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Lead Acetate Potentiates Brain Catalase Activity and Enhances Ethanol-Induced Locomotion in Mice

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CORREA, M., M. MIQUEL AND C. M. G. ARAGON. *Lead acetate potentiates brain catalase activity and enhances ethanol-induced locomotion in mice.* PHARMACOL BIOCHEM BEHAV **66**(1) 137–142, 2000.—Several reports have demonstrated that acute lead acetate administration enhances brain catalase activity in animals. Other reports have shown a role of brain catalase in ethanol-induced behaviors. In the present study we investigated the effect of acute lead acetate on brain catalase activity and on ethanol-induced locomotion, as well as whether mice treated with different doses of lead acetate, and therefore, with enhanced brain catalase activity, exhibit an increased ethanol-induced locomotor activity. Lead acetate or saline was injected IP in Swiss mice at doses of 50, 100, 150, or 200 mg/kg. At 7 days following this treatment, ethanol (0.0, 1.5, 2.0, 2.5, or 3.0 g/kg) was injected IP, and the animals were placed in the open-field chambers. Results indicated that the locomotor activity induced by ethanol was significantly increased in the groups treated with lead acetate. Maximum ethanol-induced locomotor activity increase was found in animals treated with 100 mg/kg of lead acetate and 2.5 g/kg of ethanol. Total brain catalase activity in lead-pretreated animals also showed a significant induction, which was maximum at 100 mg/kg of lead acetate treatment. No differences in blood ethanol levels were observed among treatment groups. The fact that brain catalase and ethanol-induced locomotor activity followed a similar pattern could suggest a relationship between both lead acetate effects and also a role for brain catalase in ethanol-induced behaviors. © 2000 Elsevier Science Inc.

Ethanol Catalase Lead Acetate Locomotor activity Acetaldehyde

BRAIN catalase activity has been shown to be involved in several acute psychopharmacological effects of ethanol (24,27). Thus, it has been shown that catalase inhibition by 3-amino-1,2,4-triazole (AT) produces a reduction in some ethanol-induced behavioral effects in ethanol-naive rodents (17,24). For example, it has been shown that AT reduces ethanol-induced changes in locomotion (2,6,22). In the same way, other studies using other catalase blockers as cyanamide (22) or sodium azide (23) have also demonstrated that the reduction of brain catalase runs parallel to the inhibition of ethanol-induced locomotion. Also, it has been shown that genetically catalase-deficient mice have lower ethanol-induced locomotor activity than normal mice (4,6). The effects of all these manipulations on ethanol-induced effects cannot be attributed to pharmacokinetic changes, because there are no differences in ethanol blood levels between saline and catalase-deprived animals (2,4,6,23). Likewise, this catalase deficiency does not modify the behavioral changes produced by other substances. Thus, cocaine (6), *d*-amphetamine or *tert*-butanol–induced locomotor activity (22,23) was similar in controls and in catalase-deprived animals. Therefore, the fact that brain catalase and ethanol-induced locomotor activity followed a similar pattern could suggest a relationship between both inhibitor effects, and also a role for brain catalase in ethanol-induced behaviors.

However, it could be argued that the extensive use of inhibitors, as the only tool to assess a putative role of brain catalase activity on ethanol behavior, could be a limitation (17). Thus, given these findings, it seems logical to further extend these studies on the role of the enzyme catalase in the mediation of the central effects of ethanol, and employing, for this goal, a different strategy: the potentiation of catalase activity.

It has been shown that exposure of immature rats to lead acetate results in an increase in catalase activity in brain, possibly, as a mechanism for detoxification processes in this tissue (26). Other authors have displayed that administration of

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lead to chick embryos increases brain catalase activity 72 h following a lead acetate injection (25). These authors suggest that the enhancement of catalase could provide an efficient mechanism against lead-induced lipid peroxidation. Finally, other authors reported that catalase-reactive peroxisomes appear to increase in number in the spinal cords of lead-treated chick embryos after acute intoxication by lead nitrate (11). Together, all these findings suggest that acute lead acetate exposure results in an enhancement of brain catalase activity, possibly as an antioxidant defense in response to the presence of this metal in organisms.

