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p-Chloro-diphenyl diselenide reverses memory impairment-related to stress caused by corticosterone and modulates hippocampal [^{3}H]glutamate uptake in mice

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HIGHLIGHTS

- (p-ClPhSe)$_2$ reversed memory deficits caused by corticosterone in mice.
- (p-ClPhSe)$_2$ modulated hippocampal [^{3}H]glutamate uptake in mice.
- There was no sign of toxicity in mice treated with (p-ClPhSe)2.

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ABSTRACT

Chronic stress or chronically high levels of glucocorticoids can result in memory impairment. This study aimed to investigate if 4,4′-dichloro-diphenyl diselenide (p-ClPhSe)$_2$ reverses memory impairment-related to stress caused by corticosterone administration in mice and its possible mechanism of action. Swiss mice received corticosterone (20 μg/ml) in their drinking water during four weeks. In the last week, the animals were treated with (p-ClPhSe)$_2$ (1 or 5 mg/kg) by the intragastric route (i.g.) once a day for 7 days. The cognitive performance of mice was assessed through the object recognition test (ORT), the object location test (OLT) and the step-down passive avoidance test (SDPA), some of predictive tests of memory. Biochemical parameters were determined and locomotor activity of mouse was performed to gain insight in (p-ClPhSe)$_2$ toxicity. The findings demonstrated that treatment with (p-ClPhSe)$_2$ in both doses was effective in reversing memory deficits in the ORT, the OLT and the SDPA caused by corticosterone exposure in mice. Treatment with (p-ClPhSe)$_2$ at both doses reversed the increase in the [^{3}H] glutamate uptake by hippocampal slices of mice treated with corticosterone. By contrast, [^{3}H] glutamate uptake by brain cortical slices was not altered in mice exposed to corticosterone. The Na^+K^+ ATPase activity was not altered in hippocampus and cerebral cortices of mice treated with corticosterone. There was no sign of toxicity in mice treated with (p-ClPhSe)$_2$. This organoselenium compound reversed memory impairment-related to stress caused by corticosterone and modulated hippocampal [^{3}H]glutamate uptake in mice.

1. Introduction

Stress is characterized by physiological changes that occur in response to novel or threatening stimuli. These changes comprise a cascade of neuroendocrine events mediated by stress systems such as the hypothalamic–pituitary–adrenal (HPA) axis. Its activation triggered the release of hypothalamic corticotropin-releasing hormone (CRH) which in turn releases pituitary adrenocorticotropin-releasing hormone (ACTH), culminating in the secretion of adrenal glucocorticoids (cortisol in humans and corticosterone in rodents) into the circulatory system [1].

Experimental and clinical data have shown a hypersecretion of glucocorticoids in neurodegenerative diseases such as Alzheimer's disease [2]. Corticosterone, the major glucocorticoid in rodents, plays a critical role in the regulation of the HPA axis and in manifold effects on health, emotion, and cognition [3,4]. It has been reported impairment in the memory function and its interconnection with increased glucocorticoid levels in animal models of stress. This condition could be experimentally

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mimicked through systemic administration of corticosterone or glucocorticoid receptor agonists which trigger an inhibitory influence on learning and memory retrieval [5].

Selenium is an essential trace element for growth, metabolism, development, immune function and antioxidant defense system in rodents and in human beings as well [6,7]. This element is involved in the maintenance of physiologic functions especially due to its in selenium containing proteins known as selenoproteins [8] provides protection from free-radical-induced cell damage [9,10], modulates the function of the thyroid gland and has been shown potential antiviral effects [11,12]. An inverse relationship between Se status and the incidence of various diseases has been observed in epidemiological studies [10,13]. Abnormal levels of Se were found in the plasma of patients with impaired cognitive functions and neurological disorders [14]. In addition, it is important to remark that diminished selenium concentrations in the brain affect its normal function and can cause neuronal loss and metabolic disturbances [15]. One of the most studied organoselenium compounds is diphenyl diselenide, $(PhSe)_2$, a simple synthetic compound which exhibits numerous biological actions. It has been reported that this compound is a potent anti-inflammatory, antioxidant, antidepressant- and anxiolytic-like agent in different animal models [16,17]. In addition, evidence has been found to support the idea that $(PhSe)_2$ improves memory and learning in mice [18] and enhances acquisition and retention of spatial memory of rats in the water maze and *T*-maze tests [19]. In this way, 4,4′-dichloro-diphenyl diselenide $(p\text{-ClPhSe})_2$, a derivative compound of $(PhSe)_2$, has been reported to have antidepressant-like activity in the rat forced swimming test [20], anorexigenic [21] and memory enhancer actions in the object location test in aged rats [20].

Regarding the promising memory enhancer actions of $(p\text{-ClPhSe})_2$ in old rats [20] and the search for drugs that minimize memory impairment induced by glicocorticoids, the aim of the present study was to investigate whether $(p\text{-ClPhSe})_2$ reverses memory impairment- related to stress caused by corticosterone administration in mice and its possible mechanism of action.

