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Effects of Lead and Sucroses Long-Term Consumption on Biochemical and Behavioral Parameters in Aging Rats

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Abstract

Lead is a well know neurotoxic metal whose exposure has been associated with hyperglycemia and insulin resistance. Sucrose is a worldwide consumed foodstuff and experimental data have indicated that its intake can disrupt glucose metabolism in different animal models. The aim of this study was to investigate whether the simultaneous exposure to these agents could enhance the incidence of orofacial dyskinesia (OD) as well as alter behavioral and hematological parameters in aging rats. The experiments were conducted in female Wistar rats, which received lead acetate (Pb^{2+} 100 or 400 ppm) in drink water, 20% of sucrose or sucrose plus lead (100 or 400 ppm) for 12 months. The incidence of OD increased significantly as a function of age. The ingestion of lead and/or sucrose per se was not associated with an increase in OD occurrence. However, Pb^{2+} (400 ppm) when associated with sucrose decreased OD incidence. The locomotor activity of animals decreased in function of age, but was not changed by sucrose plus Pb^{2+} consumption. In addition to body weight gain, sucrose intake lowered the hematocrit and increased the blood levels of insulin and glucose of animals. Most of these effects were not induced and/or exarcebated by Pb^{2+}. Our findings confirm that the aging culminates with OD onset and that the chronic consumption of Pb^{2+} or sucrose did not cause further increase in this condition. It is possible that some adaptative mechanism(s) have been developed to block the neurotoxicity of Pb^{2+} and/or sucrose after long-term exposure as verified in locomotor activity and OD. Interesting, here we described for the first time that prolonged ingestion of sucrose causes anemia in aging rats.

Keywords: Lead acetate; Sucrose; Orofacial dyskinesia; Anemia

Introduction

Lead (Pb^{2+}) is a common occupational and persistent environmental contaminant [1] and the routes of lead exposure may include ingestion or inhalation of lead-contaminated dust [2,3]. Lead exposure has been well documented by disrupting the central nervous system and producing motor and behavioral deficits in several animal species [4-8]. Impairment of cognitive functions and reduction in activity-dependent synaptic plasticity are effects related with lead intoxication [6]. In terms of mechanisms there are evidence that Pb^{2+} exposure disturbs glutamatergic, cholinergic, and dopaminergic signaling pathways, calcium homeostasis and induces oxidative stress [5,8-14]. In addition, experimental findings have demosntrated that exposure to Pb^{2+} can alter the glucose metabolism, causing hyperglycemia and insulin resistance [15-17]. Similarly, lead exposure has been associated with hyperglycemia and diabetes in humans [18]. Recently, the exposure of Pb^{2+} in a transgenic murine model for the AD has been reported to accelerate the deposition of amyloid in the hippocampus of female mice [19].

Hypercaloric diet intake has been considered an important factor for the development of multiple metabolic disorders. In this sense, studies from our research group have shown that the ingestion of diets rich in fat or in free-sugar elicits oxidative stress in rodents [20,21]. The mechanisms underlying to the detrimental effects from high-sucrose diets in animal models are still not fully understood. However, some findings have suggested that the harmful effects of high-sucrose diets could be resultant from its fructose content, a molecule that has pro-oxidant activity [22-24]. Of particular importance, there is evidence that high sucrose diet induces insulin resistance, which has been associated with an increased risk of progressive neurodegenerative disease such as Alzheimer disease [25,26]. Literature data have also reported that high-fat diet ingestion, a major risk factor for type 2 diabetes mellitus, decrease the levels of striatal dopamine [27] and facilitate the appearance of orofacial dyskinesia in rats [28].

Orofacial dyskinesia (OD) in animal models and tardive dyskinesia (TD) in humans are extrapyramidal disorders characterized by repetitive involuntary movements, involving the mouth, face, and tongue, and sometimes limb and trunk musculature [29,30]. In humans, the syndrome is most frequently found in older patients prevailing in those using typical antipsychotic agents [30]. The molecular mechanisms that underlie the neuropathophysiology of orofacial dyskinesia are still not completely clear. However, one hypothesis that has been reinforced by experimental data is that free radical derived from the metabolism of dopamine and/or from an enhancement of glutamatergic neurotransmission caused by blocking

presynaptic dopamine receptor participates in the genesis of orofacial dyskinesia [30-32]. In line with the hypothesis of oxidative stress, aging has been reported to cause an increase in the incidence of OD in rats [33,34].

