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Subacute Pb Exposure During Development and Unbaited Tunnel Maze Performance in Mice

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STEWART, P. W., V. DELBAGNO, J. NG, R. BURRIGHT AND P. DONOVICK. *Subacute Pb exposure during development and unbaited tunnel maze performance in mice.* PHARMACOL BIOCHEM BEHAV **59**(1) 183–189, 1998.—Although research has linked chronic, low-level Pb exposure to behavioral and cognitive changes in humans and animals, far less is known about the effects of transient, subchronic Pb exposure during early postnatal development. The need to understand such effects is underscored by the possibility that subchronic Pb exposure may not produce chronically elevated blood–Pb levels, but may produce long-term behavioral changes. To test this hypothesis, we investigated the effect of low-level Pb exposure on unbaited tunnel maze performance in Binghamton Heterogeneous Stock mice. Mice were either nontreated or given subchronic sodium acetate, 5, 10, or 25 mg/kg Pb acetate intragastrically on postnatal (PN) days 6, 9, 12, 15, and 18. No further Pb exposures were given after postnatal day 18. Blood–Pb measurements were taken from selected mice on PN 18, 19, 23, 28, and 38. On PN 38–42, all mice were individually tested in an unbaited tunnel maze under nondeprived conditions. Locomotor activity, exploration, and experience-dependent changes in cul-de-sac entries were recorded. Although Pb did not affect bodyweight and blood–Pb levels were below 10 μg/dl at the time of behavioral testing, a history of low-level preweaning Pb exposure caused a dose-dependent increase in cul-de-sac entries. This behavioral change was dissociable from changes in bodyweight, degree of exploration or an a priori bias to enter cul-de-sacs. The current results support the hypothesis that brief, subchronic Pb exposure during development produces behavioral changes that last well beyond the exposure period, even when blood–Pb declines to within "acceptable" levels (10 μg/dl). © 1998 Elsevier Science Inc.

Subacute Pb exposure Tunnel maze performance Mice

CLINICAL research has suggested that chronic exposure to low levels of lead (Pb) is related to cognitive impairments including decrements in I.Q. (20). Evidence has been provided (2) that low levels of blood-Pb (less than or equal to 10 μg/dl) are associated with performance impairments on the McCarthy Scales of Children's Abilities, which corroborates earlier research showing an inverse relationship between dentine Pb level and IQ (20). Further, a meta-analysis (19) of more than 20 human studies of chronic, low-level Pb exposure indicated that the bulk of data collected in humans are indicative of cognitive impairments induced by Pb per se.

While both human (2,19,20) and animal (5–10) data indicate that chronic exposure to low levels of Pb lead to behavioral changes, much less is understood about the behavioral consequences of brief, subchronic Pb exposure. This may be due in part to the fact that acute subchronic exposure may not lead to chronically elevated blood–Pb levels. Indeed, the majority of the human data is based upon blood–Pb, which has a half-life of approximately one month and is therefore only a sensitive measure of chronic, ongoing exposure. Hence, transient exposure is difficult to measure and therefore often not amenable to study.

Animal models may potentially address the behavioral effects of subchronic exposure during development, but most work performed to date has not directly addressed this issue. Most rodent studies of postnatal Pb exposure model a chronic,

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low-dose Pb regime where blood–Pb levels remain at a significantly elevated steady-state [greater than or equal to 20 μg/dl in rats (6,7,10), or greater than or equal to 11 μg/dl in monkeys (22)] at the time of behavioral testing. Further, Pb exposure is typically employed postweaning, well after several major periods of brain development (24). While these studies have contributed significantly to understanding the behavioral effects of chronic, low-level Pb exposure, they do not address behavioral effects of transient, subchronic exposure during early postnatal development, nor if such effects persist after blood–Pb levels have declined to extremely low levels (i.e.; less than 10 μ/dl).

To address this issue, we examined the effect of brief, subacute Pb exposure in preweaning mice on maze learning well after blood–Pb levels declined to below 10 μg/dl. Because developing mice show poor tolerance of food deprivation, we examined maze learning in an unbaited maze exploration task similar to those previously published (1,3,4,12,13,25–28,30). Rodents spontaneously explore an unbaited tunnel maze and decrease the probability of reentering previously explored cul-de-sacs as a function of experience between and within test sessions. Performance in unbaited mazes has been impaired by experimental manipulations which impair learning in more conventional learning tasks. Both hippocampal and basal forebrain (28) lesions produced deficits in unbaited tunnel maze performance has also been impaired by acute scopolamine administration (13) as well as trimethyltin exposure (1). Most notably, chronic, low-dose Pb exposure has impaired unbaited tunnel maze performance by increasing the number of reentries into previously explored alleys in laboratory rats (5).