2. Experimental procedure

2.1. Animals

The study was conducted using adult (2 months) male Swiss mice (25–35 g), conventional, which were obtained from a local breeding colony from The Central Animal Facility that provides a centre for the maintenance, by skilled and experienced personnel, of quality animals in a controlled environment of the Federal University of Santa Maria. The animals were maintained at 22 ± 2 °C under a 12:12 h light/dark cycle, with lights turned on at 7:00 a.m. Commercial diet (Guaiba, RS, Brazil) and water are sterilized and were supplied ad libitum.

The experiment was performed using a randomized schedule on separate groups of animals that were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources of the Federal University of Santa Maria, Brazil (n° 6997050115). The procedures in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

2.2. Drugs

The compound $(p\text{-ClPhSe})_2$ (Fig. 1) was prepared and characterized by the method previously described to Paulmier [22] and accurately evaluated before its use. Analysis of the ^1H NMR and ^{13}CNMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. $(p\text{-ClPhSe})_2$ chemical purity (99.9%) was determined by GC–MS. Corticosterone was obtained from Sigma (St. Louis, MO, USA) and all the other chemicals were of analytical grade and obtained from standard commercial suppliers.

$(p\text{-ClPhSe})_2$ and corticosterone were dissolved in mineral oil and in water with ethanol (1% EtOH/H_2O), respectively. The organoselenium compound was administered to mice in a constant volume of 10 ml/kg of body weight and appropriate vehicle-treated groups were simultaneously assessed as well.

2.3. Experimental design

The experimental design of this study is depicted in Fig. 1. The animals were randomly assigned in six different groups (n = 10 mice/group) as following:

- ✓ Group I: vehicle (1% EtOH/H_2O) + mineral oil
- ✓ Group II: corticosterone + mineral oil
- ✓ Groups III and IV: vehicle (1% EtOH/H_2O) + $(p\text{-ClPhSe})_2$ (1 or 5 mg/kg/day)
- ✓ Groups V and VI: corticosterone + $(p\text{-ClPhSe})_2$ (1 or 5 mg/kg/day).

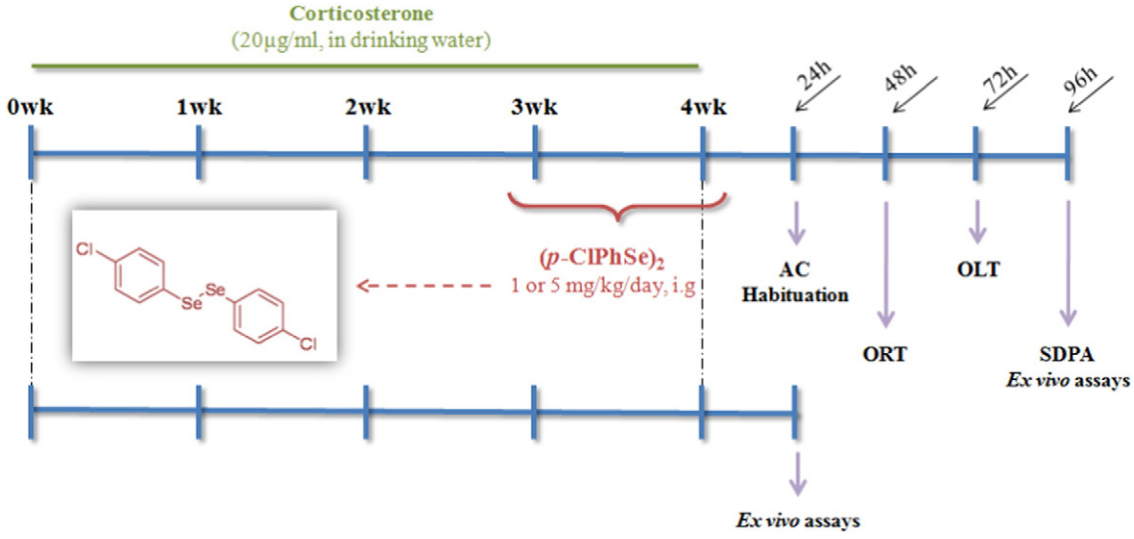

Fig. 1. Schematic representation of the experimental design. Corticosterone solution or vehicle was given to mice during 4 weeks. In the last week, mice received a daily i.g. administration of $(p\text{-ClPhSe})_2$ (1 or 5 mg/kg) represented by the chemical structure. Behavioral tests started at 24 h after the last dose of $(p\text{-ClPhSe})_2$ and were performed in consecutive days as illustrated in this figure, activity chamber (AC), object recognition test (ORT), object location test (OLT) and step-down passive avoidance test (SDPA). *Ex vivo* assays were determined at 96 h after the last dose of $(p\text{-ClPhSe})_2$.