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Diphenyl diselenide reverses cadmium-induced oxidative damage on mice tissues

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Abstract

The concept that selenium-containing molecules may be better antioxidants than classical antioxidants, has led to the design of synthetic organoselenium compounds. In the present investigation subchronic deleterious effects of cadmium-intoxication in mice and a possible protective effect of diphenyl diselenide $(PhSe)_2$ (5 μmol/kg) were studied. Male adult Swiss albino mice (25–35 g) received $CdCl_2$ (10 μmol/kg, subcutaneously), five times/week, for 4 weeks. A number of toxicological parameters in blood, liver, kidney, spleen and brain of mice were examined including δ-aminolevulinic acid dehydratase (δ-ALA-D) activity, lipid peroxidation and ascorbic acid content, the parameters that indicate tissue damage such as plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine and lactate dehydrogenase (LDH) were also determined. The results demonstrated that cadmium caused inhibition of δ-ALA-D activity in liver (24%), kidney (33%) and spleen (73%) and $(PhSe)_2$ therapy was effective in restoring enzyme activity in all tissues. A reduction in ascorbic acid content was observed in kidney (11%) and spleen (10.7%) of cadmium-treated mice and $(PhSe)_2$ was only effective in improving this reduction in kidney. An increase of lipid peroxidation induced by cadmium was noted in liver (29%) and brain (28%) tissues and $(PhSe)_2$ therapy was effective in restoring TBARS levels in both tissues. We also observed an increase on plasma LDH (1.99-times), AST (1.93-times) and ALT (4.24-times) activities. $(PhSe)_2$ therapy was effective in restoring AST activity at control level. $(PhSe)_2$ did not present toxic effects when plasma parameters were evaluated. The results suggest that the administration of an antioxidant $(PhSe)_2$, during cadmium intoxication may provide beneficial effects by reducing oxidative stress in tissues.

Keywords: Antioxidant; Cadmium; Selenium; Organoselenium; Mice

1. Introduction

The exposure of human populations to a variety of heavy metals has been a public health concern

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[1]. Cadmium (Cd) is one of the most abundant non-essential elements due to its immense usage in various industrial applications [2]. Therefore, human intoxication has been investigated following occupational as well as environmental exposure [3]. The molecular mechanism responsible for the toxic effects of cadmium is far from being completely understood. However, lipid peroxidation has long been considered the primary mechanism for cadmium toxicity [4–7]. Thus, it is believed that antioxidant should be one of the important components of an effective treatment of cadmium poisoning. In line with this, several studies have been performed with different natural substances possessing antioxidant properties to investigate their possible protective effects in cadmium-induced tissues damage. Among those melatonin, α-lipoic acid, quercetin, hydroxytyrosol and coenzyme Q10 have been addressed to have protective functions [8–12].

The concept that selenium-containing molecules may be better nucleophiles (and therefore antioxidants) than classical antioxidants, has led to the design of synthetic organoselenium compounds [13]. Several reports have been published on glutathione peroxidase (GSH-px)-mimetic seleno-compounds, which, like the native enzyme, rely on the redox cycling of selenium. In fact, recent study has shown that the diaryl diselenides were potent antioxidants in mice [14]. A variety of seleno organic compounds are now considered as potential pharmacological agents [15–18].

Recently, we demonstrated that diphenyl diselenide was as effective in restoring acute cadmium-induced oxidative damage in mice testes as the chelating compounds succimer [6] and DMPS [7]. In the present study we investigated the beneficial effects of diphenyl diselenide on subchronic cadmium-poisoning. Thereby, we evaluated the effect of cadmium on toxicological parameters in mice tissues.

2. Materials and methods

2.1. Chemicals

$CdCl_2$, δ-aminolevulinic acid (δ-ALA) and *p*-dimethylaminobenzaldehyde were purchased from Sigma (St. Louis, MO, USA). Diphenyl diselenide (Fig. 1) was synthesized according to Paulmier [19]. Analysis of the ^{1}H NMR and ^{13}C NMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of diphenyl diselenide (99.9%) was determined by GC/HPLC. All other chemicals were of analytical grade and obtained from standard commercial suppliers. $(PhSe)_2$ was dissolved in DMSO (dimethylsulfoxide).

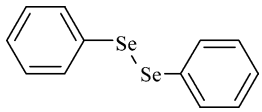

Fig. 1. Diphenyl diselenide.

2.2. Animals

Male adult Swiss albino mice (25–35 g) from our own breeding colony were used. The animals were kept on separate animal rooms, on a 12 h light/dark cycle, at a room temperature of 22 °C, with free access to food and water. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Medicine Veterinary and Animal Science of the University of Sao Paulo, Brazil.

2.3. Experimental design

Groups of six to eight mice were usually tested. Mice received cadmium chloride ($CdCl_2$), subcutaneously, at 10 μmol/kg dose (dissolved in saline at 0.25 mg/ml), five times/week, for 4 weeks [20] Table 1. Thirty minutes later they were injected subcutaneously with diphenyl diselenide (5 μmol/kg), an effective and non-toxic dose [6,7,17].

Twenty-four hours after the last $CdCl_2$ treatment, animals were slightly anesthetized with ether for blood collect, by heart puncture. After that, liver, kidney, brain and spleen were removed.

Table 1
Protocol of mice treatment

Groups	Treatments
Group 1 ($n = 6$)	Saline (s.c.) + DMSO (s.c.)
Group 2 ($n = 8$)	$CdCl_2$ (10 μmol/kg, s.c.) + DMSO (s.c.)
Group 3 ($n = 6$)	Saline (s.c.) + $(PhSe)_2$ (5 μmol/kg, s.c.)
Group 4 ($n = 8$)	$CdCl_2$ (10 μmol/kg, s.c.) + $(PhSe)_2$ (5 μmol/kg, s.c.)

Animals received treatments during 4 weeks, five times/week. "*n*" represents the number of mice tested in each group.