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Effects of 4,4′-dichloro-diphenyl diselenide $(ClPhSe)_2$ on toxicity induced by mercuric chloride in mice: A comparative study with diphenyl diselenide $(PhSe)_2$

Mayara L. de Freitas[a], *Andreia R.H. da Silva*[a], *Silvane S. Roman*[b], *Ricardo Brandão*[a,*]

[a] *Departamento de Análises Clínicas e Toxicológicas, Centro de Ciências da Saúde, Universidade Federal de Santa Maria, Santa Maria, CEP 97105-900, RS, Brazil*

[b] *Departamento de Ciências da Saúde, Universidade Regional Integrada do Alto Uruguai e das Missões, Campus de Erechim, Erechim, CEP 99700-000, RS, Brazil*

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ABSTRACT

The effects of 4,4′-dichloro-diphenyl diselenide $(ClPhSe)_2$ on the toxicity induced by mercuric chloride ($HgCl_2$) were investigated and compared with diphenyl diselenide $(PhSe)_2$. Mice received $HgCl_2$ for three days and, on the third day, received $(PhSe)_2$ or $(ClPhSe)_2$. The results verified that the administration of $(ClPhSe)_2$ in mice exposed to $HgCl_2$ increased renal δ-aminolevulinate dehydratase (δ-ALA-D), Na^+, K^+-ATPase activities and non-protein thiol (NPSH) levels and also decreased thiobarbituric acid-reactive substances (TBARS) and ascorbic acid levels, when compared to mice exposed to $HgCl_2$ + $(PhSe)_2$. Plasma and urinary protein, hemoglobin and hematocrit levels and histological parameters were also ameliorated in mice exposed to $HgCl_2$ + $(ClPhSe)_2$. In addition, the hepatic damage in mice exposed to $HgCl_2$ + $(PhSe)_2$ was reduced in animals exposed to $(ClPhSe)_2$. To sum up, the introduction of a functional group (chloro) in the aromatic ring of diaryl diselenide reduced the toxicity of this compound in liver and kidney of mice exposed to $HgCl_2$.

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1. Introduction

Mercury (Hg) is a toxic metal that results in a variety of adverse health effects, which include neurological, renal, respiratory, immune, dermatologic, reproductive and developmental sequelle (Risher and Amler, 2005). Several studies have demonstrated that Hg exposure can induce lipid peroxidation (Huang et al., 1996) and inhibition of sulfhydryl enzymes such as δ-aminolevulinate dehydratase (δ-ALA-D) (Emanuelli et al., 1996) and Na^+, K^+-ATPase (Anner and Moosmayer, 1992). The risks to health which are caused due to this metal are generally related to specific human activities from unintentional occupational exposure (Rohling and Demakis, 2006). Recently discussed, the main forms of Mercury exposure are amalgam filling (inorganic Hg), food, especially fish (methyl Hg) and as a preservative in vaccines (thimerosal) (Clarkson and Magos, 2006).

Selenium (Se) was recognized as an essential trace element within a relatively low concentration range (Schwartz and Foltz, 1957) and its physiological role was established when it presented to be one of the glutathione peroxidase (GPx) components (Rotruck et al., 1973). Diphenyl diselenide $(PhSe)_2$, an organoselenium compound, has been reported as a molecule

* *Corresponding author*. Tel.: +55 55 3220 8941.
E-mail address: ricardo_br79@yahoo.com.br (R. Brandão).
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"janus-face" (Nogueira and Rocha, 2010), with pharmacological properties such as anti-inflammatory, antinociceptive, anti-ulcer, neuroprotective and antioxidant in different experimental models (Nogueira et al., 2004). In addition, $(PhSe)_2$ seems to be useful in reducing cadmium levels and in ameliorating lipid peroxidation, a process that is important for cadmium toxicity (Santos et al., 2004, 2005). On the other hand, Nogueira et al. (2003a) discovered that $(PhSe)_2$ inhibits δ-ALA-D activity from human blood and cerebral Na^+, K^+-ATPase activity (Borges et al., 2005) by interacting with SH groups of these enzymes and also with negative neuronal effects (Nogueira et al., 2003b; Prigol et al., 2008).

Organoselenium compounds have received considerable attention as useful synthetic reagents and intermediates in organic synthesis (Patai and Rappoport, 1987). In addition, metals like Hg, cadmium (Cd) and zinc (Zn) has been also used in organic synthesis for the isolation of selenolates (Mugesh and Singh, 1998). In fact, mercuric chloride ($HgCl_2$) is utilized with other chemical compounds to reductive cleavage of the Se–Se in diselenides chemically synthesized (Wang and Zhang, 1999). Therefore, workers of organic synthesis labs are subject to simultaneous exposure to diselenides and heavy metals, such as Hg.

