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The neuroprotective role of L-cysteine towards the effects of short-term exposure to lanthanum on the adult rat brain antioxidant status and the activities of acetylcholinesterase, (Na^+,K^+)- and Mg^{2+}-ATPase

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Abstract Lanthanum (La) is a rare earth element that is widely used for industrial, medical and agricultural purposes. Its neurotoxic effects are linked to its physical and chemical properties and its interaction with certain trace elements and membrane-bound enzymes. The aim of this study was to investigate the effects of short-term La-administration (as $LaCl_3$, 53 mg/kg) on the adult rat whole brain total antioxidant status (TAS) and the activities of acetylcholinesterase (AChE), Na^+,K^+-ATPase and Mg^{2+}-ATPase, as well as the potential effect of the co-administration of the antioxidant L-cysteine (Cys, 7 mg/kg) on the above parameters. Twenty-eight male Wistar rats were divided into four groups: A (saline-treated control), B (La), C (Cys),and D (La and Cys). All rats were treated once daily with intraperitoneal injections of the tested compounds, for 1-week. Rats were sacrificed by decapitation and the above mentioned parameters were measured spectrophotometrically. Rats treated with La exhibited a significant reduction in brain TAS (−36%, $P < 0.001$, BvsA), that was partially limited by the co-administration of Cys (−13%, $P < 0.01$, DvsA), while Cys (group C) had no effect on TAS. The rat brain AChE activity was found significantly increased by both La (+23%, $P < 0.001$, BvsA) and Cys (+59%, $P < 0.001$, CvsA), while it was adjusted to control levels by the co-administration of La and Cys. The activity of rat brain Na^+,K^+-ATPase was significantly decreased by La-administration (−28%, $P < 0.001$, BvsA), while Cys supplementation could not reverse this decrease. The activity of Mg^{2+}-ATPase exhibited a slight but statistically significant reduction due to La (−8%, $P < 0.01$, BvsA), that was further reduced by Cys co-administration (−25%, $P < 0.001$, DvsA). The above findings suggest that La short-term in vivo administration causes a statistically significant decrease in the rat brain TAS and an increase in AChE activity. Both effects can be, partially or totally, reversed into control levels by Cys co-administration, which could thus be considered for future applications as a neuroprotective agent against chronic exposure to La. The activities of Na^+,K^+- and Mg^{2+}-ATPase that were inhibited by La, could not be reversed by Cys co-administration. A role for the already reported concentration-dependent interaction of La with Ca-binding sites (such as Ca^{2+}-ATPase) might be considered for certain of the above phenomena.

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Introduction

The rare earth elements (REEs) comprise a group of metallic elements that have similar chemical and physiological properties (Das et al. 1988; Evans 1983). Lanthanum (La) is a REE used for medical (as a treatment of hyperphosphatemia due to chronic renal failure) (Hutchison et al. 2004) and agricultural (as a trace fertilizer) (Guo et al. 1990) purposes. Moreover, La is also released into the aquatic environment through industrial (electronic-manufacturing), mining (of gold and uranium) and energy-producing (through coal-fired power plants) activities (Goetz et al. 1982; Noller 1991, 1994). In fact, it has been suggested that lanthanides (the series of elements relevant to La) are released into the environment in amounts that largely exceed the environmental release of mercury or cadmium by 50 times, of selenium, uranium or tin by 10 times, and of arsenic or lead by 2–3 times (Sabbioni et al. 1982). Thus, the amounts of La that reach the human body, either through the food chain, medical applications or via atmospheric particles, are high (Zhu et al. 1997).

The REEs are not considered as highly toxic for mammals (Haley 1979). However, studies have shown that children living near lanthanides' ore areas tend to have lower IQ levels than those from other regions (Fan et al. 2004; Zhu et al. 1996). A number of experimental studies have focused on the La-induced neurotoxicity, and have revealed some very interesting findings (Basu et al. 1982, 1984; Feng et al. 2006; Gundersen and Miledi 1983). It has been recently suggested that La could possibly impair the learning ability due to a disturbance of the homeostasis between trace elements, enzymes and neurotransmitter systems in the rat brain (Feng et al. 2006). However, this hypothesis has been questioned on the ground of La being an element that can difficultly cross the blood–brain barrier and has questionable concentration-dependent biological effects (Damment et al. 2007).

