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Differential Experience Following Developmental Lead Exposure: Effects on Brain and Behavior[1]

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PETIT, T. L. AND D. P. ALFANO. *Differential experience following developmental lead exposure: Effects on brain and behavior.* PHARMAC. BIOCHEM. BEHAV. 11(2) 165–171, 1979.—Long Evans hooded rat pups were exposed to lead (Pb) via the maternal milk supply from Postnatal Day 1 (PN 1) to PN 25. Mothers were fed diets containing either 4% Pb CO_3 (High Pb), 0.4% Pb CO_3 (Low Pb) or 2.2% Na_2 CO_3 (Controls) throughout this period. Pups were weaned at PN 30 and littermates randomly assigned to either an Enriched or Isolated environment for a period of 30 days. Increases in activity levels and decreases in passive avoidance latencies were observed in Pb exposed animals. However, there were minimal effects due to Pb on symmetrical maze performance. Experience in the enriched environment had no effect on open field activity levels but resulted in a marked reduction in symmetrical maze errors. While enrichment had no effect on passive avoidance performance in High Pb animals, it was capable of raising latencies in Low Pb animals to Control values. Thus, the therapeutic value of environmental enrichment in Pb exposed animals depends on both the task employed and the severity of the pre-enrichment brain damage. From both brain regional analysis and behavioral testing results, it appeared that the hippocampus was a major site of Pb action. From comparison of blood Pb levels of our animals and those reported in children, it became apparent that the rat may have a greater tolerance for Pb, and as such, caution must be used in making direct comparisons between the two species in terms of blood Pb levels.

Lead Lead exposure Mental retardation Hyperactivity Hippocampus

EXPOSURE to lead (Pb) in infants and children has profound effects on the development of both the central nervous system (CNS) and behavior [7,36]. Exposure to chronic low levels of Pb has received particular attention in recent years because of reported cases of hyperactivity, impulsiveness, aggressiveness and learning disabilities in children [10, 15, 29]. Although largely neglected, an area of equal importance concerns the effects of exposure to high levels of Pb. Mental retardation and seizures are seen only following exposure to levels of Pb within the range that produces overt encephalopathy [3, 25, 26]. While Pb exposure is no longer a frequent cause of mental retardation, exposure to high levels of Pb remains of experimental significance since developmental Pb encephalopathy is one of the few known models of mental retardation which can be easily reproduced and studied in the laboratory.

Morphological changes observed in the brains of developmentally Pb exposed rats include reduction in brain weight [22], hemorrhagic lesions in and reduction in size of the cerebellum [24], reduced thickness of cerebral cortex [21] and hippocampus [27], and alterations in cortical vascularization [35]. Reported behavioral effects have included increases in activity [14, 39, 42] and aggression levels [37], impaired motor coordination [30], deficient task solving capacities in a number of different testing situations [5,31] and deficits in response inhibition [30].

Environmental enrichment paradigms have frequently been used to demonstrate the plasticity of the developing brain. Major reported changes include increases in neocortical weight and thickness, increased dendritic branching and connectivity [16, 18, 44] and increases in the number of neocortical synapses [28,45]. Superior problem solving abilities have also been demonstrated in enriched animals [11,40].

Recently, environmental enrichment has been employed as a therapy in the treatment of disadvantaged animal populations. It has been used in animals suffering from, amongst others, developmentally produced brain lesions [38, 46, 47] and hypothyroidism [8]. These studies have reported improvement in the behavioral capacities of their enriched brain damaged animals.

Recent observations in our laboratory have indicated that developmental lead exposure also causes a reduction in the dendritic growth and branching of neocortical neurons, as

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well as reduced numbers of neocortical synapses [34]. Considering the opposing effects of Pb exposure and environmental enrichment on the developing brain and behavior, the following study was undertaken to assess the potentially ameliorative value of this type of experience on developmentally Pb exposed rats.

METHOD

Animals

For each of two replications female Long Evans hooded rats (Charles River strain) were placed with males for one week, after which they were moved to individual nesting cages and maintained ad lib on standard laboratory chow (Purina) and tap water. Approximately one week prior to delivery, to facilitate transfer to the Pb contaminated diet, ground laboratory chow was substituted for the food pellets. Females were checked each morning and afternoon for litters, and the day on which a litter was discovered was taken as Postnatal Day 0 (PN 0) for that group.

