressed animals GPx was not disturbed and SOD markedly increased (de Vasconcellos *et al.* 2006). Lithium pretreatment caused significant decrease in CAT and SOD in brain of rats treated with ouabain (Brüning *et al.* 2012). Several studies revealed that the influence of lithium on brain SOD can depend on the studied part. In rats receiving lithium cerebrum SOD was enhanced, whereas in cerebellum no changes were observed (Bhalla *et al.* 2007). On the other hand, lithium given to rats treated with aluminium significantly decreased CAT and SOD activities in cerebrum and cerebellum (Bhalla and Dhawan 2009). Fourteen-day-treatment with lithium markedly decreased SOD in prefrontal cortex and caused no changes in hippocampus, whereas in the case of CAT a slight, insignificant decrease was observed irrespective of the studied region (Frey *et al.* 2006). The differences in lithium influence on the SOD depending on the studied region of brain were also reported by Souza *et al.* (2014) who found no effect of lithium treatment on SOD in cerebral cortex, whereas in hippocampus significant decrease was observed. Interestingly, in the case of CAT and GPx no changes were observed in both studied regions.

Dietary lithium caused no significant changes of TBARS in rats (de Vasconcellos *et al.* 2006). The similar results were obtained in brain of mice receiving intraperitoneal injection of lithium carbonate (Nciri *et al.* 2008) as well as in brain of mice given lithium in diet (Riadh *et al.* 2011). Bhalla *et al.* (2007) observed significant increase in lipid peroxidation in cerebrum and cerebellum of rats treated with lithium. Short-term (14 days) lithium treatment resulted in no significant alterations of MDA in prefrontal cortex and hippocampus of rats (Frey *et al.* 2006).

In the current experiment selenium alone did not cause significant changes vs. control. Other scientists reported rather divergent results. In hippocampus of rats receiving DL-selenomethionine and exposed to mercury hippocampal SOD and MDA were found to be markedly increased (Su *et al.* 2008). Sreekala and Indira (2009) in turn found that sodium selenite depressed MDA and enhanced SOD, CAT and GPx in brain of rats. In brain of rats exposed to a carcinogenic substance selenium administered in organic form diminished MDA and increased CAT, SOD and GPx (Selamoglu Talas *et al.* 2008). GPx and SOD was practically unchanged, whereas CAT increased in brain of mice exposed to cigarette smoke and receiving seleno-L-methionine for 3 months.

The lengthening of the experiment period up to 5 months resulted in unchanged CAT and increased SOD and GPx (Ozkan *et al.* 2007). Selenium did not affect cortex brain GPx in rats (Naziroğlu *et al.* 2008). In mice treated with inorganic sodium selenite brain GPx was markedly increased while no significant effect was observed in those treated with methylmercury. TBARS was significantly enhanced by Se-administration both in animals without any other treatment and in those treated by methylmercury (Glaser *et al.* 2010). In contrast, in mice treated with organic selenium (diphenyl diselenide) cortical mitochondrial GPx was not altered while MDA was significantly depressed. The same results were shown in mice exposed to methylmercury (Glaser *et al.* 2013). Ghodbane *et al.* (2011) observed no significant influence of inorganic selenium on brain GPx in mice. However, in animals additionally subjected to static magnetic field a slight increase was noted.

There is not too much data concerning relationships between lithium and selenium. However, some studies have revealed interesting outcomes. The positive correlation between urinary selenium and T_4 and negative one between lithium urinary concentration and plasma free T_4 level were found in women inhabiting in areas of high lithium level in drinking water (Broberg *et al.* 2011). Some selenoorganic compounds have been found to show lithium-mimetic properties (Brüning *et al.* 2012, Singh *et al.* 2013). In the current study selenium given together with lithium did not markedly disturb any studied parameter in rat brain when compared with control group. Although the majority of the observed changes were insignificant, co-administration of selenium seems to display a tendency to restoration action in the case of parameters slightly altered by lithium alone (GPx after 3 weeks and the other studied parameters after 6 weeks). The obtained results are consistent with those obtained in our previous study in blood (Kiełczykowska *et al.* 2014).

Conclusion

The obtained results let suggest that this pilot study resulted in encouraging outcomes as the disturbances observed in Li-given rats were restored by co-administration of selenium. Having regarded the presented studies concerning the application of other (organic) forms of selenium, further studies could also include organic selenium compounds which have already been investigated in regard to their possible use as Se-supplements (Musik *et al.* 2013).

Conflict of Interest

There is no conflict of interest.

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