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The investigation of possible protective influence of selenium on antioxidant barrier in heart of rats exposed to lithium

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ABSTRACT

Aims: Selenium is an essential element possessing antioxidant properties and the treatment with it has displayed protective effects against toxicity of different substances occurring in the environment and food as well as against the side effects of some drugs. Lithium is used in medicine although numerous side effects can occur during therapy, including disturbances of the heart. For these reasons studies to find protective adjuvants have been performed. In the current study the possibility of selenium (as sodium selenite) application as a protective adjuvant in lithium treatment was studied.
Main methods: Male Wistar rats were treated: control — with saline; Li-group — with Li_2CO_3 (2.7 mg Li/kg b.w.); Se-group — with Na_2SeO_3 (0.5 mg Se/kg b.w.); Li + Se-group simultaneously with Li_2CO_3 and Na_2SeO_3 (2.7 mg Li/kg b.w. and 0.5 mg Se/kg b.w., respectively) by a stomach tube for a period of three weeks, once a day. In heart homogenate activities of antioxidant enzymes — catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx), concentrations of low-molecular-weight antioxidants — ascorbic acid (AA) and reduced glutathione (GSH) as well as total antioxidant status (TAS) values were determined. GPx/SOD and CAT/SOD ratios were evaluated.
Key findings: In comparison with control selenium caused no significant changes of the studied parameters except for GPx, whereas lithium slightly disturbed TAS and markedly GPx, CAT and CAT/SOD ratio. In Li-treated rats co-administration of selenium displayed tendency towards restoring the impaired parameters.
Significance: The results suggest that research on selenium application as an adjuvant in lithium therapy is worthy to be continued.

1. Introduction

Selenium is an essential element possessing antioxidant properties. As many pathological conditions include oxidative stress, the growing interest in the possible application of selenium in medicine is still being observed. Selenium treatment has been found to display protective effect against toxicity of substances occurring in environment and food as acrylamide [3], mycotoxins [10,36], lead [23,28], cadmium [20,41], methylmercury [15], manganese [46], arsenic [29] as well as against side effects of some drugs e.g.: cisplatin or neuroleptics [14,22]. Different forms of selenium have been studied including both inorganic selenite [20] and organic compounds [15,41] as well as selenium-enriched natural products [23,28]. Recently, the development of nanotechnology has prompted the attempts towards medical application of selenium nanoparticles [29,39].

Selenium has been found to affect functions of the cardiovascular system. Its deficiency has been reported to induce cardiomyocyte injury [11] as well as to increase cardiotoxicity of drugs and heart dysfunctions observed in pathological conditions [37,40]. The effect of selenium supplementation in the form of sodium selenite has been studied in patients with coronary artery disease and the outcomes have been encouraging [33].

Lithium has been used in medicine for more then sixty years. As its beneficial effect has been revealed in the cases of psychiatric and neurological diseases [16,47], as well as an adjuvant in the cure of thyroid disorders [25], lithium is still applied despite numerous side effects [30]. The most important ones include disturbances of the heart, kidney, glands and gastrointestinal system functions [6,35,47]. Electrocardiographic changes in patients receiving lithium have been reported, even with lithium being in the therapeutic range [4,18,35]. Teratogenic effects of lithium therapy can also include cardiac injuries [13]. These effects can considerably influence the living conditions and compliance of patients.

For these reasons the studies of finding protective adjuvant which could alleviate the side effects of lithium treatment have been performed recently, including substances possessing antioxidant properties [27,43], and the outcomes seem to be promising. Aiming at contributing to this research we performed the current study with the purpose of evaluating if selenium could be applied as a protective adjuvant in patients undergoing lithium treatment. An easily assimilated inorganic form of selenium — sodium selenite, was chosen as it is still an

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acknowledged selenium supplement used both in clinical and animal studies [10,33,36].

2. Materials and methods

2.1. Animals

The experiment was carried out on adolescent male Wistar rats (24 animals, 130–160 g body weight). Rats had free access to standard feed and drinking water. The study was performed according to the statutory bioethical standards and approved by I Local Ethical Commission of Medical University of Lublin, acceptance no. 1/2013.

2.2. Experimental design

After an acclimatization period of three days the animals were randomly divided into four groups (six animals each):

- control — treated with saline;
- Li-group — treated with lithium (as Li_2CO_3) at a dose of 2.7 mg Li/kg b.w.;
- Se group — treated with selenium (as Na_2SeO_3) at a dose of 0.5 mg Se/kg b.w.;
- Li + Se-group — treated simultaneously with lithium (Li_2CO_3) and selenium (Na_2SeO_3) at a dose of 2.7 mg Li/kg b.w. and 0.5 mg Se/kg b.w., respectively.

