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Short communication

Antidepressant and anxiolytic-like activity of sodium selenite after acute treatment in mice

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ABSTRACT

Background: Selenium (Se) is an essential trace element for humans and animals, that is needed for a broad variety of physiological functions including thyroid hormone metabolism, protection against oxidative stress, and immunity associated functions. Human nutritional Se deficiencies are associated with neuropsychiatric diseases, like Alzheimer's disease, Parkinson's disease, obsessive – compulsive disorder, stroke, epilepsy as well as depressive behaviours. In this study we examined antidepressant- and anxiolytic-like activity of Se in the inorganic form of sodium selenite and investigated whether Se influence on the locomotor activity in mice.

Methods: The antidepressant-like and anxiolytic-like activity of Se was assessed using forced swim test (FST) and elevated plus-maze test (EPM), respectively. Spontaneous locomotor activity was measured using photoresistor actimeters.

Results: Sodium selenite administered at the doses of 0.5, 1, and 2 mg/kg, *ip* reduced immobility time in the FST exerting antidepressant-like activity. In the EPM test, sodium selenite at the same doses, produced anxiolytic-like effect; the doses active in both tests did not affect locomotor activity, indicating that these effects of Se are specific.

Conclusions: These potential antidepressant- and anxiolytic-like effects of Se require more detailed experimental study using animal models to approach a clear conclusion regarding the potential mechanism of the observed effect.

Introduction

Selenium (Se) is an essential trace element for humans and animals, needed for a broad variety of physiological functions, such as thyroid hormone metabolism, protection against oxidative stress and immunity associated functions. Se is also crucial for the central nervous system (CNS), where it is preferentially held and protects brain regions (hippocampus, striatum, frontal cortex) against oxidative damage. Much of this beneficial impact is attributed to selenoenzymes, like glutathione peroxidases (Gpx) and thioredoxin reductases (TrxR), in which Se has its site, although Se may act on the CNS directly, as in the form of selenite, and it is possible that Se may have some other special functions as well [1–7]. Neuroprotective properties of Se may be also attributed to its ability to modulate Ca^{2+} influx [8–10] and anti-inflammatory effect [11,12]. Literature data shows that Se may take part in neurotransmission mechanisms [5] by affecting dopaminergic [13–16], gamma amino butyric acid (GABA)-ergic [17–20], cholinergic [21] and glutamatergic pathways [22].

Human nutritional Se deficiencies manifest as decreased plasma Se levels and are associated with nonspecific clinical signs, such as neuropsychiatric diseases, like Alzheimer's disease (AD), Parkinson's disease (PD), stroke and epilepsy [23–26]. In animals with insufficient brain Se levels, spasticity, abnormal movements and spontaneous seizures may develop [2,7]. A few preclinical and clinical studies have demonstrated a positive role of Se in cognitive performance [21]. Some studies on sodium selenite demonstrated its efficacy in different animal AD [21,27,28] and epilepsy models [8,29]. Moreover, Se deficits have been related to depressive behaviors, while Se supplementation has been observed to improve mood and decrease anxiety [2,30–33]. All above-mentioned studies suggest that Se plays a crucial role in the CNS, is a potent protective agent for neurons and may be potentially helpful as preventive or therapeutic agent in

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neuropsychiatric disorders, however its mechanism of action is not well understood and requires further investigation.

Several studies have shown that Se in organoselenium compounds exert antidepressant- and anxiolytic-like effects in animal models [16,34,35], while there is no data about such effects exerted by inorganic forms of Se. However, according to the literature data, sodium selenite – present in many dietary supplements – is one of the most recommended Se-containing compounds, as a god dietary source of Se [36], especially in cancer chemoprevention, [2,37,38] and in autoimmune disorders, such as Hashimoto's disease and rheumatoid arthritis [39,40]. Besides, it is worth emphasizing that selenite is one of the most often studied Se species in the context of neurodegeneration, e.g. AD, PD, epilepsy [23–26], and neurotransmission [5]; and both organic and inorganic forms of Se can be metabolized to hydrogen selenide, the starting point for selenoprotein synthesis [2,5].

Because depression and anxiety coexist in clinical practice and prognosis in depression, complicated by anxiety, is worse than prognosis of depression alone, the literature data prompted us to examine the antidepressant- and anxiolytic-like activities of Se in the form of selenite. We used mice models with the forced swim test (FST) and elevated plus-maze test (EPM). We also investigated whether the effects of Se were specific, measuring its effects on the locomotor activity in mice. Those *in vivo* experiments were a part of a series of studies designed to check the central activity of inorganic Se.