A recent study (10) has approached the consequences of an acute lead acetate administration on brain catalase activity and ethanol-induced locomotion. This report demonstrated that a single administration of lead acetate to mice 5 and 7 days before an ethanol treatment boosted the locomotion produced by ethanol. Interestingly, identical treatment of lead acetate also increased brain catalase activity with the same time course as was observed for the behavioral effects. Moreover, the effects of lead acetate were specific for the locomotion induced by ethanol because neither *d*-amphetamine nor *tert*-butanol–induced locomotion were modified by a pretreatment with lead acetate (10). Further, a significant correlation was shown between brain catalase activities and locomotor activity produced by ethanol. It is interesting to note, however, that although lead is accumulated in the brain even 11 days after its administration, no correlation was observed between the brain lead levels and the brain catalase or ethanol-induced locomotor activity (10). Nevertheless, in this article no data are reported about the effects of several doses of lead acetate on ethanol biphasic effect on locomotion. Because acute lead exposure may have toxicological side effects, systematic dose–response analyses should be conducted.

The present article undertakes a detailed study about the effects of different doses of lead acetate on ethanol-induced locomotor activity. Moreover, because it has been reported that lead acetate can exert toxicological effects on the brain, it is necessary to analyse to what extent the effects of lead acetate on locomotor activity are due to specific action on brain catalase, or conversely, these effects are due to a more unspecific toxic effect on brain tissue. Therefore, the present study is an attempt to further investigate the effects of lead exposure on brain catalase activity and on ethanol-induced behavioral effects to improve the knowledge of the nature of the relationship between ethanol and brain catalase.

METHOD

Subjects

Male Swiss–Webster mice (32–42 g) purchased from Harlan–Interfauna Ibérica S.A. (Barcelona, Spain) were housed in groups of four per cage, with standard laboratory rodent chow and tap water available ad lib. Subjects were maintained 7 days prior to experimentation at 22 ± 1°C with lights on from 0800 to 2000 h. Testing was conducted between 1000 and 1300 h. All experimental procedures complied with the European Community Council Directive (86/609/ECC) for the use of laboratory animal subjects.

Drugs

Lead acetate (Sigma Aldrich S.A., Spain) was dissolved in distilled water at a concentration of 0.5 mg/10 ml. Ethanol solution (20% v/v) was prepared from ethanol 96% (Panreac Química S.A., Spain) in saline solution.

Apparatus

The open-field apparatus consisted of a clear glass cylinder 25 cm in diameter and 30 cm high. The floor of the cylinder was divided into four equal quadrants by two intersecting lines drawn on the floor, and a locomotion score (count) was assigned each time an animal crossed over from one quadrant to another with all four legs. The behavioral room was illuminated with a soft light, and external noise was attenuated.

Lead Acetate Doses on Ethanol-Induced Locomotor Activity

Following 7 days of habituation to laboratory conditions, animals were randomly sorted into different groups. All drugs were administered to mice by an IP injection. Lead acetate (50, 100, or 150 mg/kg) or saline was injected in mice and, at 7 days following this treatment, physiological, behavioral, or biochemical tests started. This time was chosen following preliminary studies (10). In the test day saline or ethanol (2.5 g/kg) were injected in animals and testing started. Mice were placed individually in the open-field chambers for 20 min. Individual measures of locomotor activity were recorded for the last 10 min period following the administration of ethanol. This delay was chosen to decrease the effects of animal handling and the environmental novelty of the open-field (12,18).

Ethanol Doses Induced Locomotor Activity

In a second study, lead acetate (100 mg/kg) or saline was injected in mice and, at 7 days following this treatment, saline or ethanol (1.5, 2.0, 2.5, or 3.0 g/kg) was injected and locomotor activity was recorded as mentioned above.

Brain and Body Weight Analysis

Lead acetate (50, 100, 150, or 200 mg/kg) or saline was injected into mice (n = 10 per group) and, at 7 days following this treatment, individual mouse body and brain weights were registered.

Brain Catalase Activity Determination

Brain catalase activity was measured in mice treated (IP) with saline or lead acetate (50, 100, or 150 mg/kg). The brains were collected 7 days following the treatment. Mice were perfused using 50 ml of heparinized (1000 units/l) isotonic saline. The whole brain was removed and homogenized in a phosphate buffer (50 mmol/l; pH 7.0) with digitonin (0.01%). Brain homogenates were centrifuged at 10,000 rpm for 10 min in an Eppendorf microcentrifuge. Supernatant aliquots were used to determine brain catalase levels. Catalase activity was assayed spectrophotometrically in the supernatants by measuring the decrease in absorbance of H_2O_2 at 240 nm (1). Protein levels were determined from supernatants (7).

