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Drug and Food-Deprivation Modulation of Activity in Rats Given Chronic Dietary Lead: Significance of Type of Activity Measure

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YAMAMOTO, B. K. AND C. L. KUTSCHER. *Drug and food-deprivation modulation of activity in rats given chronic dietary lead: Significance of type of activity measure.* PHARMAC. BIOCHEM. BEHAV. 15(3) 505–512, 1981.—In Experiment 1, rats were given a 1% lead acetate diet from Day 100 of life to the termination of the experiment. After 82 days of lead feeding behavioral tests were started. Lead exposure increased wheel-turning hyperactivity produced by food deprivation and phenylethylamine injection. Lead produced no activity change in the unchallenged condition. In the open field, lead-exposed rats were less responsive to the stimulating action of PEA and amphetamine and to the sedating action of pentobarbital. In Experiment 2, the interaction of lead with food deprivation or PEA on wheel-turning was replicated in naive animals given only a 32-day exposure. Chemical analysis was made of tissues. Ingested lead entered the brain. Regional steady-state levels of brain norepinephrine, dopamine and serotonin were not altered by lead treatment when measured following four days of starvation at a time when lead-induced behavioral change was distinct. It was concluded that pharmacological challenges on activity may be sensitive indicators of lead exposure, but the type of activity measure is critical.

Activity Amphetamine Lead Pentobarbital Phenylethylamine Starvation

SINCE the nervous system is a sensitive target of absorbed lead [49], the neurobehavioral actions of lead have been widely studied in humans [36] and in animals [49]. Lead is widespread in the environment [30]. Following absorption into the body it enters the brain more slowly than peripheral tissues [28]. In humans, extensive lead exposure has been accompanied by mental retardation, convulsions, blindness and deviant behavior [2,34]. Rats exposed from birth to high lead diets developed motor abnormalities including ataxia, paraplegia and grossly abnormal gait [33,39]. Chronic lead exposure in rats has produced axonal degeneration, demyelinization of peripheral nerves [19], cerebellar hemorrhages and breakdown of the blood-brain barrier [8].

In recent years attention has been directed toward the latent sequelae in children exposed to low or moderate levels of lead and who may exhibit no clinical symptomatology. For example, children exposed to low levels of lead showed deficits in intelligence test performance and in gross and fine motor performance [1]. Since the human nervous system is not accessible for study of the mechanisms of lead intoxication, animal models are indicated. Because it is widely held that behavior change may be an early and sensitive indicator of lead-induced neurologic alteration, many studies have been made of the behavioral consequences of low-level lead exposure in animals [49].

This research was given impetus by the discovery of a possible link between lead exposure and minimal brain dysfunction (MBD) in humans. A common symptom of MBD [52] and a frequent concommitant of lead exposure [20] is a high level of behavioral activity which is apparently not goal-related. Beginning in 1973 [46], many studies have found that chronic lead exposure can increase spontaneous motor activity in mice [44,48] and rats [9, 18, 32, 41] suggesting that there may be a practical animal model for MBD and also a sensitive behavioral indicator of lead exposure. Other investigators, however, found decreased activity in rats [4,38] and mice [23] given chronic lead exposure. In two studies, lead administration produced no activity change [11,50].

The case for an animal model of hyperactivity was further strengthened by the study of drug action on activity in lead-exposed animals. Hyperactivity in children is sometimes diminished by amphetamine and methylphenidate and exacerbated by barbiturates [22], contrary to drug effects in normal children. Paradoxical drug actions were seen in lead-exposed hyperactive mice. Amphetamine and methylphenidate reduced activity and phenobarbital increased it [47]. In lead-exposed rats showing hyperactivity, the stimulatory action of amphetamine was attenuated and the learning deficits attributed to lead toxicity were ameliorated

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by amphetamines [50], pharmacologic responses similar to those seen in hyperactive children.

