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Antioxidant protection of gallic acid against toxicity induced by Pb in blood, liver and kidney of rats

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ABSTRACT

The effect of the antioxidant gallic acid (GA) on Pb toxicity in blood, liver and kidney was investigated in the present study. Rats Wistar received Pb nitrate (50 mg/Kg/day, i.p., 5 days) followed by GA (13.5 mg/Kg, p.o., 3 days) or a chelating agent (EDTA, 55 mg/Kg, i.p.). As result, Pb decreased body weight, hematocrit and blood δ-aminolevulinic acid dehydratase (ALA-D) activity. In addition, high Pb levels were observed in blood and tissues, together with increased (1) lipid peroxidation in erythrocytes, plasma and tissues, (2) protein oxidation in tissues and (3) plasma aspartate transaminase (AST) levels. These changes were accompanied by decreasing in antioxidant defenses, like superoxide dismutase (SOD) activity in tissues and catalase (CAT) activity and reduced glutathione (GSH) in liver. GA was able to reverse Pb-induced decrease in body weight and ALA-D activity, as well as Pb-induced oxidative damages and most antioxidant alterations, however it did not decrease Pb bioaccumulation herein as EDTA did. Furthermore, EDTA did not show antioxidant protection in Pb-treated animals as GA did. In conclusion, GA decreased Pb-induced oxidative damages not by decreasing Pb bioaccumulation, but by improving antioxidant defenses, thus GA may be promising in the treatment of Pb intoxications.

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1. Introduction

Lead (Pb) is a non essential toxic heavy metal and one of the most widely used metal in industries. Pb may be found in printing, rubber, batteries, ceramics, dye, porcelain manufacturing, in accumulator industry and as a gasoline additive. Especially, the workers of these industrial branches are exposed to Pb [10,43]. In addition, the general population may getting exposed to Pb by contaminated food and water and by air pollution caused by industrial emission [40,45]. Unfortunately, even small quantities of Pb in the organism may are harmful [5,42].

The main body structures affect by Pb exposure includes erythrocytes, liver and kidney [46]. The erythrocytes have a high affinity for Pb and contain about 99% of the Pb present in the blood, which they can spread to different organs of the body [61]. Liver, organ responsible for maintaining the body's metabolic homeostasis, has been considered as the target organ for the toxic effects of Pb [48] and the largest Pb repository of softy tissues followed by kidney [28,49]. It has been known that Pb accumulation in these structures can interfere with several bioelements, whole role is critical for physiological processes.

Actually, Pb toxicity is related with oxidative stress (OS), due the capacity of Pb in disturbance the oxidant and antioxidant balance that is found in cells [39]. Lipids, proteins and carbohydrates can be oxidized by reactive oxygen species (ROS) in OS situa-

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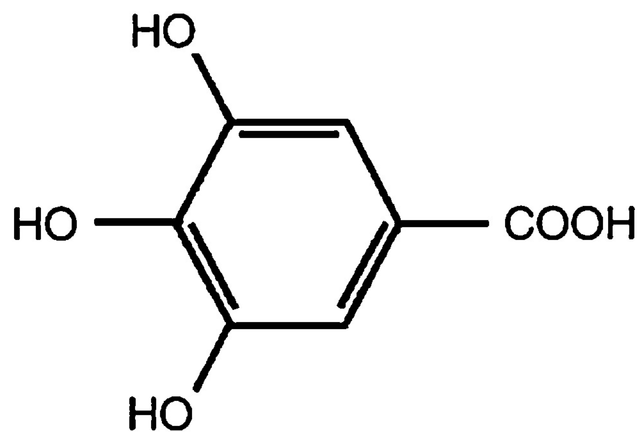

Fig. 1. Chemical structure of gallic acid (3,4,5-trihydroxybenzoic acid).

tions [24,60]. To minimize the potential damages caused by OS, the body has a combination of antioxidants [41], which can be enzymatic [e.g. superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, and glutathione reductase] or non-enzymatic [e.g., non-protein thiol groups, reduzed glutathione (GSH) and vitamin C (VIT C) e E] [22]. Several studies had showed increase in oxidative damages parameters, like lipid peroxidation and protein oxidation, as well as decrease in antioxidant defenses, like CAT, SOD, GSH and ascorbic acid, in blood/tissues of Pb-exposed animals [9,13,15,31,32,34,46,53,64]. In these studies, antioxidants have been designed to mitigate Pb-induced toxicity.

The current therapeutic approved to Pb intoxications is realized with chelation agents [2], like calcium disodium ethylenediamine tetraacetic acid (EDTA), 2,3-dimercaptopropanol (British Anti Lewisite, BAL) or meso 2,3-dimercaptosuccinic acid (DMSA), which increase the body excretion of Pb preventing the damages induced by this metal. However these compounds have a toxic potential in themselves [19] and cannot be used at therapeutically adequate dose for a prolonged period of time [16].