Blood Ethanol Assay

Mice were injected with saline or lead acetate (50 or 100 mg/kg). Seven days after this treatment, an ethanol injection (2.5 g/kg) was administered IP. Trunk blood was collected 15, 30, and 60 min after ethanol administration from the nine groups of mice. Each sample of blood was collected in heparinized microcentrifuge tubes and immediately placed in a Eppendorf centrifuge where the samples were spun down for 5 min at 5000 rpm. A micropipette was then used to extract 160 μl of plasma and to add it to 1.44 ml of TCA (20%). The mixture was spun down again (5 min at 5000 rpm) to obtain a clear, protein-free supernatant. This protein-free serum was

then placed in cuvets with optical properties suitable for use with a spectrophotometer set at 340 nm. Blood ethanol content was enzymatically determined with an Alcohol Diagnostic Kit (Sigma Aldrich S.A. Spain).

Statistical Analyses

Data were analyzed by means of analyses of variance (ANOVA). Post hoc comparisons were undertaken if a significant main effect or interaction was found at $p \leqslant 0.05$. These comparisons were made using Fisher's Least Significant Difference Tests (LSD). Statistical computerized program STATISTICA 4.1 was used in this study.

RESULTS

Brain and Body Weight Analyses

These analyses were conducted to evaluate the effect of increasing doses of lead acetate on two different physiological parameters: body and brain weight 7 days after the administration of the metal. In the Table 1 the mean body weight of mice after the treatment with several doses of lead acetate is shown. A one-way ANOVA showed a significant effect of the lead dose factor, $F(4, 48) = 13.6$, $p < 0.01$. Post hoc comparisons revealed that 150 and 200 mg/kg of lead acetate had a significant effect on body weight ($p < 0.01$). Because 200 mg/kg of lead acetate have a deleterious effect on body weight, this dose was not used for the rest of studies. Also, this dose produce 30% lethality (data not shown). An ANOVA of the second parameter, wet brain weight, did not reveal a significant effect of the lead doses factor, but post hoc analyses showed a difference ($p < 0.05$) between groups 150 and 0 mg/kg, and 200 mg/kg and 0 mg/kg of lead acetate.

Brain Catalase Activity Determination

In this experiment, the effect of several doses of lead acetate on brain catalase activity was explored. Table 2 represents the levels of brain catalase activity 7 days after lead acetate administration. A one-way ANOVA showed a significant effect on doses of lead acetate factor, $F(3, 22) = 21.1$, $p < 0.01$. Post hoc LSD testing revealed that, all lead acetate-treated mice (50, 100, and 150 mg/kg) showed an increase in brain catalase activity, and this increase was statistically different from group 0 mg/kg ($p < 0.01$). The increase in brain catalase activity was 39% for the dose 50 mg/kg, 50% for the dose 100 mg/kg of lead acetate, and 55% for the dose 150 mg/kg of lead acetate compared to the control group.

TABLE 1

EFFECT OF ACUTE LEAD ACETATE ON BODY AND BRAIN WEIGHT

Lead Acetate Doses (mg/kg)	Body Weight (g)	Brain Weight (g)
0	37.70 ± 0.76	0.474 ± 0.005
50	38.48 ± 0.51	0.455 ± 0.012
100	36.30 ± 0.93	0.460 ± 0.006
150	33.42 ± 0.68†	0.449 ± 0.008*
200	31.56 ± 1.10†	0.441 ± 0.008*

Mean ± SEM of body ($n = 10$) or wet encephalic ($n = 13$) weight of mice 7 days following an acute (IP) administration of lead acetate (0, 50, 100, 150, 200 mg/kg).

*$p < 0.05$. †$p < 0.01$ significantly different from group 0 mg/kg of lead acetate on their respective variable.

TABLE 2

BRAIN CATALASE ACTIVITY FOLLOWING LEAD ACETATE ADMINISTRATION

Lead Acetate (mg/kg)	Brain Catalase Activity (mmol H_2O_2/min/mg protein)	n
0	0.90 ± 0.07	7
50	1.25 ± 0.03*	7
100	1.35 ± 0.03*	7
150	1.39 ± 0.03*	5

Mean ± SEM of brain catalase activity (mmol H_2O_2/min/mg protein) following lead acetate (0, 50, 100, or 150 mg/kg) administration. Subjects were sacrificed by exsanguination under ether anesthesia 7 days following an acute IP injection of lead. Perfused brain homogenates were assayed for brain catalase activity to measure the decrease in absorbance of H_2O_2 at 240 nm.