In the following experiments, we investigated aspects of the animal model of the neurobehavioral toxicity of lead which have received little attention. (a) Most investigators have used the Pentschew-Garro [33] procedure of administering lead to neonatal rats (either directly by gavage or indirectly in the mother's milk) plus various regimens of post-weaning lead administration. We studied the impact of lead administration in adults; (b) We studied the impact of starvation challenge on activity in addition to various pharmacologic challenges; (c) We used two different activity measures, the open field and the activity wheel to study the interaction of these challenges and lead exposure on activity; (d) We utilized phenylethylamine (PEA) as a drug challenge.

PEA is an endogenous sympathomimetic amine similar in structure to amphetamine except that PEA has no methyl group at the alpha carbon. PEA is found in both human [12] and rat brain [53] and is the preferred substrate for monoamine oxidase B [24]. It produces hyperactivity in rats [24] and mice [13] and stereotypy consisting of choreic head movements, backward locomotion, enhancement of sniffing and depression of grooming, eating and drinking [24]. In humans, PEA has been linked to depression [5], schizophrenia [27] and phenylketonuria [31]. It has been argued that PEA is either a neurotransmitter or a neuromodulator [40].

EXPERIMENT 1

In this experiment, a variety of behavioral tests were employed to determine which paradigm would be sensitive to dietary lead administration. In Experiment 2, two of these tests were replicated in naive animals and assays were made of tissue lead and brain neurotransmitters.

METHOD

Animals

Twenty, naive, male hooded rats from the Charles River stock, bred in the Syracuse University Psychology Research Laboratory, were used in this experiment. Rats were 95–112 days old when lead diets were initiated. Rats were maintained on Purina chow pellets prior to special diets.

Apparatus

Rats were group housed from weaning until the start of lead administration when they were housed individually in 22×30×35 cm steel and wire-mesh cages. Lights were on for 14 hr/day and ambient temperature was maintained at 21±1°C. Humidity was maintained at 50±10%. Activity was measured in standard Wahmann running wheels and in an open field. The latter was a square, wooden arena, 91 cm on a side. The outside walls were 30 cm high and walls and floor were painted with a medium gray enamel. The floor was divided into squares 11 cm on a side. The arena illumination was provided by overhead fluorescent room lighting. Both activity tests were conducted in a quiet room adjoining the colony room.

Procedure

Ten rats were given a 1% lead acetate diet and 10 were given the control diet. The lead diet was prepared by dissolving 5 g of lead acetate flakes into 600 ml of demineralized water which was then mixed into 495 g of powdered Purina chow. The wet mash was placed into a foil pan, sliced into blocks and dried overnight at 55°C in a forced-draft oven. The control diet was prepared in the same manner except that no lead was added. From the time of diet initiation, body weights and water intakes were measured by weighing the bottles every two days for 82 days. The lead-diet rats were indistinguishable from the control rats in physical appearance and rate of weight gain. Only the behavioral tests differentiated them.

Food deprivation, wheel-turning. On Day 82 of the dietary regimen, rats were placed in running wheels and baseline (unchallenged) daily wheel running was measured for 3 days with food present. Food was removed to initiate 5 days of total food deprivation. Tap water was continuously available. Rats were weighed only at the beginning and end of the deprivation period to minimize possible effect of this procedure on behavior.

PEA, open field. On Day 110 of the diet, rats were assigned to one of two injection conditions: (a) PEA, 40 mg/kg in 0.15 M NaCl or (b) 0.15 M NaCl. All injections in this experiment were IP, 5 ml/kg. Immediately following injection, rats wers placed into the open field and line crossings in 30 min were counted by the observer who was unaware of the injection condition. A line crossing was defined as the extension of both forepaws across a line.

PEA, wheel-turning. On Day 126 of the diets, the 10 animals in each diet group were placed into activity wheels and 60-min baseline activity was recorded. Animals were then removed from the wheel, injected with PEA (40 mg/kg) and immediately returned to the wheels for the next 60 min.

Pentobarbital, open field. On Day 130 of the diets, the 10 rats from each group were injected with either 0.15 M NaCl or 6.5 mg/kg sodium pentobarbital mixed in 0.15 M NaCl. This dosage is far below that required for a surgical plane of anesthesia (40–50 mg/kg). Immediately following each injection, rats were placed in the open field and line crossings were recorded for 15 min.