In the current experiment, we hypothesized that brief, subchronic Pb exposure during development would increase the proportion of cul-de-sac entries in an unbaited tunnel maze. More importantly, we tested the hypothesis that such effects would occur well beyond the initial Pb exposure, even when blood–Pb levels were extremely low (<10 μg/dl).

METHOD

Subjects

Fifteen litters of the Binghamton Heterogeneous Stock (14) mice were used for behavioral testing (47 females and 71 males). An additional seven litters were bred to provide blood samples for Pb analysis as dams became available. All animals were given Purina lab chow and tap water ad lib and were kept on a 12 L:12 D schedule with lights on at 0700 h.

Design

This study was a 2 × 5 factorial design. The between-group factors were gender (male and female), and lead exposure [five groups of subjects receiving treatments of: NI (not intubated), Sodium acetate, 5, 10, and 25 mg/kg lead acetate]. If more than one pup (of any one gender) per litter was represented in a given treatment group, the data for these pups on any measure were averaged to form a single score as recommended by (15). Thus, the number of independent observations in each condition (collapsed across gender) were as follows: NI (n = 17), NaAc (n = 23), 5 (n = 18), 10 (n = 22), 25 (n = 22).

Apparatus

A clear, Plexiglas runway maze [modified from (11)] consisted of four 30.48 × 10.16 cm sections. Each section contained two lanes, one dead end (hereafter referred to as a cul-de-sac) and the other the open lane. Pilot work has shown that Binghamton HET mice placed in this maze initially choose cul-de-sacs approximately 50% of the time. As the mice gain experience in the maze, they learn to avoid previously visited cul-de-sacs.

PROCEDURES

Treatment

Dams were checked for litters daily. The first day of life was considered day 0. On day 3, the genders were determined and the litters culled to eight pups. Pups were individually identified using a common toe-clipping procedure. On day 6, mice from every litter were randomly assigned to each treatment group. Using a previously published protocol (17) lead (0.001 M, 0.002 M or 0.005 M) or sodium acetate (0.01 M) was administered via intragastric intubation on postnatal (PN) days 6, 9, 12, 15, and 18 using 1 cc syringes with 6.45 cm of 0.027 × 0.060 cm polyethylene tubing fitted to the syringe. These doses were chosen based upon pilot work that indicated that the highest dose would be below that which produced any effects on growth rate. The sodium acetate solution contained an isomolar amount of acetate relative to the 25 mg/kg (0.005 M) Pb group. Subjects in the NI group were not intubated. All pups were weaned and individually housed on day 23.

Behavioral Testing

At approximately 38 days of age, all mice of a given litter were tested in the same runway under blind conditions. Testing typically occurred between 1000 and 1700 h. Each mouse was placed at the opening of the maze and the entrance was closed after the mouse entered. Both open-alley and cul-de-sac choices were recorded at the 5-, and 10-, and 15-min mark. In addition, a composite activity score (cul-de-sac entries + open-alley entries) was recorded to assess overall activity. The test area was cleaned with a 30% alcohol after each mouse to remove any olfactory trail left by a previous mouse. To further reduce olfactory trails as a cue, the runway was shifted 3–4″ in a semirandom direction after each mouse. Because the "floor" of the runway was the table itself, this caused any scents left on the table to shift relative to the runway's position after every mouse.