The administration was performed in the form of water solutions by a stomach tube. The compounds were given for a period of three weeks, once a day. The body mass of each animal was measured every day before administration and the appropriate amount of selenium and/or lithium solutions was calculated. The doses and period of treatment were established based on our previous studies regarding lithium and selenium effects on animal organisms to enable the comparison of the obtained results [19,24].

After the end of the treatment the animals were sacrificed under thiopental narcosis and samples of heart were collected. Ten percent (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 × g for 30 min.

2.3. Biochemical investigations

The following oxidant parameters were determined in heart homogenates: total antioxidant status (TAS), activities of antioxidant enzymes — catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD) as well as concentrations of low-molecular-weight antioxidants — ascorbic acid (AA) and reduced glutathione (GSH).

TAS values in plasma were assayed using a diagnostic kit produced by RANDOX and expressed in mmol of TAS/g of protein.

CAT activity was determined using a spectrophotometric method described by Aebi [1] and expressed in U of CAT/mg of protein. One unit of CAT was defined as such an amount of the enzyme which causes the decomposition of 1 μmol of H_2O_2/min at 25 °C.

SOD and GPx activities were assayed 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.

AA concentration was determined using the modified Kyaw method [32] and expressed in μmol of AA/g of protein.

GSH concentration was determined using BIOXYTECH® GSH-400™ kit produced by OxisResearch™ and expressed in μmol of GSH/g of protein.

Protein was assayed using the method of Bradford [7].

The measurements were performed with the use of a spectrophotometer SPECORD M40 (Zeiss Jena).

GPx/SOD and CAT/SOD ratios were evaluated.

2.4. Statistics

All statistical analyses were performed using STATISTICA programme (version 10.0). The normality of data distribution was verified using the Shapiro–Wilk test. The differences among the studied groups were analysed using a one-way analysis of variance (ANOVA), followed by the Tukey test (for normally distributed variables) or the Kruskal–Wallis ANOVA test followed by a multiple comparisons test (for non-normally distributed variables). Values were considered significant with $p < 0.05$.

3. Results and discussion

TAS was decreased in Li-given animals in comparison with all the other groups although no statistical significance was obtained vs. control. However, in the Se and Li + Se groups TAS was markedly increased compared to the lithium group.

CAT was significantly increased in the Li-treated group vs. control. In the selenium group a well-marked decrease vs. Li group was observed.

GPx was significantly depressed in the Li and Se groups vs. control, whereas in Li + Se-treated animals a significant increase compared to both the Li and Se alone groups was found.

SOD activity was significantly decreased in the Li + Se-treated rats in comparison to control. The other studied groups displayed no significant differences.

AA and GSH concentration values did not show any distinct differences.

The obtained results are presented in Fig. 1.

GPx/SOD ratio was slightly diminished in animals treated with lithium or selenium alone vs. control. In rats given lithium and selenium together a significant increase compared to both the lithium and selenium alone groups was observed. The CAT/SOD ratio was significantly increased in the Li-given rats compared to control. Selenium alone and co-administered with lithium did cause any significant differences in comparison to control. The obtained results are presented in Fig. 2.

In the present study most studied parameters were not disturbed by selenium given alone or together with lithium compared with control. It is important as excess of selenium can result in cardiotoxicity as well as act as a prooxidant [37]. The obtained outcomes are partially consistent with the results reported by other scientists.

Similarly as in the current experiment, Wu and Huang observed no statistical differences in heart total antioxidant capacity activity of weanling rats receiving Se-deficit diet or supplemented with Se in drinking water compared to control fed Se-adequate food [44]. Interestingly, in arterial walls and aorta Se-supplementation resulted in no well-marked effects, whereas dietary selenium deficit caused a significant depletion of the total antioxidant capacity activity [44,45]. According to Danesi et al., in rats receiving dietary selenium a significant increase in heart total antioxidant activity was found but the period of treatment was considerably higher. In our study in animals receiving lithium, co-administration of selenium caused a well-marked increase in TAS vs. the Li-treated group. Similarly, in rats additionally exposed to a drug (Adriamycin) a significant increase was caused by additional Se-treatment [12].

With regard to heart CAT, the same lack of effect of selenium on heart CAT was found in rats receiving Se-supplemented diet [5,12]. The investigations regarding the influence of selenium in animals undergoing exposure to other substances resulted in divergent outcomes. A distinct increase in CAT activity was reported in rats exposed to carcinogen and receiving organic selenium [34]. In rats exposed to Adriamycin dietary selenium did not alter CAT or caused only a slight increase [12]. In those exposed to a pesticide and treated with sodium selenite a significant decrease was obtained [5]. Similarly, we observed a slight decrease in rats given lithium + selenium compared to the

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