Amphetamine, open field. On Day 135 of the diet, 5 rats from each group were injected with 1 mg/kg of d-amphetamine. Animals were immediately placed in the open field and line-crossings were recorded for 30 min.

Amphetamine, wheel-turning. On Day 138, the 5 animals in each group not previously injected with amphetamine were placed into the activity wheels for a 60-min baseline measure. They were then removed, injected with amphetamine (1 mg/kg) and returned to the wheels for 60 min.

RESULTS

Data were analyzed with analysis of variance. Differences between pairs of means were evaluated with Tukey A tests [17].

Food deprivation, wheel-turning. One control animal failed to reach the activity criterion of 100 revolutions/day and these data were removed from the analysis. For daily, predeprivation wheel-turning, there was no significant effect of diet (lead vs control) or days of running and no significant interaction. Daily wheel-turning during deprivation was normalized for each animal for each day by converting each score to a percentage of the mean daily activity of that animal measured during the 3-day predeprivation period. Deprivation activity is shown in Fig. 1. Both groups increased activity during the 5-day period, $F=4.31$, $p<0.04$, but the lead animals were more active, $F=5.32$, $p<0.05$. The interaction was significant, $F=4.31$, $p<0.04$. Post hoc tests

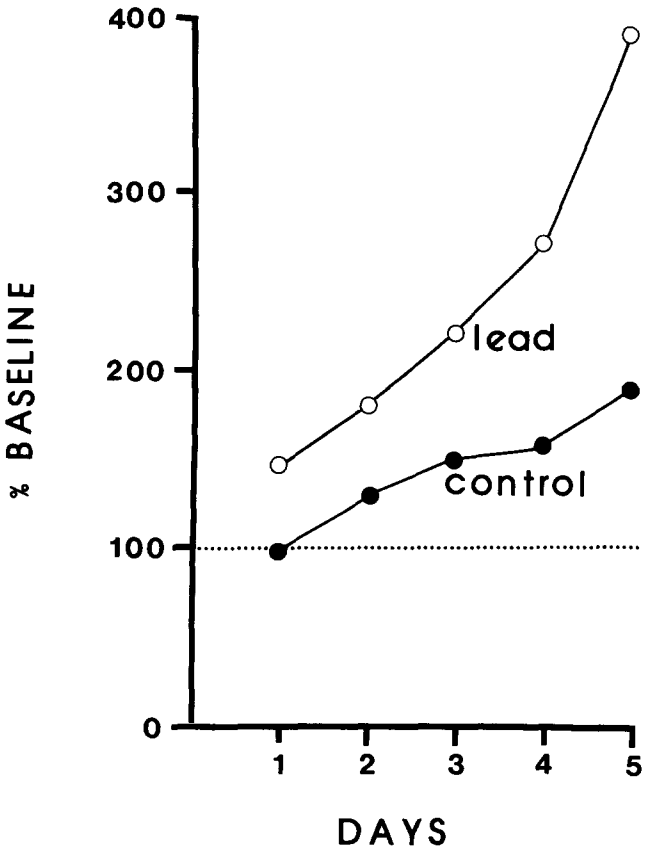

FIG. 1. Daily wheel-turning during total food deprivation as a percentage of daily predeprivation baseline.