Considering the possible synergistic effects of lead and sucrose toward the neurophysiological and metabolic processes, the aim of this study was to investigate whether the simultaneous exposure to these agents could enhance the occurrence of OD in aging rats and metabolic disturbances caused by prolonged ingestion of Pb^{2+} or sucrose.

Materials and Methods

Animals

Sixty female Wistar rats (60 days old; ~120 g) were maintained on a natural cycle in a controlled temperature room (22-26°C). The animals received food ad libitum (Guabi, RS, Brazil, free of Pb2+and Sucrose) and Pb^{2+} and/or sucrose via drink water for 12 months. Animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources of the University of Santa Maria, Brazil.

Exposure to lead and sucrose

Rats were divided in six groups (n=10 animals per group): (1) control (tap water); (2) sucrose 20%; (3) lead acetate 100 ppm; (4) sucrose 20% + lead acetate 100 ppm; (5) lead acetate 400 ppm; (6) sucrose 20% + lead acetate 400 ppm. Experimental exposure was carried out for 12 months. To prevent lead acetate precipitation, 0.5 ml/L of glacial acetic acid was added to the water of all groups. The concentrations of sucrose and lead used in this protocol were based in related *in vivo* studies [23,35]. The body weight of animals was measured monthly. After the treatments, the animals were submitted to the behavioral tests (orofacial dyskinesia and open-field) in two consecutive days. Behavioral tests were performed in a same period of the day (11:00 AM to 4:00 PM).

Behavioral analysis

Orofacial dyskinesia: Orofacial dyskinesia was analyzed according Burger et al. [31]. The rats were observed individually in a glass cage (20 × 0 × 19 cm) equipped with a mirror under the floor and behind the back wall of the cage to allow behavioral quantification when the animal was faced away from the observer. The OD episodes were measured continuously for 6 min after a period of 6 min adaptation. The trained observer scored and analyzed the following behavioral categories: vacuous chewing movements (VCM) and tongue protrusion. VCM is defined as single mouth openings in the vertical plane not directed towards physical material. The behavioral parameters were not scored during grooming or rearing, and were assessed 4 and 12 months after the beginning of treatments.

Open field: Spontaneous motor and exploratory activities were evaluated by open-field test [36]. The open field arena consisted of a white wood cage (50 × 50 × 40 cm) divided into 9 equal squares by black lines. The animals were placed individually at the center of the apparatus and observed for 2 minutes. The locomotor activity was assessed by the numbers of lines crossed with the four paws while the exploratory activity by the number of rearing on the hind paws. The apparatus was cleaned between assessments with a 20% ethanol solution. These behaviors were assessed 4 and 12 months after the beginning of the treatments.

Biochemical and hematological analysis

Twenty four hours after the last session of behavioral quantification, fasted rats were anesthetized and killed by decapitation. Whole blood of the anesthetized rats was collected by eye vein puncture in heparinized tubes for hematocrit determination. Samples were centrifuged at 4.000xg for 10 min to yield the plasma that was used to measure glucose and insulin levels.

Glucose, hematocrit and insulin determination

Serum glucose content was determined using a glucose oxidase kit (LabTest, Minas Gerais, Brazil). For hematocrit determination, the blood collected in hematocrit tubes was centrifuged and afterwards the length of the column of packed erythrocytes was measured, divided by the length of the column of whole blood and multiplied by 100%.

Plasma levels of insulin were determined using radioimmunoassay kit specific for rat insulin (Cloud-Clone Corp., Houston, USA) according to the manufacturer's instructions.

Statistical Analysis

Body weight and the behavioral parameters were analyzed by a three-way analysis of variance (ANOVA) (2 Pb × 2 sucrose × 4 age) with the age factor treated as a repeated measure. Statistical analysis was followed by Duncan's Multiple Range test when appropriate. Results with $P<0.05$ were considered significant.

Results

Body weight gain

The statistical analysis of body weight gain showed that there was a significant interaction between treatments and time ($F(6,165)=2.75$, $p<0.01$). All groups exposed to sucrose for 12 months (sucrose 20%; sucrose 20% + lead acetate 100 ppm; sucrose 20% + lead acetate 400 ppm) had a marked increase in body weight gain ($F(1,55)=11.61$, $p<0.01$) in comparison to the others. This response to sugar was not influenced by lead. In addition, lead per se did not modify the body weight gain of animals when compared to the control group (Table 1).