It should be noted that La has many chemical and physical characteristics in common with calcium (Ca) (Evans 1983), and that its biological actions are mainly mediated through the displacement or replacement of Ca in certain Ca-binding sites (Das et al. 1988), as well as through its high affinity for the phosphate groups of certain macromolecules (Howells and Coult 1971). Moreover, since REEs are believed to be excluded by the plasma membrane and cannot enter the cytoplasm, the plasma membrane molecules are considered as their primary target (Gao et al. 1998).

The aim of this study was to shed more light on the effects of short-term high-dose La-administration on: (a) the adult rat brain total antioxidant status (TAS) and (b) the activities of acetylcholinesterase (AChE; a crucial membrane-bound enzyme involved in cholinergic neurotransmission) (Kouniniotou-Krontiri and Tsakiris 1989) and two important adenosinetriphosphatases, namely Na^+,K^+-ATPase (an enzyme implicated in neuronal excitability, metabolic energy production, as well as in the uptake and release of catecholamines, serotonin and glutamate) (Bogdanski et al. 1968; Hernandez 1987; Lees et al. 1990; Mata et al. 1980; Sastry and Phillis 1977; Swann 1984) and Mg^{2+}-ATPase (an enzyme functioning in order to maintain high brain intracellular Mg^{2+}, thus possibly controlling the rate of protein synthesis and cell growth) (Sanui and Rubin 1982). Moreover, since L-cysteine (Cys) is a well known antioxidant and chelating-agent (Carageorgiou et al. 2004; Patrick 2003), it was co-administered with La, in order to evaluate its efficacy on protecting the rat brain against the La-induced (toxic) effects on the above parameters.

Materials and methods

Animals

Male adult albino Wistar rats (4 months old, weighting 279 ± 25 g) were used in all experiments. The rats were purchased from the Hellenic Pasteur Institute (Athens, Greece) and were housed four in a cage, at a constant room temperature (22 ± 1°C) under a 12-h light:12-h dark (light 08:00–20:00 h) cycle. Food and water were provided ad libitum. Animals were cared for in accordance with the principles for the care, use and protection of experimental animals as set by the European Economic Community (EEC) Council Directive 86/609/EEC

(EEC Council 1986) and aligned according to the Recommendation 2007/526/EU.

Lanthanum and L-cysteine administration

Rats were divided into four groups ($n = 7$ at each group), as follows: (a) control (saline-treated), (b) La (53 mg/kg of body weight, as $LaCl_3 \cdot 7H_2O$, which equals to the ½ of the LD_{50}), (c) Cys (7 mg/kg of body weight), and (d) La + Cys (on the pre-mentioned doses). All rats received intraperitoneal (ip) daily injections for 7 days. No behavioral or physiological effects were observed over this period of administration.

Tissue preparation

The animals were sacrificed by decapitation 1 h after the last injection and their whole brains were rapidly removed (and stored at −80°C until use). The tissue was homogenized in 10 vol ice-cold (0–4°C) medium containing 50 mM Tris (hydroxymethyl) aminomethane–HCl (Tris–HCl), pH 7.4 and 300 mM sucrose, using an ice-chilled glass homogenizing vessel at 900 rpm (4–5 strokes). Then, the homogenate was centrifuged at 1,000×*g* for 10 min to remove nuclei and debris (Tsakiris 2001; Tsakiris et al. 2000). In the resulting supernatant, the protein content was determined according to the method of Lowry et al. (1951) and then the enzyme activities were measured.

Determination of the brain total antioxidant status

TAS was evaluated in each fresh homogenized rat brain (Carageorgiou et al. 2003, 2005). The total antioxidant capacity was measured spectrophotometrically by a commercially available kit (Randox Laboratories Ltd., Cat No NX2332) as previously described (Tsakiris et al. 2000). Briefly, ABTS (2,2′-Azino-di-(3-ethylbenzthiazoline sulphonate)) was incubated with a peroxidase (metmyoglobin) and H_2O_2 in order to produce the radical cation $ABTS^{\cdot+}$. The latter had a relatively stable blue–green color, which was measured at 600 nm. Decreased values of TAS reflect the increase of brain free radical production, whereas increased TAS values show the decrease of free radical production and the protective antioxidant effect on the brain of the administered substance.