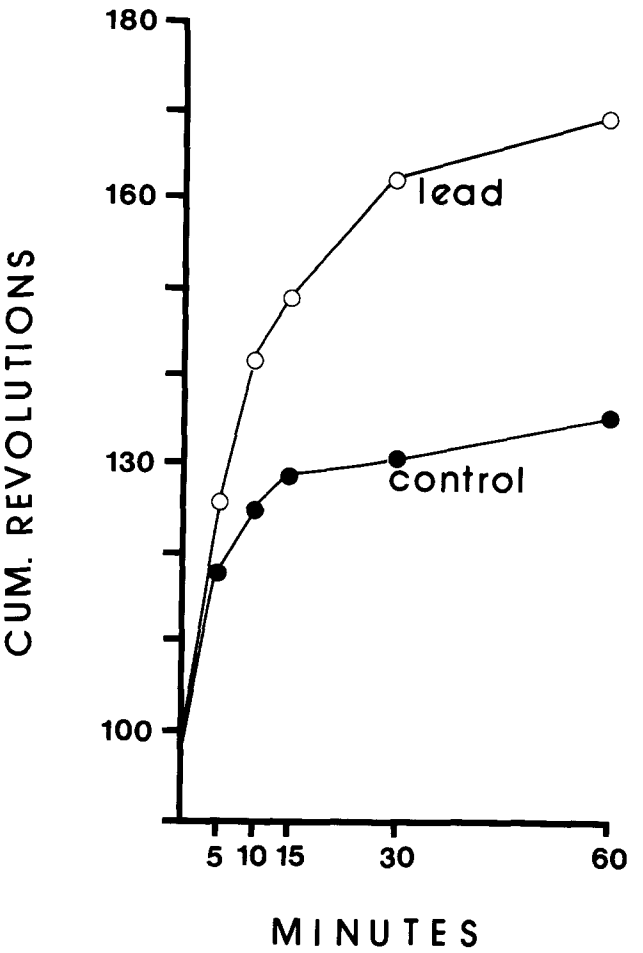

FIG. 2. Wheel-turning following PEA injection for rats on lead or control diet.

revealed that lead rats were significantly more active than controls on Day 4 and 5 of the diet ($p<0.05$).

PEA, open field. Mean line crossings are shown in Table 1. Analysis of variance revealed that lead decreased open field activity, $F=5.76$, $p<0.03$, and PEA increased activity, $F=18.12$, $p<0.001$. Groups did not differ under saline injection but under PEA, lead rats were less active than controls. In both groups, PEA increased activity.

PEA, wheel-turning. Wheel-turning following PEA injection is shown in Fig. 2. Mean 60-min preinjection baselines did not differ for the two groups (control=99.1; lead=99.8). Plots of postinjection activity are shown as cumulative starting from the 60-min cumulative preinjection point. PEA produced more activity in 60 min in the lead animals than in the controls, $t=2.41$, $p<0.05$. Differential PEA action was seen within 30 min, possibly within 15 min.

Pentobarbital, open field. The effect of pentobarbital is shown in Table 2. The analysis of variance showed no significant effect of either diet or injection. Post hoc tests showed that the interaction, $F=10.62$, $p<0.005$, was produced by contrasting effects of injection; pentobarbital produced a decrease in activity for the control group and an increase in activity for the lead group.

Amphetamine, open field. The lead diet modulated the action of amphetamine on open field activity. The control group had a higher ($t=2.85$, $p<0.05$) line crossing score (650±167.4) than the lead group (489.0±79.4).

TABLE 1

PEA AND LINE CROSSINGS IN THE OPEN FIELD

Injection	Control Diet	Lead Diet
Saline	226.8 ± 32.4*	117.0 ± 35.8
PEA	891.6 ± 164.4†	426.0 ± 128.7‡

*Mean ± S.E.M.
†Significantly different from Lead-PEA condition ($p<0.03$) and from Control Saline ($p<0.01$).
‡Significantly different from Lead-Saline condition ($p<0.001$).

TABLE 2

PENTOBARBITAL AND LINE CROSSINGS IN THE OPEN FIELD

Injection	Control Diet	Lead Diet
Saline	155.6 ± 34.1	199.2 ± 37.2
Pentobarbital	129.2 ± 21.4*	281.0 ± 32.6†

*Significantly different from Control Diet-Saline ($p<0.05$).
†Significantly different from Control Diet-Pentobarbital ($p<0.05$).

Amphetamine, wheel-turning. Wheel-turning during the 60 min following amphetamine injection was not altered by the lead diet. Mean revolutions per hr for the lead-diet group was 38.8±10.7 and 39.6±12.7 for the control-diet group.

EXPERIMENT 2

METHOD

Animals

Forty naive male rats were used in this experiment. They are of the same strain described previously.