*$p < 0.01$ significantly different from 0 mg/kg.

Lead Acetate Doses on Ethanol-Induced Locomotor Activity

Figure 1 shows the effect of several acute doses of lead acetate on spontaneous and ethanol-induced locomotor activity. Different groups of animals were injected (IP) with 0, 50, 100, or 150 mg/kg of lead acetate. Following a period of 7 days, locomotor activity tests were conducted as described in the Method section. The test day, each animal received an IP injection of ethanol (2.5 g/kg) or the corresponding volume of saline. A two-way ANOVA: dose of lead acetate (0, 50, 100, or 150 mg/kg) × dose of ethanol (0.0 or 2.5 g/kg), yielded a significant effect of both main factors: dose of lead acetate, $F(3, 72) = 2.8$, $p < 0.05$, and dose of ethanol, $F(1, 72) = 84.0$, $p < 0.01$, as well as a significant effect for the interaction, $F(3,$

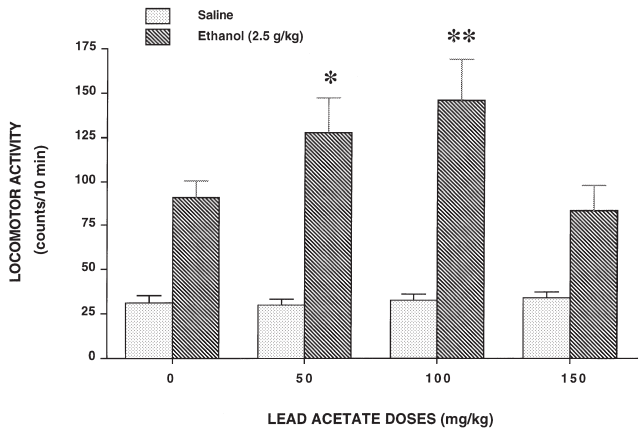

FIG. 1. Lead acetate dose effect on ethanol-induced locomotor activity. Mean ± SEM locomotor activity (counts/10 min) for all treatment groups ($n = 10$ per group). Lead acetate (0, 50, 100, or 150 mg/kg) was injected IP to mice 7 days before testing with saline or ethanol (2.5 g/kg). (** $p < 0.01$, * $p < 0.05$ significantly different from group 0 mg/kg of lead acetate/ethanol).

72) = 2.9, $p < 0.05$. Post hoc Fisher's least significant difference test revealed that spontaneous locomotor activity (groups 0.0 g/kg of ethanol) was similar in all lead-treated groups. In addition, ethanol (2.5 g/kg) significantly induced locomotor activity in all the groups injected with different doses of lead compared to corresponding saline (0.0 g/kg of ethanol)-injected animals. Furthermore, subjects treated with lead acetate (50 and 100 mg/kg) showed a potentiation of ethanol-induced locomotor activity ($p < 0.05$ and $p < 0.01$, respectively) compared to controls (0 mg/kg lead acetate). However, the higher dose of lead acetate (150 mg/kg) does not have an effect on ethanol-induced locomotor activity compared to control. In summary, while acute administration of lead acetate has no effect on spontaneous locomotion at any dose tested, lead acetate (50 and 100 mg/kg) potentiates ethanol-induced locomotion 7 days after administration of the metal.

Blood Ethanol Levels Assay

To discard the possibility that the above observed effect is not produced through a peripheral interaction between lead and ethanol, we assessed the plasma ethanol levels in mice treated with saline or lead acetate after an IP injection of ethanol. These results are presented in Table 3. A two-way ANOVA: treatment (0, 50, 100 mg/kg of lead acetate) × time (15, 30, or 60 min) yielded a significant time effect, $F(2, 27) = 59.0$, $p < 0.01$. Conversely, the treatment factor and its interaction with the time factor failed to reach statistical relevance. LSD comparisons revealed that ethanol clearance was directly related to time. Lead acetate does not change blood ethanol levels at any time compared and at any dose of lead acetate compared with the saline group.