Determination of brain acetylcholinesterase activity

AChE activity was determined by following the hydrolysis of acetylthiocholine according to the method of Ellman et al. (1961), as previously described by Tsakiris (2001). The incubation mixture (1 ml) contained 50 mM Tris–HCl, pH 8, 240 mM sucrose and 120 mM NaCl. The protein concentration of the incubation mixture was 80–100 μg/ml. The reaction was initiated after addition of 0.03 ml of 5,5′-dithionitrobenzoic acid (DTNB) and 0.05 ml of acetylthiocholine iodide, which was used as substrate. The final concentration of DTNB and substrate were 0.125 and 0.5 mM, respectively. The reaction followed spectrophotometrically by the increase of absorbance ($\Delta\overline{OD}$) at 412 nm.

Determination of Na^+,K^+-ATPase and Mg^{2+}-ATPase activities

(Na^+,K^+)-ATPase activity was calculated from the difference between total ATPase activity (Na^+,K^+, Mg^{2+}-dependent ATPase) and Mg^{2+}-dependent ATPase activity. Total ATPase activity was assayed in an incubation medium consisting of 50 mM Tris–HCl, pH 7.4, 120 mM NaCl, 20 mM KCl, 4 mM $MgCl_2$, 240 mM sucrose, 1 mM ethylenediamine tetraacetic acid K_2-salt (K^+-EDTA), 3 mM disodium ATP and 80–100 μg protein of the homogenate in a final volume of 1 ml. Ouabain (1 mM) was added in order to determine the activity of Mg^{2+}-ATPase. The reaction was started by adding ATP and stopped after an incubation period of 20 min by addition of 2 ml mixture of 1% lubrol and 1% ammonium molybdate in 0.9 M H_2SO_4 (Bowler and Tirri 1974; Tsakiris 2001). The yellow color which developed was read at 390 nm.

Statistical analysis

The data were analyzed by Student's *t*-test followed by Bonferroni post-hoc test when needed. All analyses were performed by SPSS 10.0 statistical package for windows software, while P values of <0.05 were considered statistically significant.

Results

The effects of La and/or Cys on the adult rat brain TAS are presented in Fig. 1. A La-induced statistically significant decrease in TAS was recorded (−36%, $P < 0.001$), that was partially limited by the co-administration of Cys (−13%, $P < 0.01$). The rat brain AChE activity was found significantly increased by both La (+23%, $P < 0.001$) and Cys (+59%, $P < 0.001$), while it was adjusted into control levels by the co-administration of La and Cys (Table 1). The

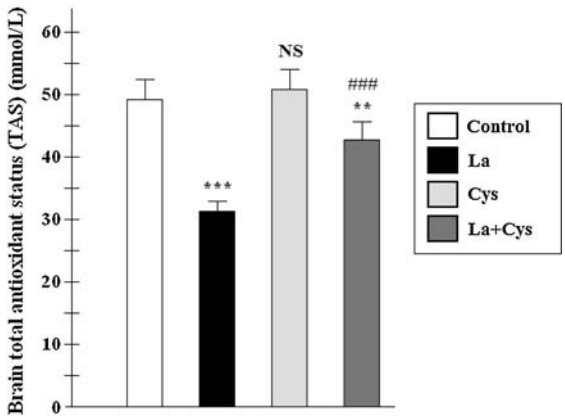

Fig. 1 Effects of lanthanum (La) on the brain total antioxidant status (TAS) of adult rats and modulation by L-cysteine (Cys) co-administration. Each value indicates the mean ± SD of seven independent experiments (seven rats per group). The average of each experiment arose from three evaluations of the homogenized brain of each animal. *NS* non statistically significant (as compared to the control group); $^{**}P < 0.01$ (as compared to the control group); $^{***}P < 0.001$ (as compared to the control group); $^{\#\#\#}P < 0.001$ (as compared to the La-treated group)