Seven litters (see the Subjects section) were bred exclusively for providing blood samples for Pb analysis. Mice used for behavioral testing could not be used to provide blood samples because the required 0.2 cc volume of blood necessitated sacrificing the mouse. The protocol for the intubation of these mice was identical to the experiment proper. These mice (total n = 37) were randomly selected to construct a blood–Pb "pulse curve." This curve shows the levels for the control, 10, and 25 mg/kg Pb groups at five time points: PN18 (2 h prior to final intubation), PN19 (within 24 h after the final intubation), PN21 (3 days after the final intubation), PN28 (10 days after the final intubation), and PN38 (time of behavioral testing). Blood samples were collected around the time of final intubation because this would be where the blood-Pb levels would likely be at their highest, given that all five intubations were complete by this time. Although 37 samples were analyzed, in cases where more than one pup per litter was represented in a single treatment group, an average of such pups' blood data was taken. This procedure increases statistical power relative to selecting only one pup randomly (15), but does not result in inflation of the nominal alpha (15). This procedure produced 21 independent observations. Eleven of these observations

were from female mice, the other 10 were from male mice. Gender was evenly distributed across the treatment groups. However, because of the relatively small sample sizes, gender could not be analyzed as a between-groups factor.

Blood samples were collected as follows: animals were asphyxiated with CO_2 followed by postmortem intracardial puncture. Blood was taken from heart with a 1-cc syringe and injected into a vacutainer. At no time was the blood directly exposed to air. Samples were sent to the Cornell School of Veterinary Medicine for Pb analysis via graphite furnace atomic absorption spectrophotometry (21).

RESULTS

Bodyweights

Bodyweights are displayed in Table 1. All treatment groups grew normally [Time, $F(4, 452) = 96.72$, $p < 0.0001$]. Lead exposure did not affect growth rate at any dose employed (p.n.s.).

Maze Behavior

Cul-de-sac entries. The means of cul-de-sac entries for all groups are displayed in Fig. 1. A repeated-measures ANOVA (factors: Gender, Pb, and Time) was used to analyze the cul-de-sac entry data over the three 5-min test intervals. Because the mean performance of the NI and the Na Acetate controls were almost identical, the data of these two groups were combined in the analysis to form a single control group. One-way analysis of variance indicated a significant effect of Pb on cul-de-sac entries, $F(3, 98) = 3.41$, $p < 0.05$. Post hoc *t*-tests performed on the total number of cul-de-sac entries indicated that both the 10 mg/kg Pb group ($p < 0.05$) and the 25 mg/kg Pb group ($p < 0.05$) were different from controls. A borderline difference was noted between the 25 mg/kg and the five mg/kg Pb groups ($p = 0.06$). These post hoc tests confirm a linear dose-dependent change. There was no effect of gender performance ($p > 0.10$).

The performance means of all groups are plotted across the three 5-min intervals in Fig. 2. Although cul-de-sac entries declined as a function of time, $F(2, 200) = 13.28$, $p < 0.001$, there was no significant interaction between Pb and time.