Ethanol Doses Induced Locomotor Activity

In this experiment we study whether the potentiating effect of lead acetate on ethanol-induced locomotor activity appears with different doses of ethanol. For this test, we use the dose of lead acetate that, on interaction with ethanol, produced the highest increase in locomotion. Figure 2 represents the effect of an (IP) injection of lead acetate (100 mg/kg) or saline on locomotion induced for different doses of ethanol. A two-way ANOVA: treatment (saline or lead acetate) × ethanol dose (0.0, 1.5, 2.0, 2.5, or 3.0 g/kg) revealed a significant effect for factor treatment, $F(1, 90) = 8.3$, $p < 0.01$, for ethanol dose, $F(4, 90) = 17.6$, $p < 0.01$, and for the interaction, $F(4, 90) = 4.4$, $p < 0.01$. Post hoc comparisons for the interaction were made by means of Fisher's least significant difference test and revealed that in the saline group, ethanol (2.0, 2.5, and 3.0 g/kg) produced a significant induction of locomotor activity respect to 0.0 g/kg ethanol group ($p < 0.01$). Interestingly, lead acetate (100 mg/kg) potentiates ethanol-induced locomotor activity at doses of 2.5 and 3.0 g/kg ($p < 0.01$) respect to corresponding controls.

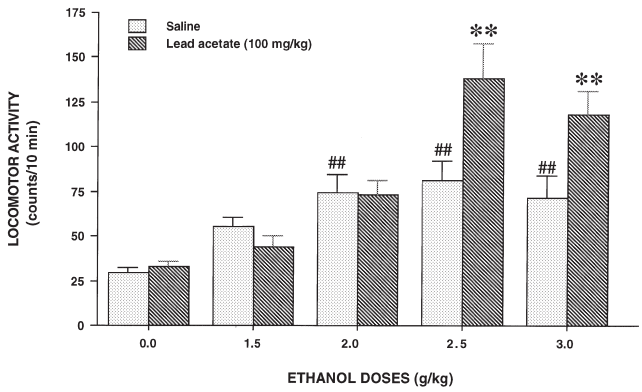

FIG. 2. Lead acetate effect on locomotion activity induced by several doses of ethanol. Mean ± SEM locomotor activity (counts/10 min) for saline or lead acetate (100 mg/kg) treated mice as a function of ethanol dose (0.0, 1.5, 2.0, 2.5, or 3.0 g/kg). Saline or lead acetate was injected 7 days before administration of ethanol ($n = 10$ per group). (** $p < 0.01$ significantly different from equivalent dose in saline group. ##$p < 0.01$ significantly different from 0.0 g/kg ethanol/saline group).

TABLE 3

EFFECT OF LEAD ACETATE ON BLOOD ETHANOL LEVELS (mg/dl)

Time (Minutes)	Lead Acetate (mg/kg)		
	0	50	100
15	269.8 ± 6.3	286.7 ± 14.1	265.5 ± 18.9
30	242.5 ± 4.8	241.2 ± 6.0	244.1 ± 11.8
60	183.0 ± 12.3	182.6 ± 7.2	175.1 ± 5.9

Mean ± SEM of blood ethanol levels (mg/dl) following an acute IP administration of 2.5 g/kg ethanol to mice pretreated with lead acetate (0, 50, or 100 mg/kg, IP, 7 days before). Trunk blood was collected 15, 30, and 60 min following ethanol administration ($n = 6$ per group).

DISCUSSION

The results reported in the current article show that lead acetate administration boosts the ethanol-induced locomotor activity in mice without altering spontaneous locomotion. This effect confirms and extends previous reports (10). Mice in the present study display an enhancement in locomotor activity after being treated with moderately high doses of ethanol. Interestingly, lead acetate potentiates the ethanol-induced locomotor activity at two of these doses of ethanol (2.5 and 3.0 g/kg). This significant enhancement of ethanol-induced deambulation was produced after the administration of 50 and 100 mg/kg of lead acetate. This potentiation reaches its highest effect at 100 mg/kg (52%). Nevertheless, the lead acetate dose of 150 mg/kg does not show any difference in ethanol-induced locomotor activity compared to control subjects. A possible explanation for this result could be a toxicological effect of this very high dose of lead on these animals. It is interesting to point out that this dose alters physiological parameters (e.g., brain and body weights). Accordingly, the lower doses of lead acetate (50 or 100 mg/kg) produce an enhancement of ethanol-induced locomotion and did not show a deleterious action on mice body or brain weight as happens with the higher doses tested (150 or 200 mg/kg).