Table 1 Effects of lanthanum (La) on the brain acetylcholinesterase (AChE) activity of adult rats and modulation by L-cysteine (Cys) co-administration

Group ($n = 7$)	AChE ($\Delta\overline{OD}$/min × mg protein)		
	Mean ± SD	vs. Control	vs. La
Control	0.721 ± 0.054[a]	–	–
La	0.890 ± 0.035[b]	(+23%)	–
Cys	1.146 ± 0.031[c]	(+59%)	–
La + Cys	0.750 ± 0.041[d]	(+4%)	(−16%)

Each value indicates the mean ± SD of seven independent experiments (seven rats per group). The average of each experiment arose from three evaluations of the homogenized brain of each animal. Statistics: a/b, a/c, b/c, b/d, c/d: $P < 0.001$; a/d: $P > 0.05$

Table 2 Effects of lanthanum (La) on the brain Na^+,K^+-ATPase activity of adult rats and modulation by L-cysteine (Cys) co-administration

Group ($n = 7$)	Na^+,K^+-ATPase (μmol Pi/h × mg protein)		
	Mean ± SD	vs. Control	vs. La
Control	2.56 ± 0.28[a]	–	–
La	1.85 ± 0.19[b]	(−28%)	–
Cys	1.47 ± 0.31[c]	(−43%)	–
La + Cys	1.86 ± 0.23[d]	(−27%)	(+1%)

Each value indicates the mean ± SD of seven independent experiments (seven rats per group). The average of each experiment arose from three evaluations of the homogenized brain of each animal. Statistics: a/b, a/c, a/d: $P < 0.001$; b/c, c/d: $P < 0.05$; b/d: $P > 0.05$

Table 3 Effects of lanthanum (La) on the brain Mg^{2+}-ATPase activity of adult rats and modulation by L-cysteine (Cys) co-administration

Group ($n = 7$)	Mg^{2+}-ATPase (μmol Pi/h × mg protein)		
	Mean ± SD	vs. Control	vs. La
Control	7.25 ± 0.31[a]	–	–
La	6.66 ± 0.36[b]	(−8%)	–
Cys	6.13 ± 0.18[c]	(−15%)	–
La + Cys	5.46 ± 0.24[d]	(−25%)	(−18%)

Each value indicates the mean ± SD of seven independent experiments (seven rats per group). The average of each experiment arose from three evaluations of the homogenized brain of each animal. Statistics: a/c, a/d, b/d, c/d: $P < 0.001$; a/b, b/c: $P < 0.01$

activity of rat brain Na^+,K^+-ATPase was significantly decreased by La-administration (−28%, $P < 0.001$), while Cys co-administration could not reverse this decrease (Table 2). The activity of Mg^{2+}-ATPase exhibited a slight but statistically significant reduction in its activity (−8%, $P < 0.01$) due to La, that was further reduced by Cys co-administration (Table 3).

Discussion

Exposure to La is known to cause a variety of biological effects in a time- and dose-dependent manner (Zheng et al. 2000). Lipid peroxidation of plasma membranes is depressed by low and enhanced by high La concentrations, while the reduction rate of $Fe(CN)_6^{3-}$ (a redox system activity marker) is

increased by low and decreased by high La concentrations (Zheng et al. 2000). Our data revealed a statistically significant La-induced reduction of whole rat brain TAS (Fig. 1), following high-dose short-term in vivo administration. The co-administration of Cys was able to partially correct the La-induced TAS-decrease, possibly due to the chelating properties of Cys (assisting to the biological inactivation and/or excretion of La ions) and/or to the possible elimination of the La-induced free radical production. However, Cys (at least under the examined experimental conditions) was not proved efficient enough to neutralize the La-induced oxidative stress.