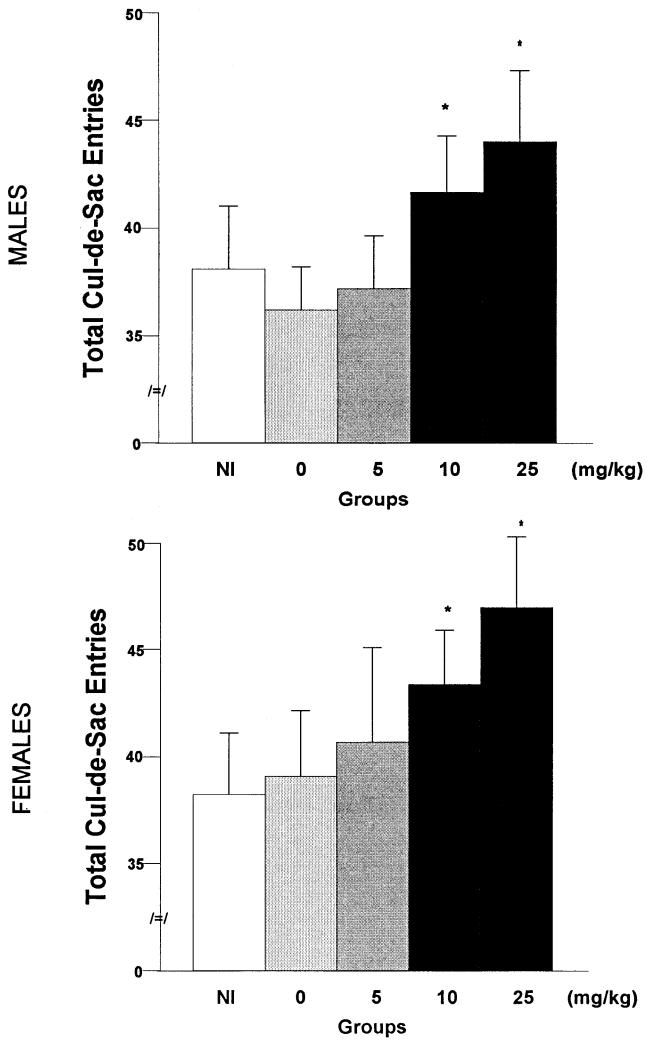

FIG. 1. Dose-dependent increase in cul-de-sac entries associated with Pb exposure in male and female mice. The data are the total number of cul-de-sac entries across the 15-min exploration task. The NI and 0 group were combined for purposes of statistical analysis, but are shown separately here. Error bars are SEM. $*p < 0.05$ vs. NI and control combined; $**p < 0.05$ vs. NI or control.

TABLE 1

BODY WEIGHTS AT PN18 FOR ALL GROUPS (MALE AND FEMALE) IN EXPERIMENTS 1 AND 2

	Females		Males		
Group	Weight	SD	Group	Weight	SD
A. EXPERIMENT 1					
NI	8.23	1.2	NI	8.0	0.67
NaAc	8.13	0.82	NaAc	8.62	0.89
5	8.36	0.63	5	8.65	0.71
10	8.40	0.76	10	8.55	0.71
25	8.50	0.58	25	8.53	0.77
B. EXPERIMENT 2					
H20	9.48	0.97	H20	9.24	0.91
Na	9.75	0.72	NA	9.30	0.88
10	9.57	0.80	10	9.66	0.68
25	9.30	0.86	25	9.20	0.88

Total activity. Due to a technical error, the number of open-alley choices made were only recorded for approximately half of each group. Thus, composite activity scores could only be computed for 63 mice. The data for the NI, 0, 5, 10, and 25 mg/kg groups were 80.3, 90.9, 91.8, 90.6, and 87.7 total choices made, respectively. One-way analysis of variance showed no differences among any of the treatment groups ($p = 0.81$).

Blood–Pb

The blood–Pb pulse curve is displayed in Fig. 3. Blood–Pb levels were analyzed as follows: single-df comparisons were first made between the control and the 25 mg/kg group. If a significant difference was found, the control group was then compared with the 10 mg/kg group. If no significant difference was found, the 10 and 25 mg/kg groups were combined to form a single, Pb-exposed group to increase statistical

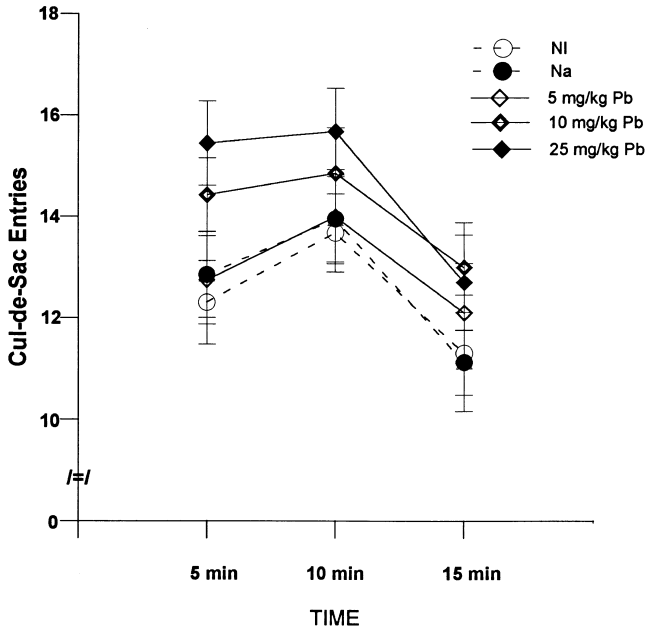

FIG. 2. The number of cul-de-sac entries made by the NI, 0, 5, 10, and 25 mg/kg Pb groups every 5 min across the 15-min test (noncumulative). Data are collapsed across gender. Error bars are SEM.