Previous studies of our research group demonstrated that $(PhSe)_2$ potentiates toxicity induced by $HgCl_2$ in mice (Brandão et al., 2006, 2010), affecting then hepatic and renal tissue. Studies of our research group have also demonstrated that the introduction of functional groups in the aromatic ring of diaryl diselenide (*p*-chloro-diphenyl diselenide, *m*-trifluoromethyl-diphenyl diselenide, *p*-methoxy-diphenyl diselenide) can present less toxicity than $(PhSe)_2$ (Nogueira et al., 2003b). In the present study, we investigated if the introduction of a functional group (chloro) in the aromatic ring of $(PhSe)_2$ (4,4′-dichloro-diphenyl diselenide $(ClPhSe)_2$) can be less toxic, when compared to $(PhSe)_2$ in liver and kidney of mice exposed to $HgCl_2$. To this end, we carried out δ-ALA-D, catalase (CAT) and Na^+, K^+-ATPase activities as well as thiobarbituric acid-reactive substances (TBARS), non-protein thiol (NPSH), ascorbic acid levels and histological findings. Some parameters in plasma (urea and protein), whole blood (hematocrit and hemoglobin) and urine (glucose and protein) were also evaluated.

2. Materials and methods

2.1. Chemicals

Mercuric chloride ($HgCl_2$) was obtained from Merck (Darmstadt, Germany). δ-Aminolevulinic acid (δ-ALA), adenosine triphosphate (ATP) and *p*-dimethyl aminobenzaldehyde were purchased from Sigma (St. Louis, MO, USA). $(PhSe)_2$ and $(ClPhSe)_2$ were synthesized according to Paulmier (1986). Analysis of the ^1H NMR and ^{13}C NMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of $(PhSe)_2$ (99.9%) was determined through GC/HPLC. All other chemicals were of analytical grade and they were obtained from standard commercial suppliers. $(PhSe)_2$ and $(ClPhSe)_2$ were dissolved in dimethylsulfoxide (DMSO).

2.2. Animals

Male adult Swiss albino mice (30–35 g) from our own breeding colony were used. The animals were kept in separate animal rooms, on a 12 h light/dark cycle, at a room temperature of $22 \pm 2\,^{\circ}C$, 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 at the Federal University of Santa Maria, Brazil.

2.3. Exposure

A group of six mice was usually tested in each experiment. Mice received one daily injection of $HgCl_2$ subcutaneously (s.c.) at a dose of 4.6 mg/kg (dissolved in saline; 10 mL/kg) for three consecutive days. The dosage of $HgCl_2$ was determined according to a previous study, and this given dosage was sufficient to elicit mild or moderate damage for $HgCl_2$ (Emanuelli et al., 1996; Perottoni et al., 2004). Thirty minutes after the last injection of $HgCl_2$, mice received only one dose of 100 μmol/kg of $(PhSe)_2$ or $(ClPhSe)_2$ (dissolved in DMSO; 2.5 mL/kg) (Nogueira et al., 2003b).

The protocol of mouse treatment is given below:

Group 1: saline (s.c.) + DMSO (s.c.)
Group 2: saline (s.c.) + $(PhSe)_2$ (s.c.)
Group 3: $HgCl_2$ (s.c.) + DMSO (s.c.)
Group 4: $HgCl_2$ (s.c.) + $(PhSe)_2$ (s.c.)
Group 5: saline (s.c.) + $(ClPhSe)_2$ (s.c.)
Group 6: $HgCl_2$ (s.c.) + $(ClPhSe)_2$ (s.c.)

Five hours after the $(PhSe)_2$ or $(ClPhSe)_2$ administration (maximum time for survival of mice exposed to $HgCl_2$ + $(PhSe)_2$) (Brandão et al., 2010), urine and blood samples were collected in mice anesthetized with isoflurane. The urine samples were collected by puncture of the bladder, when it was possible. Subsequently, mice were decapitated and had liver and kidney removed, one portion of the tissues was separated for histology, the other one was rapidly homogenized in 50 mM Tris–HCl, pH 7.4 (1/10, w/v) and centrifuged at $2400 \times g$ for 15 min. The supernatants (S1) were separated and used for biochemical assays.

2.4. δ-ALA-D activity

Renal and hepatic δ-ALA-D activities were assayed by the modified method of Sassa (1982) by measuring the rate of formation of a product called porphobilinogen (PBG), in 100 mM potassium phosphate buffer, pH 6.8 and 2.4 mM of aminolevulinic acid (ALA) were used (Barbosa et al., 1998). Incubations of S1 were carried out for 30 (liver) or 60 min (kidney) at 37 °C. The reaction product was determined by using modified Ehrlich's reagent at 555 nm, with a molar absorption coefficient of 6.1×10^4/M for the Ehrlich-porphobilinogen salt.

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