The measurement of blood ethanol levels reveals no difference between control and lead acetate-treated mice at any lead acetate dose employed. Therefore, the interaction between lead acetate action and ethanol-related locomotion does not seem to be due to different peaks of blood ethanol levels. The lack of effects of lead acetate on blood ethanol lev-

els suggests that acute IP lead acetate could interact with ethanol in a central site, rather than a peripheral one. These results support previous data. Consistently, catalase manipulations fail to alter peak blood ethanol levels in animals treated with moderate doses of ethanol (2,4,6,10,23).

On the other hand, the data obtained in the present study support other previous findings that showed the inductor effect of an acute lead acetate administration on brain catalase activity (10,25,26). In this study, a significant induction of total brain catalase activity appeared at all doses of lead acetate tested: 50, 100, or 150 mg/kg. This effect was maximal for the highest dose. So far, there is not a clear explanation for this effect of acute lead acetate on catalase, although a mechanism whereby this metal may alter brain catalase activity has been suggested (11,25,26). Thus, an increase in the formation of brain lipid hydroperoxides in lead-intoxicated animals acts as a signal to maintain higher levels of catalase to enhance the triggering of the detoxification process for the metal (25).

It is interesting to note that the same doses of lead acetate that enhance brain catalase activity also increase ethanol-elicited locomotion. This result could suggest a close relationship between both lead acetate effects. In fact, in the previous stuy (10), a significant correlation between the two effects of lead acetate was presented. Therefore, enhanced levels of cerebral catalase activity may have been an important factor influencing the changes observed in ethanol-induced behavior. The proposed parallelism agrees with previous data that demonstrate that brain catalase manipulations consistently result in alterations of ethanol-induced behavior (24). Thus, a reduction of ethanol-induced locomotor activity has been observed in AT, cyanamide, or sodium azide-pretreated mice as well as in acatalasemic mice (2,4,6,22,23). In all these studies, catalase-depleted mice demonstrated lower ethanol-induced locomotion. On the other hand, when brain catalase activity of mice is potentiated, ethanol-induced locomotion is higher than in control animals, as seen in earlier (10) and the present reports. Therefore, all these data suggest a relationship between brain catalase and behavioral consequences of an acute ethanol challenge.

It has been proposed that the putative role of the enzyme catalase in mediating some of the psychopharmacological effects of ethanol may be through its ability to produce acetaldehyde in the CNS (3,5,15,24). In several in vitro studies, brain homogenates of rodents incubated in the presence of ethanol (4–6,15) have shown to oxidize ethanol to acetaldehyde via the peroxidatic activity of catalase. Similar results have been obtained when neural tissue cultures (14,16) and primary cultures of hypothalamic neurons (21) were incubated with ethanol. Moreover, others authors have demonstrated that prior IP administration of ethanol to rats protects brain catalase activity from inhibition by several catalase blockers as AT, cyanamide, and 4-hydroxpyrazole (3,9). This prevention of the inhibitory effect in vivo by these compounds has been taken as indirect support for evidence of the oxidation of ethanol in the CNS via catalase (3,9). Furthermore, the identification and presence of ethanol-metabolizing enzymes in cerebral tissue by biochemical or histochemical methods provide some indirect evidence for this metabolism and the subsequent presence of acetaldehyde in the brain (8,20). Nonetheless, the subsequent central levels of acetaldehyde would be very low if compared to liver metabolism capacity (13). However, to date, how much acetaldehyde is needed in the brain to produce any change in behavior has not been determined (24).

Besides the above, other mechanisms for the effects of lead acetate on ethanol-induced behavior may be proposed. Thus, Valenzuela et al. (26) have demonstrated, in vivo, an induction of glutathione peroxidase activity with an acute treatment of lead acetate. However, at present, no relationship between glutahione peroxidase and ethanol-elicitated behaviors has been noted. On the other hand, it has been demonstrated that in vitro, lead acetate increases dopamine release from striatal synaptosomes (19). Nevertheless, if the same took place in vivo, no specifity of lead treatment for ethanol-induced behavior should be observed, and therefore, locomotor activity produced by amphetamine, a prodopaminergic drug, should be affected by lead, but was not the case (10).

In conclusion, the present results tend to reinforce the postulation that cerebral catalase may be involved in ethanol-induced behaviors. This putative role of the enzyme catalase in some of the psychopharmacological effects of ethanol may be through its ability to oxidize ethanol to acetaldehyde in the central nervous system (24,27,28), and this capacity exerts at least some influence on ethanol's behavioral effects.

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