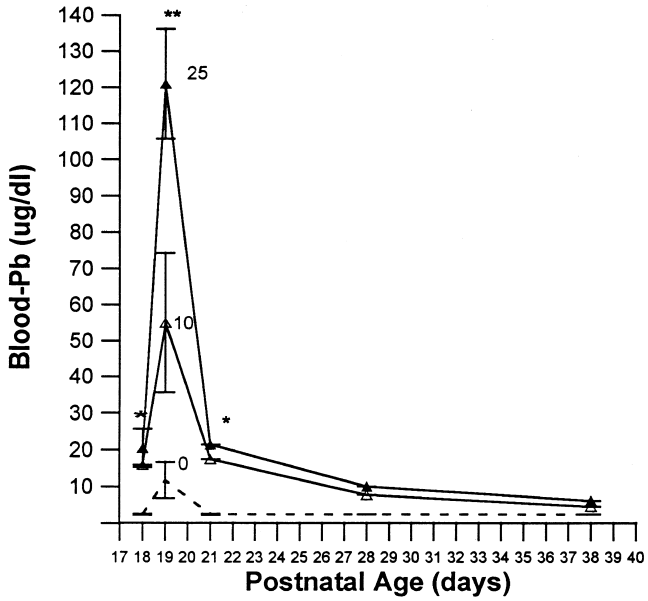

FIG. 3. Blood-Pb pulse curve at final intubation. No behavioral effects were noted in the 5 mg/kg Pb group, thus blood–Pb for that group were not analyzed. PN28 and 38 Pb data were significantly different from controls when combined. Error bars are SEM. $^{**}p < 0.05$ (25 mg/kg vs. control); $^{*}p < 0.05$ (10 and 25 mg/kg groups combined vs. control).

power. Blood–Pb levels were analyzed separately for PN18, PN19, PN21, and the combined data from PN28 and 38. These latter 2 days did not significantly differ and were thus combined for purposes of statistical analysis.

One-way analysis of variance indicated that Pb exposure produced significantly elevated blood–Pb levels on PN18 [control vs. 10 and 25 mg/kg data; $F(1, 3) = 18.99$, $p < 0.05$], PN19 [control vs, 25 mg/kg $F(1, 2) = 47.7$, $p < 0.05$; control vs. 10 mg/kg, $F(1, 2) = 4.58$, $p < 0.16$], PN21 [control vs. 10 and 25 mg/kg data, $F(1, 2) = 73.02$, $p < 0.05$], and PN28 and 38 [control vs. 25 mg/kg $F(1, 2) = 18.04$, $p < 0.05$; control vs. 10 mg/kg, $F(1, 2) = 15.02$, $p < 0.06$]. Notably, by PN 28 and 38 there was extremely little variance in the data and all blood–Pb values were at or well below 10 μg/dl.

EXPERIMENT 2

Experiment 2 was conducted to replicate Experiment 1 and to further address the nature of the Pb-related behavioral differences. Recording both cul-de-sac and open-alley choices in all mice in a replication was needed to confirm the hypothesis that the Pb-induced increases in cul-de-sac entries were indeed an increase in the proportion of cul-de-sac entries, rather than an increase in choice behavior in general. Not only is such a measure important for interpreting between-groups differences, but it is equally important for interpreting within-groups changes. Changes in locomotion within groups across the 15-min maze test must be dissociated from experience-dependent changes in cul-de-sac entries if the latter is to be a valid measure of maze learning. The protocol for Experiment 2 was identical to Experiment 1 with the following exceptions.

Subjects

Fifteen litters were used in Experiment 2. One litter was omitted from behavioral testing due to apparent illness. Although the total number of pups available for this experiment was 125, when more than 1 pup per litter existed in a treatment group, their data were averaged to produce a single observation (15). Thus, the total number of independent observations in this experiment was 93 (39 females and 54 males).

Design

Experiment 2 was a 2 × 4 factorial design. The between-group factors were Gender (male and female), and lead exposure (four groups of subjects received solutions of water, sodium acetate, 10, or 25 mg/kg lead acetate). The number of mice in each treatment group (collapsed across gender) were as follows: water ($n = 26$), NaAc ($n = 20$), 10 ($n = 23$), and 25 ($n = 24$).

Behavioral Testing

Testing occurred once at approximately 38 days of age and again at approximately 55 days of age. The second test was performed in order to assess the effects of repeated testing on maze performance, and to see if the differences between Pb-exposed and control mice would increase as a function of repeated testing. In addition to the measures recorded in Experiment 1, two new behavioral endpoints were measured during behavioral testing. These endpoints were as follows.