Materials and methods

Animals and drugs administration

The study was carried out on male Albino Swiss mice (18–23 g), 8–10 per cage, at room temperature of 22 ± 1 °C, with free access to food (LSM, Poland) and water. All the experiments were performed between 09:00 and 16:00 h, according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and to the European Community Directive for the Care and Use of Laboratory of 24 November 1986 (86/609/EEC), and approved by the Local Ethics Committee for Animal Experimentation of the Medical University of Lublin (Permit Number: 80/2016). Sodium selenite was purchased from Sigma-Aldrich and administered at doses of 0.5, 1 and 2 mg/kg (equivalent to 0.225, 0.45 and 0.9 mg of elemental Se/kg body weight). The selection of doses of sodium selenite and administration time before the tests was based on literature data [29,41,42] and on own pilot studies.

The route of administration was intraperitoneal (*ip*), enabling a more precise control of Se amounts. Prior to administration, the agent was dissolved in saline and injected 30 min before the tests, in volumes of 10 ml/kg body weight. Each experimental group consisted of eight to twelve animals per dose. The controls received equivalent volumes of the solvent (saline) at the respective time before the tests.

Behavioral tests

Forced swim test (FST, Porsolt's test)

The studies were carried out on mice, according to the method of Porsolt and co-workers [43]. Mice were individually propped into glass cylinders (height 25 cm, diameter 10 cm) with 10 cm of water, maintained at 23–25 °C. The animals were left in the cylinder for 6 min. After the first 2 min the total duration of immobility was measured during a 4-min test. The mouse was regarded immobile when floating passively in water.

Elevated plus-maze test

The elevated plus-maze test was adapted for mice by Lister [44] and it now includes two open (30 × 5 × 0.25 cm) and two closed arms (30 × 5 × 15 cm), as well as a common, centrally placed square (5 × 5 cm). The test apparatus (Bioseb) was made of Plexiglas, located 45 cm above the floor and illuminated with weak red light. The mice were individually placed at the central square of the plus-maze apparatus, facing the open arm, while their behavior was observed for 5 min (using a stopwatch totalizer). The following measures were obtained from the test: the time spent in the open arms expressed as a percentage of the time spent in both the open and closed arms, as well as the percentage of open arm entries. The total number of entries into either type of arm was used as a measure of overall locomotor activity.

Locomotor activity

Spontaneous locomotor activity was measured by photoresistor actimeters (circular cages, diameter of 25 cm, two light beams, Multiserv, Poland). The mice were individually placed in cages for 10 min habituation period and then their activity was measured from 2 to 6 min, corresponding to the observation periods in the FST. The number of light beams, crossed by the mice, was recorded as their locomotor activity indicator.

Statistics

The obtained data were processed by one-way analysis of variance – ANOVA, followed by the Dunnett's *post hoc* test. The results are presented as mean ± standard errors (SEM). The level of $p < 0.05$ was considered as statistically significant. All the figures were prepared by the GraphPad Prism program in version 5.00 for Windows, (San Diego, California, USA) www.graphpad.com.

Results

Effects of Se in the forced swim test (FST) in mice

Statistical analysis of the results obtained in the FST revealed that sodium selenite, at the doses of 0.5, 1 and 2 mg/kg exerted statistically significant antidepressant effect ($p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively), which manifested in the reduction of total immobility time in comparison with the control group [Fig. 1A; ANOVA: $F(3,36) = 7.147$; $p < 0.001$; Dunnett's *post hoc* test].

Effects of Se in the elevated plus-maze (EPM) test in mice

Sodium selenite, at the doses of 0.5, 1 and 2 mg/kg produced an anxiolytic-like effect, significantly increasing the percentage of time spent in the open arms [Fig. 2A; ANOVA: $F(3, 28) = 3.814$; $p < 0.05$; Dunnett's *post hoc* test], but it neither significantly changed the number of entries into the open arms [Fig. 2B; ANOVA: $F(3,28) = 1.534$; $p = 0.2275$] nor altered the number of total arm entries [Fig. 2C; ANOVA: $F(3,28) = 0.06016$; $p = 0.9803$] (Table 1).

Effect of Se on spontaneous locomotor activity in mice

Sodium selenite, in used doses, did not influence locomotor activity in mice, since one-way ANOVA did not show any differences in motility between groups [Fig. 1B; Table 1 ANOVA: $F(3,28) = 0.3526$; $p < 0.7876$; Dunnett's *post hoc* test].