The co-administration of La and Cys was, on the other hand, efficient enough in order to maintain AChE into the control levels (Table 1) and reverse the La-induced AChE activation. This finding is of importance, since most in vitro studies have reported a La-induced decrease in AChE activity (Ghosh et al. 1991; Gundersen and Miledi 1983; Marquis and Black 1985). Could this finding support the view of Damment et al. (2007) that La can difficultly cross the blood–brain barrier? Could this support the idea that the observed AChE activation is an indirect effect of La? If so, what is the reason of this in vivo AChE activation, and how does Cys manage to reverse it?

Recent studies (Feng et al. 2006; Xiao et al. 2005) have suggested that lanthanides can penetrate the blood–brain barrier when administered in high concentrations, and can accumulate in certain crucial rat brain regions (such as those of the cerebral cortex, the hippocampus and the cerebellum). Moreover, La has been shown to inhibit the Ca-dependent neurotransmitter release (Przywara et al. 1992) and modulate the ion homeostasis within the central nervous system (CNS) (Feng et al. 2006). Since Cys also activates the rat brain AChE, the mechanism by which Cys exerts its neuroprotective effect towards La cannot be directly related to the enzyme, but is possibly taking place through a chelator-metal ion interaction that limits extracellular free La^{3+} levels within the CNS and/or restricts the indirect (oxidative or deregulating) effects of La (towards other enzymes and mechanisms of neurotransmission) within the body and/or the CNS. However, this hypothesis requires further investigation, since: (a) it is not clear whether La is directly affecting AChE activity through its physical presence within the CNS (Damment et al. 2007), (b) little is known about the consequences of the reported ion homeostasis deregulation (Feng et al. 2006), while (c) the mechanisms by which the La-induced cognitive decline is believed to develop do not implicate any change in acetylcholine levels (Feng et al. 2006).

The La-induced decrease of the whole rat brain Na^+,K^+-ATPase activity (Table 2) was expected (Li et al. 1998), while the Cys-induced decrease in Na^+,K^+-ATPase activity has already been reported by Carageorgiou et al. (2004). In contrast to the prementioned parameters (TAS and AChE activity), Cys was not able to reverse this La-induced inhibition of Na^+,K^+-ATPase. This finding suggests that La might interfere with neuronal excitability, metabolic energy production, as well as with the uptake and release of catecholamines, serotonin and glutamate (Bogdanski et al. 1968; Hernandez 1987; Lees et al. 1990; Mata et al. 1980; Sastry and Phillis 1977; Swann 1984), in a way that cannot be reversed by the administration of an antioxidant and chelating-agent, such as Cys. This finding seems to be very important: previous studies have implicated La-administration in glutamatergic, serotoninergic and dopaminergic dysfunction (Basu et al. 1984; Feng et al. 2006). Moreover, the ability of La to cause a (slight but significant) decrease of Mg^{2+}-ATPase activity, that could also not be reversed by Cys co-administration (Table 3), leads to the conclusion that La also affects the cellular mechanisms functioning in order to maintain high brain intracellular Mg^{2+}, and thus possibly controlling the rate of protein synthesis and cell growth (Sanui and Rubin 1982). The observed effects of La on the examined adenotriphosphatases could be the result of Ca^{2+}-ATPase inhibition (Basu et al. 1982; Zheng et al. 2000), resulting in Ca-homeostasis deregulation, membrane signaling dysfunction, ATP consumption and/or ion redistribution.

In conclusion, our findings suggest that short-term in vivo La-administration causes a significant decrease in the rat brain TAS and a significant increase in AChE activity. Both effects can be, partially or totally, reversed into control levels by Cys co-administration, which could thus be considered for future applications as a neuroprotective agent against poisoning and/or chronic exposure to La. The activity of Na^+,K^+-ATPase as well as that of Mg^{2+}-ATPase were inhibited by La, in a non-reversible by Cys way. These findings suggest that La, at least under the examined experimental conditions, might interfere

with neuronal excitability, metabolic energy production, as well as with the uptake and release of catecholamines, serotonin and glutamate. Some of these phenomena might be the result of oxidative stress, cholinergic dysfunction and/or other intracellular deregulating phenomena associated with its chemical resemblance to other elements such as Ca. However, the matter requires further investigation in order to elucidate the exact mechanisms that lead (or at least have the potential to lead) to the (already reported in the literature) La-induced cognitive impairment.

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