Spatial distribution of exploratory activity. As mice explored the maze, each choice they made was coded with a coefficient

(1 through 4), which denoted the maze section (section 1 through 4) in which the choice occurred. This allowed for testing of possible lead × maze position interactions as well as whether Pb and control animals were exploring all areas of the maze equally.

Initial choice per section. The choice each animal made upon first entering each maze section was recorded to evaluate possible choice bias a priori to experience in each maze section.

RESULTS: EXPERIMENT 2

Bodyweights

Bodyweights are presented in Table 1 (Panel B). All treatment groups grew normally (Time, $F(4, 520) = 1849.9$, $p < 0.0001$]. Lead exposure had no effect on growth rate at any dose observed (p.n.s.).

Maze Behavior

Proportion of cul-de-sac entries. Inspection of the raw data indicated that the behavior of the Water and Na Acetate control groups was nearly identical and were thus combined to form a single control group. Unexpectedly, the 25 mg/kg Pb group's performance was also nearly identical to that of the 10 mg/kg Pb group. Thus, these two groups were also combined to form a single, Pb-exposed group and increase statistical power. The data were analyzed using a 2 × 2 × (2) × (3) RMANOVA, which included following respective factors: Pb (con or Pb), gender (m or f), test (I or II) and Time (5, 10, and 15 min).

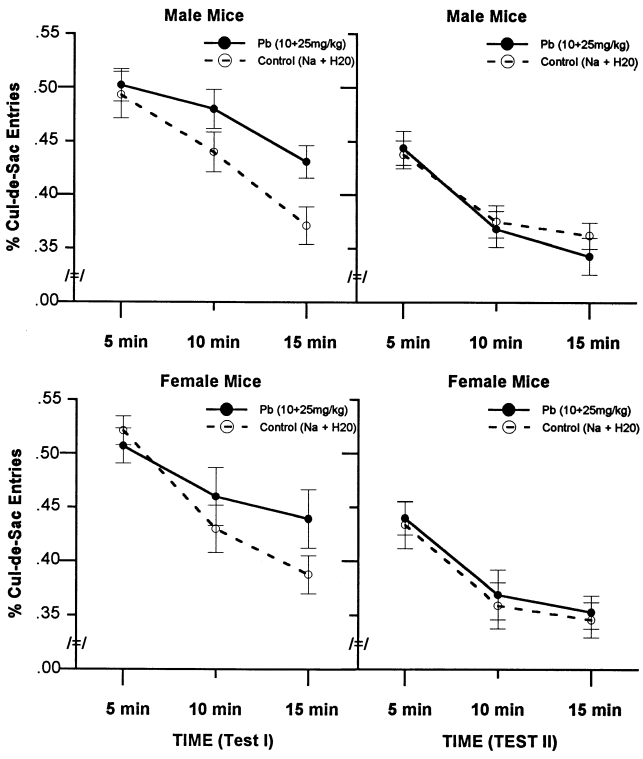

FIG. 4. Proportion of cul-de-sac entries for combined Pb (10 + 25; solid line) and control (Na + H_2O; dashed line) groups across two consecutive, 15-min tests. Pb-exposed mice took longer to reduce the rate of cul-de-sac entries in Test I. Pb-exposed mice reached control levels of performance by Test II. Error bars are SEM.

The proportion of cul-de-sac entries for the control and Pb-exposed groups is displayed in Fig. 4. A lead × test × time interaction, $F(2, 178) \times 3.08$, $p < 0.05$, indicated that mice with a history of Pb exposure reduced their cul-de-sac entries at a slower rate than controls in Test I, but reached control levels of performance by Test II. Post hoc *t*-tests confirmed this finding. Mice exposed to Pb were equivalent in performance to controls during Test I in the first 5 min, but showed a trend for more cul-de-sac entries at 10 min ($p < 0.09$), and made significantly more cul-de-sac entries at 15 min ($p < 0.009$). No differences were noted between Pb-exposed and control mice at Test II.

Total exploration, spatial distribution, and initial choice. Lead had no significant effects on mean total choices: control (NA + H_2O): 82.3, Pb (10 + 25 mg/kg): 83.4 (p.n.s.).

The number of choices made in each of the four sections (S1–S4) for controls and Pb-exposed mice did not differ; control: 25.2 (S1), 27.5 (S2), 17.3 (S3), and 12.5 (S4); Pb: 26.2 (S1), 28.5 (S2), 17.9 (S3), and 11.8 (S4) (p.n.s. for S1–S4).