Apparatus

Apparatus and facilities are the same as described in Experiment 1. Rats were administered diets from Day 100 to Day 132 of life.

Procedure

Food deprivation, wheel-turning. Ten rats were given the lead diet and ten were given the control diet. On Day 132 of life they were placed into the activity wheel for 2 days of nondeprived, baseline activity measurement. Then rats were totally deprived of food for 4 days. Body weights were recorded before and after the deprivation interval.

PEA, wheel-turning. Ten rats were given lead diet and ten were given control diet. On Day 132 of life rats were placed into activity wheels for 60 min of baseline running. They were then removed, injected and replaced in wheels for 60 min post-injection running. In each diet group, half the animals received PEA and half received a saline (0.15 M NaCl) injection.

Lead Analysis

At the termination of deprivation, the animals were sacrificed by decapitation and the brain dissected out and cut in half sagittally. Tissue samples from the superior lobe of the liver and the right kidney were also removed and stored at −4°C until analysis. Samples were placed in 30 ml Kjeldahl flasks containing a 1:5 acid mixture of reagent grade sulfuric and nitric acids and allowed to digest overnight. Wet ashing consisted of gently boiling off the nitric acid on a Kontes digester until the remaining sulfuric acid and contents char black. After cooling, 5 ml of nitric acid were added and again boiled off. This procedure was repeated until the remaining 1 ml of sulfuric acid was clear and colorless. The entire prepared sample was then chelated and extracted according to the method of Yeager *et al.* [55] for determination by atomic absorption spectrophotometry. This method involves the chelation of lead with ammonium pyrrolidine dithiocarbamate at pH 8.5 and the extraction of the chelate into a small volume of methyl isobutyl ketone. This organic solvent was then aspirated into the burner of a Perkin-Elmer Model 603 atomic absorption spectrophotometer and analyzed at the 283.3 nm resonance line.

Neurotransmitter Analysis

The other half of the brain was dissected into five regions and immediately frozen on dry ice for analysis of norepinephrine, dopamine and serotonin content according to the method of Jacobowitz and Richardson [16]. The five regions consisted of forebrain, diencephalon, midbrain, brain stem and hippocampus-cortex. Forebrain was dissected out as tissue rostral to the optic chiasm. The hippocampus-cortex was dissected according to Lorden and Margules [21]. This was made by lifting the occipital and ventral regions of the cortex to expose the corona radiata and the columns of the fornix. A frontal cut through the anterior commissure separated the hippocampus-cortex from the diencephalon. The rostral and caudal outlines of the diencephalon consisted of tissue between the caudal border of the mamillary bodies and the optic chiasm. The midbrain was then dissected free by a single coronal cut through the rostral portion of the pons. The remaining brain stem portion consisted of the pons, medulla and cerebellum. All frozen regions were weighed to the nearest 0.1 mg, digested, transmitter extracted and fluorescence read on a Turner Model 430 spectrofluorometer [16].