Gallic acid (3,4,5-trihydroxybenzoic acid, GA) (Fig. 1) is a natural phenolic antioxidant extractable from plants, especially green tea [33], and is widely used in foods, drugs, and cosmetics. It received much attention because of its antioxidant actions and potent property of scavenge ROS, like superoxide anions, hydrogen peroxide, hydroxyl radicals and hypochlorous acid [52,26,51], attenuating OS. In our previous study, gallic acid showed protective action against locomotor damage and brain OS induced by Pb in rats [53], and against reserpine toxicity [54]. In this sense, the present study investigated the effect of GA in biochemical parameters of toxicity in blood, liver and kidney of Pb-treated rats.

2. Materials and methods

2.1. Drugs

Drugs were purchased from Merck (Darmstadt, Germany). Pb and EDTA were dissolved in saline and protected from light until the use time. GA was dissolved in ultra-pure water and used until 10 min after preparation, thus ensuring its properties. All other chemicals and solvents used were of analytical or pharmaceutical and used as received.

2.2. Animals

The experiment was conducted with 32 male Wistar rats weighing 240 ± 10 g (about 2-month-old) at the start of the experiment. Groups of three or four animals were kept in plexiglas cages with free access to food and water in a room with controlled temperature (22–23 °C) and in 12 h light/dark cycles with lights on at 7:00 am The number of animals used was the minimum to obtain relevant results. The experimental protocol was approved by the ethical commission for animal use of Federal University of Santa Maria (process number 109/2010), which is in accordance with the international norms of animal care and maintenance. Animals were used after 7 days of acclimation.

2.3. Experimental design

The animals were treated with saline (1 mL/Kg, i.p., n = 14) or Pb (50 mg/Kg i.p., n = 21) once a day (9 a.m.) for 5 consecutive days [46]. From day 6, the saline-treated animals received water (1 mL/Kg, twice a day) or GA (6,75 mg/Kg/mL, twice a day) by gavage for 3 consecutive days. In addition, the Pb-treated animals received water (1 mL/Kg, twice a day, p.o.), GA (6,75 mg/Kg/mL, twice a day, p.o.) or EDTA (55 mg/Kg/mL, twice a day, i.p.) for 3 consecutive days at 9 a.m. and 5 p.m. Thus, the experimental groups of the present study were: control (C group, n = 7), GA group (n = 7), Pb group (n = 6), Pb-GA group (n = 6), Pb-EDTA group (n = 6). GA and EDTA treatments were in according with methodology described by Reckziegel et al. [53].

Body weight variation of animals was monitored during the whole course of the experiment and they were expressed in% based on the weight recorded on the first day. The animals were sacrificed 15 h after the last dose under anesthesia with thiopental (50 mg/Kg body weight, i.p.) and euthanized by exsanguinations. Blood was collected by cardiac puncture and used to hematocrit and ALA-D activity and the remaining were centrifuged at 3000 rpm for 15 min to obtained plasma and erythrocytes, whose were also used for biochemical assays. The liver and kidney were removed and one part was stored at −20 °C for Pb quantification and the remaining were homogenized in 10 vols (w/v) of 0.1 M Tris-HCl buffer, pH 7.4, centrifuged at 3000 rpm for 10 min and the supernatants used for biochemical assays.

2.4. Biochemical assays

Lipid peroxidation was measured by TBARS levels in tissues [44] and in plasma and erythrocytes [25,29]. Results of TBARS were expressed as nmol MDA/g tissue, nmol MDA/mL plasma or nmol MDA/mL erythrocytes. Protein oxidation was determined by protein carbonyl levels [65]. Total carbonylation was calculated using a molar extinction coefficient of 22,000 M^{-1} cm^{-1}, according Levine et al. [30] and the results were expressed as nmol protein carbonyl/g tissue. The blood ALA-D activity was assayed according to Berlin and Schaller [6] and the results were expressed as nmol PBG (porphobilinogen)/h/mL blood. Plasma transaminases [alanine transaminase (ALT) and aspartate transaminase (AST)] were measured according to Reitman and Frankel [55] and Bessey et al. [8] and expressed as UI/L.

Antioxidant enzymatic defenses evaluated in the present study were SOD [38] and CAT [1]. SOD results were expressed as Units (U)/g tissue (1U = amount of enzyme required to produce 50% inhibition at 40 °C) and CAT activity as μmol H_2O_2/min/mL erythrocytes or μmol H_2O_2/min/g tissue. In addition, non enzymatic antioxidants measured were GSH levels in tissues and erythrocytes [11,25] and VIT C levels in plasma [18,25]. The results of GSH levels were expressed as μmol GSH/g tissue or nmol GSH/mL erythrocytes and of VIT C as μg VIT C/mL plasma.

For Pb quantification, wet tissue weight and blood volume were recorded. According to Mesko et al. [36], after sample digestion with concentrated nitric acid using a microwave-assisted digestion system (Model Multiwave 3000, Anton Paar, Austria), digests were diluted to a constant volume with ultra pure water (Millipore,

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