Available online at www.sciencedirect.com
SCIENCE DIRECT®
Food and Chemical Toxicology 43 (2005) 1037–1045
www.elsevier.com/locate/foodchemtox

Delayed effects of thallium in the rat brain: Regional changes in lipid peroxidation and behavioral markers, but moderate alterations in antioxidants, after a single administration ☆

Sonia Galván-Arzate [a,d], José Pedraza-Chaverrí [b], Omar N. Medina-Campos [b], Perla D. Maldonado [b], Beatriz Vázquez-Román [c], Camilo Ríos [a], Abel Santamaría [c,*]

[a] *Departamento de Neuroquímica, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, México D.F. 14269, Mexico*
[b] *Departamento de Biología, Facultad de Química, Universidad Nacional Autónoma de México, México D.F. 04510, Mexico*
[c] *Laboratorio de Aminoácidos Excitadores/Departamento de Neuroquímica, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, México D.F. 14269, Mexico*
[d] *Doctorado en Ciencias Biológicas, Universidad Autónoma Metropolitana, México D.F. 04960, Mexico*

Received 15 November 2004; accepted 15 February 2005

Abstract

Thallium (Tl^+) toxicity has been related with the generation of reactive oxygen species (ROS) and oxidative stress (OS) in the central nervous system. Since changes in endogenous antioxidant systems might contribute to acute Tl^+-induced OS and neurotoxicity, in this study we measured the metal concentration and the levels of lipid peroxidation (LP) in different brain regions (hypothalamus (Ht); cerebellum (Ce); striatum (S); hippocampus (Hc) and frontal cortex (Cx)) in possible correlation with the content of reduced glutathione (GSH), the activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD), and the animal performance in behavioral tests, all evaluated after a single administration of thallium acetate (8 or 16 mg/kg, i.p.) to rats. Seven days after Tl^+ administration, the metal was homogeneously and dose-dependently accumulated in all regions evaluated. LP was increased in Ht, Ce and S, while GSH was depleted in S. Cu,Zn-SOD activity was also decreased in Ht and S. All these changes occurred with 16 mg/kg dose and at 7 days after treatment, but not at 1 or 3 days. In addition, Tl^+-treated animals exhibited general hypokinesis, but no changes were observed in spatial learning. Our findings suggest that a delayed response of the brain to Tl^+ may be the result of its residual levels. Also, despite the regional alterations produced by Tl^+ in LP and the limited changes in endogenous antioxidants, there is a correlation between the Tl^+-induced oxidative damage and the affected behavioral tasks, suggesting that, although still moderate, Tl^+ evokes neurotoxic patterns under the experimental conditions tested.

Keywords: Thallium; Oxidative damage; Endogenous antioxidants; Brain regions; Neurotoxicity; Reactive oxygen species; Behavior

1. Introduction

Toxic patterns elicited by heavy metals and metalloids share a common cascade of events involving reactive oxygen species (ROS) formation and oxidative stress (OS). Under specific conditions, these agents induce a pro-oxidant state in biological systems resulting in peroxidation of polyunsaturated fatty acids. The brain is particularly sensitive to oxidative damage

☆ This work allowed Sonia Galván-Arzate to obtain her Ph.D. degree at the Programa de Doctorado en Ciencias Biológicas from the Universidad Autónoma Metropolitana-Xochimilco (México).

* Corresponding author. Tel.: +5255 5606 3822x2013; fax: +5255 5528 0095.
E-mail address: absada@yahoo.com (A. Santamaría).

0278-6915/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.fct.2005.02.006

because of its high levels of unsaturated lipids, as well as a high rate of oxidative metabolism (Chevalier et al., 1994; Goering et al., 2002). It is also known that endogenous antioxidants constitute a defense against cell damage induced by ROS in living systems. These complexes are mainly composed by metabolites such as reduced glutathione (GSH), and enzymatic scavengers such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). Approximately 4–5% of oxygen consumed will form superoxide anions, which can be readily dismuted by SOD to hydrogen peroxide and singlet oxygen. Hydrogen peroxide is then converted by GPx to H_2O and O_2. GSH, consumed during the GPx reaction, is converted back to its reduced form by glutathione reductase (GR). However, when the production of reactive oxygen intermediates exceeds the ability of the antioxidant systems to remove them, OS results (Somani et al., 1995). Therefore, SOD and GPx, as well as the content of GSH, are all critical for protection against ROS toxicity.