The proportion of mice entering a cul-de-sac upon first entering each maze section (S1–S4) for controls and Pb-exposed mice did not differ; controls: 0.52 (S1), 0.66 (s2), 0.35 (S3), and 0.58 (S4); Pb: 0.49 (S1), 0.71 (S2), 0.40 (S3), and 0.55 (S4). (p.n.s. for S1–S4).

These data indicate that Pb-exposed mice were just as active as controls, did not restrict their exploration to certain sections of the maze, and did not show an a priori bias to enter cul-de-sacs. This suggests that the effects are specific to cul-de-sac reentries and are not secondary to changes in the aforementioned behaviors.

GENERAL DISCUSSION

These experiments showed that relatively brief, subchronic exposure to incremental doses of Pb acetate between PN6 and PN18 increase the proportion of cul-de-sac entries in an unbaited runway maze when mice were tested in adolescence. Moreover, blood–Pb fell below 10 μg/dl well before behavioral testing. These data support the hypothesis that transient, subchronic Pb exposure during early postnatal development has effects on behavior that outlast significant blood–Pb elevations. Issues related to the interpretation of these experiments are outlined below.

Behavioral Changes and Blood–Pb

The most salient aspect of the data in these experiments relate to the fact that significant changes in behavior were observed well after blood–Pb levels fell below 10 μg/dl. This suggests the limitations of single point estimates of blood–Pb as a marker of behaviorally significant Pb exposure. Given that cumulative exposure in these experiments may have been the critical factor in producing changes in behavior, a more valid measure of exposure may have been the cumulative concentrations of brain Pb. A previous study (17) using a nearly identical protocol to the current experiments showed significant elevations in brain Pb in rats. It is quite likely that such brain Pb was present in the Pb-exposed mice in these experiments. Brain Pb may indeed have been significantly elevated at the time of behavioral testing, accounting for why behavioral change outlasted significant blood–Pb elevations.

Control Pb Levels

Control mice in these experiments had very low, but nonetheless detectable, peak blood–Pb levels of approximately 11 μg/dl

on PN19. Presumably, a fraction of the Pb given to mice in the experimental group is passed along to the rest of the litter via Pb elimination in the urine or feces. Voided urinary/Fecal Pb in the cage shavings could serve as a source of extremely low-level Pb.

However, such small amounts of Pb in the control group are likely of little significance in the current study. First, these blood–Pb levels represented a peak concentration, which rapidly declined to undetectable ranges within 48 h of the final intubation. This level of exposure is extremely unlikely to produce substantive levels of brain Pb relative to the Pb-dosed groups, the latter which have been shown in a previous study to produce significantly elevated brain–Pb levels (17) using a nearly identical protocol. Secondly, although chronic levels of 11 μg/dl have been associated with behavioral changes in monkeys (22), no animal study to our knowledge has linked transient Pb levels as low as 11 μg/dl to alterations in behavior. Even if such small levels did impact the behavior of the mice in these experiments, if anything it would mitigate against differences between Pb and control groups, underestimating the effect size. Thus, although there was a small, transient elevation in blood–Pb in controls, such blood–Pb is unlikely to significantly alter the interpretation of these experiments.

Replication Effects

Although Pb-s effects replicated in Experiment 2, there were some apparent discrepancies between Experiments 1 and 2 in terms growth rate and behavioral dose response. In Experiment 2 there was generally slower growth in all groups relative to Experiment 1 (Table 1). This raises the question of why such variance was present across replications. One reviewer suggested that such variation might make it difficult to detect small effects of Pb upon growth rate if, in fact, Pb did affect growth rate. However, this variance was most likely due to the fact that dams in Experiment 1 were primiparous, whereas dams in Experiment 2 were multiparous. Further, dams in Experiment 2 were approximately 60 days older than dams in Experiment 1. Both these factors affect the size and weight of pups at birth and through weaning. Thus, such replication effects were likely due to systematic differences in maternal parameters across experiments. Moreover, bodyweight variance within each replication was very small and sample sizes were large (ns = 15–25/group). If Pb even had small effects of bodyweight within either replication, such effects would likely have been detected.