Treatment	Body Weight(g)	Hematocrit (%)	Glucose (mg/dL)	Insulin (U/dL)
Control	283.7 ± 9.5a	49.3 ± 3.7a	71.6 ± 3.3a	1.3 ± 0.3a
Sucrose	342.8 ± 16.2b	45.0 ± 1.0b	97.4 ± 2.9b	3.5 ± 1.2b
Pb 100 ppm	293.5 ± 6.3a	48.5 ± 0.3a	91.9 ± 3.5b	1.9 ± 0.5a
Suc+Pb 100 ppm	323.3 ± 9.7b	43.2 ± 2.1b	100.4 ± 1.6b	4.0 ± 0.9b
Pb 400 ppm	295.7 ± 6.1a	47.2 ± 1.6a	92.3 ± 4.5b	1.4 ± 0.3a
Suc+Pb 400 ppm	312.8 ± 8.2b	45.3 ± 1.5b	68.72 ± 2.4a	2.0 ± 0.5a

Note: Whole blood collected by eye vein puncture after 12 months of treatment was used for hematocrit determination. Glucose and insulin were measured in plasma samples by specific kits. The results are represented as means ± S.E.

for 9-11 animals per group. *Different letters means difference among the groups in the same collum (p<0.05)

Table 1: Effect of sucrose and/or lead treatment on body weight, hematocrit, glucose and insulin levels in aging rats.

Biochemical and hematological parameters

Statistical analysis revealed a significant effect of sucrose on the hematocrit ($F(1,18)=11.06$, $p<0.01$). The consumtion of sucrose for 12 monts, regardless of lead treatment, caused a reduction in the hematocrit (Table 1). The chronic consumption of sucrose and lead, associated or not, increased the blood glucose levels of animals. However, this effect was not verified in the rats treated simultaneously with sucrose plus Pb^{2+} 400 ppm. In contrast to glucose, only the ingestion of sucrose increased the levels of insulin (Table 1). This hyperinsulinemia was not detected in the group exposed to sucrose plus Pb2+400 ppm. The levels of insulin of animals treated only with Pb^{2+} did not differ from control (Table 1).

Open field behavior

There is no effect of lead or sucrose intake on behavioral parameters evaluated by open field test after 4 months of treatment. On the other hand, occurred a decrease in the locomotor activity (crossing numbers) of animals from control and sucrose groups after 12 months (Table 2). Rearing behavior was increased in all groups after 12 months when compared with the period of 4 months. This response was not affected by sucrose and or Pb^{2+} treatments.

Treatments	Crossing		Rearing	
	Months of treatment			
	4	12	4	12
Control	24.5 ± 2.0	19.1 ± 3.0*	9.0 ± 1.3	13.1 ± 2.2*
Pb 100 ppm	24.5 ± 2.1	23.8 ± 1.9	9.8 ± 0.9	14.2 ± 1.4*
Pb 400 ppm	23.4 ± 3.1	22.2 ± 3.0	9.8 ± 1.6	17.8 ± 2.6*
Sucrose	25.0 ± 3.2	18.2 ± 1.3*	11.5 ± 1.7	15.2 ± 1.2*
Sucrose + Pb 100 ppm	21.7 ± 3.4	19.3 ± 2.3	9.2 ± 2.2	13.2 ± 2.1*
Sucrose + Pb 400 ppm	18.7 ± 2.9	15.7 ± 1.9	10.2 ± 1.5	13.3 ± 1.8*

Table 2: Effect of sucrose and/or lead intake on motor and exploratory behaviors in aging rats.

Orofacial dyskinesia

Vacuous chewing movements (VCM) and tongue protrusion: ANOVA of VCM yielded a main effect of age ($F(4,220)=12.64$, $p<0.01$), because VCM incidence increased as a function of age in all groups, excepting in the group exposed simultaneously to sucrose plus Pb^{2+} 400 ppm. In addition, there was a significant sucrose × lead × age interaction ($F(8,220)=2.10$, $p<0.05$) (Table 3).

Statistical analysis also revealed a significant sucrose × lead interaction for tongue protrusion ($F(2,55)=6.65$, $P<0.01$). The incidence of tongue protrusion of rats exposed to sucrose plus Pb2+400 ppm was lower after 12 months compared to 4 months (Table 3).