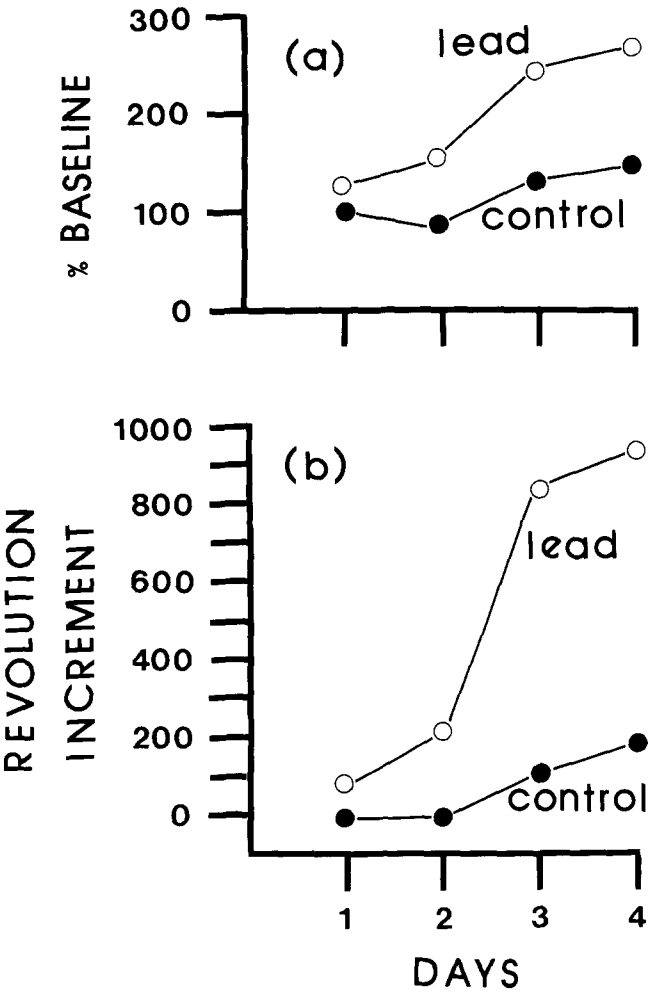

FIG. 3. Daily wheel-turning during total food deprivation shown as (a) percentage of predeprivation baseline and (b) increment in revolutions from predeprivation baseline for rats on lead or control diet.

RESULTS

Food deprivation, wheel-turning. The 32 days of lead diet produced no effect on body weight or unchallenged activity. At the termination of the lead exposure, mean body weight of control animals was 489 and lead-treated animals was 484 g. During the predeprivation activity period, no activity

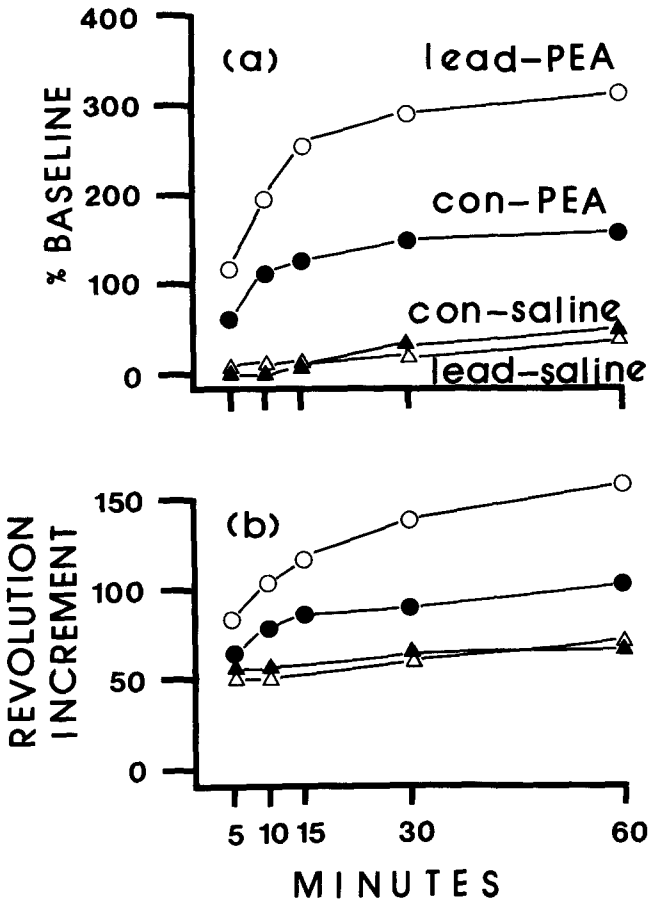

FIG. 4. Wheel-turning following PEA or saline injection shown as (a) percentage of preinjection baseline and (b) revolution increment from preinjection baseline.

differences were found as a function of days or diet. Weight loss during deprivation was 16% for both groups. Deprivation activity measures are presented in Fig. 3 and were analyzed in two forms: (a) as percentage of predeprivation baseline and (b) as absolute change from baseline in revolutions. An analysis of variance of the percentage data (Fig. 3a) showed that both groups increased activity over the deprivation period, $F=19.15$, $p<0.001$, but the lead animals were hyperactive compared to controls, $F=5.03$, $p<0.04$. No interaction was found. Analysis of the revolution data (Fig. 3b) yielded the same outcome. Lead-treated rats were more active, $F=4.60$, $p<0.05$, and both groups increased running over the deprivation period, $F=15.70$, $p<0.01$.