In terms of behavioral dose response, in Experiment 2 the mean cul-de-sac entry rate in the highest Pb-exposed group (25 mg/kg) was nearly identical to the intermediate dose (10 mg/kg). This is somewhat at variance with the data from Experiment 1, which showed clear dose-dependent behavioral trends in cul-de-sac entries (Fig. 1). However, since the completion of these experiments, further work has replicated the linear dose response in cul-de-sac entries seen in Experiment 1 (29). Thus, the failure to observe a linear dose response in Experiment 2 was a spurious exception to a repeatable finding.

Behavioral Significance of Unbaited Maze Performance

An unbaited maze was used in these experiments because pilot work showed that juvenile mice (<50 days of age) show extremely poor tolerance of the food deprivation required for runway maze performance. It has recently been argued (1) that such unbaited mazes are useful in neurotoxicology testing when food deprivation is inappropriate. Further, other unbaited maze exploration tasks have been used in the investigation of the effects of antisenescence drugs (25,26), aging (25,30), basal forebrain lesions (28), amnestic drugs (13), and trimethyltin (1) on learning and memory in rodents and mice. It has been argued that the avoidance of entering previously chosen alleys in the radial version of the unbaited maze is a measure of short-term working memory (13). Although the maze employed in the current study was not an unbaited radial maze, rodents did learn to avoid previously visited cul-de-sacs in a manner analogous to the unbaited radial maze. Further, mice exposed to Pb reentered previously explored cul-de-sacs more often than controls. This behavioral pattern is similar to that seen in other unbaited tunnel mazes in aged rats (25,30) and rats treated with scopolamine (13). These data may suggest that Pb-exposed mice in the current experiments exhibited a cognitive impairment that reduced the efficiency of maze exploration.

As such, however, any putative cognitive impairment in Pb-exposed mice in these experiments was not severe enough to prevent the animals from eventually reaching control levels of performance. Mice exposed to Pb reached an apparently asymptotic level of performance that equated control levels by a second test in Experiment 2. This does not indicate that the effect is merely transient. Rather, it suggests that repeated experience may allow the animal to overcome any putative deficits induced by Pb. Thus, there may be deficits in the rate of acquisition of the information within the maze, but once the information is learned, Pb-exposed mice demonstrate normal performance. Previous work examining the impact of Pb exposure on eight-arm radial maze performance is consistent with this finding. Rats exposed to 750 ppm Pb showed deficits in the acquisition of the eight-arm radial maze, but eventually reached control levels of performance (18).

Although the results of the experiments in this study are consistent with impairments in maze learning, one might also question whether the Pb-induced behavioral changes seen in this study are motivational in nature. This question may be particularly relevant given the absence of a clearly defined, extrinsic reinforcer such as food. While motivation cannot be completely ruled out, its utility as an explanation is made difficult by several facts. First, Pb-exposed mice did not show any physical (i.e., retarded growth, apparent illness) signs of toxicity that might lead one to predict robust changes in motivation. Second, Pb-exposed mice were just as active and explored the maze to the same degree as controls. Third, Pb-exposed mice eventually reached control levels of performance if given enough time (Experiment 2). Thus, if motivation were involved, it would be rather specific for avoiding cul-de-sacs, while having no effect on the propensity to explore the open alleys of the maze. Although this cannot be completely ruled out, the current data appears more analogous to the performance decrements seen in unbaited tunnel mazes for various brain lesions (27), amnestic drugs (13), and neurotoxicants known to affect learning and memory (1). Moreover, recent work has shown that increasing the number of sections (and, thus, the maze complexity) dramatically increases the size of the difference between Pb-exposed and control mice (29). This would be expected if greater maze complexity increases the cognitive demand of the maze.

Implications of the Study

The current experiments support the hypothesis that subchronic Pb exposure during postnatal development produces

performance changes in maze exploration that last well beyond significant blood–Pb elevations (>10 μg/dl). Although these effects are seen at approximately 38 days of age, Pb produces significant effects on this measure when mice are tested at 100 days of age (29). Because blood–Pb levels declined to below 10 μg/dl well before behavioral testing, the current study provides evidence that significant but transient Pb exposure during development does not lead to chronically elevated blood–Pb levels but, nonetheless, produces relatively long-lasting changes in behavior. These data indicate the importance of a history of transient Pb exposure, and thus suggest the limitations of reliance upon blood–Pb, whether it is used as an index of exposure or as an end point for predicting behavior.

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