Treatment	Vacuous Chewing Movements		Tongue Protrusion	
	Months of treatment			
	4	12	4	12
Control	23.6 ± 2.7	30.2 ± 6.5*	2.33 ± 0.42	2.55 ± 0.49
Pb 100 ppm	25.7 ± 3.0	29.8 ± 4.5*	1.62 ± 0.86	1.37 ± 0.68
Pb 400 ppm	18.4 ± 3.0	41.3 ± 7.3*	2.89 ± 0.81	5.78 ± 2.81
Sucrose	23.5 ± 3.3	31.9 ± 4.5*	3.10 ± 0.84	2.20 ± 0.62
Sucrose + Pb 100 ppm	19.1 ± 5.3	39.8 ± 3.6*	2.33 ± 0.73	2.55 ± 1.01
Sucrose + Pb 400 ppm	16.7 ± 1.9	16.6 ± 1.4#	1.30 ± 0.4	1.20 ± 0.34*

Table 3: Effect of sucrose and/or lead intake on orofacial dyskinesia in aging rats.

Discussion

In the present study, we demonstrated that OD appearance increased as a function of age. In line with this, a direct association between aging and drug-induced dyskinesia has been reported by several investigators [30,33,37]. However, no previous study had investigated the effect of lead and/or sucrose consumption on OD occurrence in aging rats. In this respect, the results obtained here indicated that neither sucrose intake nor lead exposure facilitated the appearance of OD in aging rats. Conversely, the increase in OD incidence in aging rats was mitigated by simultaneous exposure to the highest dose of lead (400 ppm) and sucrose. These results are in sharp contrast to our expectation because the exposition to lead and sucrose was supposed to increase the OD incidence. Moreover, the development of insulin resistance induced by sucrose consumption, which could be linked to neurologic disturbances development, also did not modify OD occurrence in this experimental protocol.

Here we have not determined the oxidative parameters after prolonged exposure to lead and sucrose, but there are several points of evidence in the literature indicating that that oxidative stress plays an important role in the pathophysiologic basis of tardive dyskinesia, especially in the elderly [30]. Similarly, OD is thought to be associated with an increase in the glutamatergic transmission in different brain structures [31,34], particularly with an overactivation of NMDA. Literature data have indicated that lead can inhibit NMDA activation [10,38,39]. Consequently, the antagonism of NMDA receptor by lead could be one plausible explanation for its lack of effect as a potential inductor of OD in this chronic experimental model. Moreover, the long-term exposure to sucrose and/or lead could have induced the development of a compensatory response in animals, precluding a further increase in OD.

In the biochemical parameters, it is interesting to note that sucrose ingestion caused per se a marked decrease in hematocrit, in addition to its expected effect on glucose and insulin levels. We were not able to

find data in the literature indicating that long-term intake of sucrose leads to a significant decrease in the hematocrit in aging rats. However, there are some evidences that sucrose consumption accelerates the development of anemia in copper-deficient rats [40,41]. The mechanism by which sucrose could enhance the severity of anemia seems to be associated with a reduction in copper levels of tissue levels and consequently, in the activity of copper-dependent enzymes such as Cu, Zn-superoxide dismutase. Disruption in these antioxidant enzymes may increase the sensitivity of cells to lysis and decrease the lifespan of red blood cells [22]. In contrast to our expectation, Pb^{2+} did not decrease the hematocrit of aging rats. In conformity, Pedroso and collaborators recently reported that short-term exposure to lead acetate did not decrease the hemoglobin levels in young rats [42]. Similarly to sucrose, isolated exposure to lead (100 and 400 ppm) caused an increase in blood glucose, result that is in accordance with other recent studies in rats [17,18]. However, the simultaneous exposure to sucrose and 400 ppm of Pb^{2+} were not associated with hyperglycemia. Thus, the long-term interaction of Pb2+ and sucrose is rather complex, which was further supported by the absence of Pb^{2+} effects in the levels of basal insulin in old rats.

It has been documented that lead toxicity is sometimes associated with an increase in locomotor activity and with the etiology of learning disabilities [4,8,43]. Thus, we investigated the effects of chronic lead exposure in the locomotor activity. Our data revealed that age and sucrose were the main factors associated with locomotor deficits. The animals exposed to lead did not present a decrease in locomotor activity, response that could indicate impairments in processes as habituation and attention caused by Pb^{2+} [8,44]. Here we have also observed that aging caused an increase in the incidence of rearing. These results indicate that the rearing behavior, differing from general activity, increase also as a function of age.

Conclusion

In conclusion, our results indicate that chronic consumption of lead and sucrose did not elicit increase in OD incidence. In this scenario, we suppose that the animals developed some compensatory mechanism(s) against to lead and sucrose toxicity after long-term exposure or that these agents have effective participation especially in neurological disorders where the hyperglycemia and insulin resistance are considered key risk factors, such as in Alzheimer disease. Novelty, here we demonstrated that prolonged ingestion of sugar may induce anemia in old rats, finding that deserves to be better explored in further studies in terms of mechanism(s).

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