PEA, wheel-turning. An analysis of variance of unchallenged preinjection activity showed no difference between rats to be injected with 0.15 M NaCl or with PEA or between lead diet and control diet. Post-injection data were analyzed as either percentage of baseline or absolute change from baseline in revolutions (Fig. 4). In the percentage analysis of 60 min activity, PEA increased activity, $F=9.61$, $p<0.01$, over saline injection and there was a significant interaction, $F=5.02$, $p<0.005$. Post hoc comparison showed that lead rats were more responsive to PEA than controls. Similarly, analysis of the revolution data also revealed a significant PEA effect, $F=12.03$, $p<0.01$, and a significant interaction effect, $F=4.62$, $p<0.05$.

TABLE 3

TISSUE LEAD ANALYSIS

Group	μg/g Tissue Brain	Kidney	Liver
Control Diet	0.19 ± 0.07	0.33 ± 0.08	0.24 ± 0.14
Lead Diet	0.83 ± 0.08*	10.59 ± 1.72	1.25 ± 0.13

*All values for Lead-Diet Group are significantly higher than Control-Diet Group ($p<0.01$).

TABLE 4

LEVELS OF CATECHOLAMINES AND SEROTONIN IN BRAIN OF FOOD-DEPRIVED RATS

Compound and Group	μg/g Tissue Forebrain	Diencephalon	Midbrain	Brainstem	Hippo-Cortex
Norepinephrine					
Control Diet	0.12 ± 0.04	2.67 ± 0.09	0.44 ± 0.06	0.47 ± 0.03	0.26 ± 0.06
Lead Diet	0.18 ± 0.06	2.65 ± 0.08	0.52 ± 0.05	0.48 ± 0.05	0.27 ± 0.03
Dopamine					
Control Diet	1.81 ± 0.16	0.41 ± 0.16	0.49 ± 0.16	0.57 ± 0.16	0.60 ± 0.16
Lead Diet	2.03 ± 0.13*	0.37 ± 0.07	0.45 ± 0.05	0.41 ± 0.04	0.64 ± 0.03
Serotonin					
Control Diet	2.07 ± 0.29	2.42 ± 0.31	1.69 ± 0.15	1.68 ± 0.12	0.74 ± 0.14
Lead Diet	2.04 ± 0.22	2.28 ± 0.34	1.77 ± 0.22	1.67 ± 0.21	0.63 ± 0.13

Values are mean ± S.E.M.
*Significantly different from Control, $p<0.01$.

Lead Analysis

Tissue lead levels of deprived animals are shown in Table 3. Brain, $t=6.79$, $p<0.001$, liver, $t=4.02$, $p<0.001$, and kidney, $t=2.73$, $p<0.01$, lead were significantly elevated in lead-exposed rats compared to controls. Lead ingested by adults does reach the brain in spite of the low absorption rate from the gut [6].

Neurotransmitter Analysis

Steady-state levels of catecholamines and serotonin are shown in Table 4. Transmitter concentrations varied as a function of brain region as expected. Lead diet produced a significant change only in forebrain dopamine.

GENERAL DISCUSSION

These experiments show that change in activity in response to two different challenges, food-deprivation and PEA can be altered by lead exposure even though that exposure was initiated in adult animals and maintained for a relatively short time period (32 days). Most previous studies on neurobehavioral impact of dietary lead started exposure at birth when rate of intestinal absorption is 80–90%. About the time of weaning, absorption rate drops to 15% or less [6]. The tissue analysis showed that dietary lead did accumulate in the brain although to a lesser degree than in other tissues (Table 3). Although lead penetrates the brain slowly, it is slow to be removed [28] and, therefore, may have a long-term behavior action.