Thallium (Tl^+) is a naturally distributed metal commonly found as a mineral compound, as well as in several inorganic salts. Tl^+ can be released into the environment from industrial sources such as coal-fired power plants, smelting operations and cement factories, among others (Galván-Arzate and Santamaría, 1998). The most non-occupational sources of Tl^+ exposure are the consumption of contaminated food (fruits and vegetables home-grown) (Borges and Daugherty, 1994) and living in the vicinity of industries, such as cement plants (Brockhaus et al., 1981). In addition, Tl^+ produces one of the most complex and serious patterns of toxicity known to humans, involving a wide range of organs and tissues. The severity of symptoms depends on the time and level of exposure, the rate of absorption, age and individual susceptibility (Repetto et al., 1998). Acute exposure to Tl^+ produces damage in central, peripheral, and autonomic nervous systems in humans, whereas chronic exposure results in alteration of the brain, spinal cord, and peripheral nerves.

Several groups (Hasan and Ali, 1981; Brown et al., 1985; Aoyama et al., 1988; Galván-Arzate et al., 2000) have investigated the effects of Tl^+ on lipid peroxidation (LP) in various tissues using different schemes of administration, as well as distinct animal species. Findings of these reports have demonstrated that Tl^+ toxicity is closely related with increased ROS formation, which in turn constitute an important risk factor for tissue damage and organ dysfunction. However, most of these investigations have been performed under chronic or subchronic conditions of Tl^+ administration. Moreover, given that even a single exposure to Tl^+ for humans may represent a risk factor for neurotoxicity and since much of the consequences of a single acute exposure to Tl^+ are still unknown, more detailed studies are needed to clarify the precise role of ROS and OS, bringing special attention to the early changes occurring in antioxidant systems as possible causes of the late toxic features of Tl^+. Therefore, the aim of this study was to investigate whether a single systemic administration of Tl^+ to rats may produce significant changes in the course of days in lipid peroxidation as indicator of oxidative damage in correlation with alterations in endogenous antioxidant systems, in order to provide further information on the relevance of the toxic patterns evoked by this metal. In addition, we evaluated whether such effects, if occur, may affect behavioral tasks as general indicators of neurotoxicity. Thus, this study represents a logic extension of that performed by Brown and coworkers on the effects of Tl^+ on biochemical and behavioral markers.

2. Materials and methods

2.1. Animals and treatment

Adult male bred-in-house Wistar rats (250–300 g) were used throughout the study ($N = 130$). Rats were housed 6 per cage and provided with water and Purina chow pellets *ad libitum*. Lighting (12:12 light:dark cycles), temperature (25 ± 3 °C) and humidity (50 ± 10%) conditions were maintained constant. All experiments were carried out with approval of the Local Bioethics Committee. Animals were randomly assigned to different experimental groups and received a single administration of thallium acetate at two different doses (8 or 16 mg/kg i.p. dissolved in water). Additional groups of rats were administered with similar volumes of deionized water as vehicle and considered as controls. One, 3 and 7 days after Tl^+ administration, rats were killed by decapitation and their brains were rapidly removed and placed on ice. Five regions were dissected according to the method described by Glowinski and Iversen (1966): hypothalamus (Ht), cerebellum (Ce), frontal cortex (Cx), hippocampus (Hc) and striatum (S).

These regions were selected on the basis of previous works demonstrating their selective vulnerability to the noxious effects of Tl^+ and capability to accumulate the metal (Ríos et al., 1989; Galván-Arzate et al., 2000), as well as their well-known susceptibility to oxidative stress (reported elsewhere).

Tissue samples were then stored at −75 °C until processed for each experimental purpose. Animals used for behavioral purposes were similarly administered with Tl^+ or vehicle and maintained alive until the corresponding tests were performed.

2.2. Thallium analysis

Tissue samples were digested in 0.5–1.0 ml of concentrated HNO_3 Suprapur (Merck, Mexico City), handled