Our lead administration regimen produced no clinical signs such as ataxia, paraplegia, weight loss or diarrhea. There was no change in unchallenged activity in wheel or open field contrary to previous findings [9, 18, 32] using the Pentschew-Garro procedure [33]. Lead-induced activity differences were seen only under the challenge of food-deprivation or PEA injection. Deprivation-induced hyperactivity has been well studied in normal (unpoisoned) rodents and has played a role in the formulation of behavior theory [26,51]. We are not aware of the use of this paradigm in a behavior toxicology experiment. No physiological mechanism of action for this interaction of lead toxicity with deprivation hyperactivity can be offered since none has been established for the phenomenon in unpoisoned animals.

Our regional brain analysis of neurotransmitters found only a small dopamine increase in forebrain on the fourth day of food deprivation (Table 4) even though large behavioral differences were seen between lead and control rats.

Some workers have found differences in brain chemistry attributed to lead, but many studies have failed to find reliable changes [9,41]. Perhaps other measures such as rate of synthesis, turnover or release might be more appropriate measures to help explain the lead-induced behavioral changes.

It is interesting to note that the lead regimen did not preclude sustained high rates of motor activity. Lead-exposed rats ran several hundred more revolutions/day than controls on Days 3 and 4 of food deprivation. This is significant because lead can impair nerve-muscle function by decreasing conduction velocity in motor nerves [42] and impairing pre- and post-junctional cholinergic function [45]. Even though cholinergic transmission is vital to motor function, drugs which facilitate cholinergic function decrease lead-induced hyperactivity and drugs which diminish cholinergic function enhance this hyperactivity [43, 45, 48]. As yet, this cholinergic modulation has not been elucidated.

There is considerable evidence that the action of PEA on activity may be mediated by catecholaminergic neurons with modulation by cholinergic neurons [13]. PEA produces depletion of norepinephrine and dopamine in both brain and peripheral nerve [7, 15, 37]. It is likely, however, that dopamine release may be critical to PEA behavioral action. Dopamine [14,35] and PEA [35] infused into the nucleus accumbens produced a rise in coordinated flat-surface activity. Dopamine infusion into the neostriatum produced stereotypy [14] suggesting that these two PEA functions may be mediated by different brain structures.

If PEA's action is mainly dopaminergic as is indicated by pharmacologic manipulations [25], then it may be particularly useful in studying behavioral effects of lead toxicity since lead may modify dopaminergic function. Apomorphine-induced aggressiveness [3] and apomorphine-stimulated flat surface activity [54] are both attenuated in lead-treated rats, possibly due to attenuated adenylate cyclase activity postsynaptically [29,54]. Apomorphine is considered a dopaminergic agonist.

Generalizations must be made cautiously, however, since lead actions may be region-specific. For example, lead retarded dopamine synthesis in the neostriatum, accelerated it in nucleus accumbens and had no effect on substantia nigra [10].

The results from the two activity measures show that activity is not a unified, but a task-specific behavior. The task must be specified when we attempt generalizations regarding the neurobehavioral actions of lead and the interactions with pharmacologic challenge. Statements regarding lead-induced hyper- or hypoactivity are possibly premature and imprecise until more experimentation is done with multiple behavioral measures. These findings also provide caution regarding generalizations about lead-induced increased or decreased responsiveness to drugs. Lead rats were more responsive than controls to PEA challenge and to deprivation challenge in the running wheel. In the open field, however, they were less responsive to the stimulating action of amphetamine and PEA. The paradoxical action to the sedative pentobaribital is interesting since it is similar to the paradoxical barbiturate action in lead-treated mice [48] and in hyperactive children [22]. Much of the research in psychopharmacology and behavioral toxicology has involved measures of free activity over a rigid horizontal surface. Our data suggest that the wheel may provide another behavioral dimension to be explored. Further, these and other experiments on lead toxicity (Yamamoto and Kutscher, unpublished observations) suggest that PEA is a reliable and sensitive challenge to detect lead toxicity. This drug may be a particularly useful tool since its mechanism of action has been well-studied [25,54] and the brain structures mediating its action on activity may have been identified [35].

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