Pb Conditions (PN 1 to PN 25)

On PN 1, all mothers were weighed, litters were reduced to six male pups, cross fostered with other litters within ± 24 hr of age, randomly assigned to one of the following drug groups, and started on the appropriate diet. Diets consisted of ad lib access to either 4% Pb CO_3 (High Pb), 0.4% Pb CO_3 (Low Pb), or 2.2% Na_2CO_3 (Controls) in ground laboratory chow. Animals were maintained on their respective diets and tap water (ad lib) until PN 25. On PN 26, all animals were returned to standard laboratory chow for the remainder of the experiment. Maternal weights were recorded daily from PN 1 to PN 10 and on PN 15, 20 and 25. Pup weights were taken on PN 5, 10, 15, 20 and 25.

On PN 25 blood samples were taken by tail cut on six animals in each of the above groups. None of these animals were used in the remainder of the study. Blood Pb determinations on these samples were done by Environmental Sciences Associates, Bedford, MA.

Environmental Conditions (PN 30 to PN 60)

At 30 days of age all pups were weaned and earmarked. Half of each litter was randomly assigned to either the Enriched (E) or Isolated (I) condition. The assignment of animals from the Pb conditions into the two environmental conditions resulted in the following six experimental groups with an N of 22 in each group: High Pb Isolated (HI), High Pb Enriched (HE), Low Pb Isolated (LI), Low Pb Enriched (LE), Control Isolated (CI), and Control Enriched (CE). Animals in the I condition were singly housed and maintained under standard laboratory conditions in a room separate from that of the E animals.

Our enriched environment closely paralleled Davenport's [8] modification of Kuenzle and Knusel's [23] "super-enriched" environment. In brief, it consisted of 33 animals placed in three gang cages interconnected by tunnels containing swinging doors. The main features of the enrichment paradigm involved daily handling of animals and changing or rearranging of toys, and periodic changing of shelf positions and alternation of door swings. Food and water were available ad lib; however, to insure shuttling between cages, they were never both available in the same gang cage. The environment was made progressively more complex by the removal of shelf and tunnel ramps. Changes in the location of water bottles required either stretching from shelves or climbing of the walls and ceiling in order to obtain water. A maze was introduced into the center gang cage on PN 45 (Day 15 of enrichment), the solving of which was required for access to food. In addition, both auditory (24 hr radio playing) and olfactory (scented air freshners) stimulation was provided.

Similar to other environmental enrichment paradigms, on PN 60, animals were removed from this apparatus and housed in individual laboratory cages similar to those of the I animals [8]. From this point until the completion of the experiment, E and I animals were treated identically.

Behavioral Testing Procedures

All animals were handled for five minutes on PN 60. Due to the earmarking scheme, all behavioral testing was done blind.

Open Field

On PN 61, each animal was placed in a 1×1 m open field activity arena with the floor area divided into 25 equal sized squares, and the number of squares entered in a five min period monitored via closed circuit television. In addition, the number of rears and boli were also recorded for each animal during this period.

Subsequent to activity testing, all animals were placed on a 23.5 hr water deprivation schedule which was continued until the termination of behavioral testing at PN 115. Between PN 66 and PN 115, half of the animals were tested first on the symmetrical maze and later on passive avoidance. This order was reversed in the remainder of the animals. Since no effect of testing order was observed, data for the two groups was pooled.

Symmetrical Maze

Animals were tested on the symmetrical maze, an automated closed field test closely resembling the Hebb-Williams maze (see [9] for details), the main differences being that motorized doors separated the endboxes from the field, endboxes were equipped with photo cells and automatic dippers were used to deliver water reinforcement. Adaptation to the maze consisted of 10 min free exploration in groups of five or six with endbox doors raised, photo cells active but no barriers present in the field or water reinforcements available. On the day following adapatation, all animals were magazine trained (one in each endbox, doors shut throughout session) until receiving approximately 30 to 40 self-administered reinforcements. Reinforcements consisted of the water filled dipper being raised for 6 sec following photo cell interruption. The following day, the animals began training on practice problems P-1 and P-3, and test problems T-2, T-6, T-7, T-9, T-10, T-12, and A-6, with one problem being administered each day (see [9] for details). An error was defined as the shoulder of the animal extending over an error line. Scoring in this manner was facilitated by direct overhead viewing of the maze via closed circuit television. Reentry or incomplete entry into the starting or goal endbox was not counted as an error. The animals were run on the practice problems for 12 trials. Test problems were run for at least 12 trials, and until animals reached a criterion of four out of five errorless trials. A maximum of 48 trials without reaching criterion was allowed. Trials were separated by an intertrial interval of 15 sec.

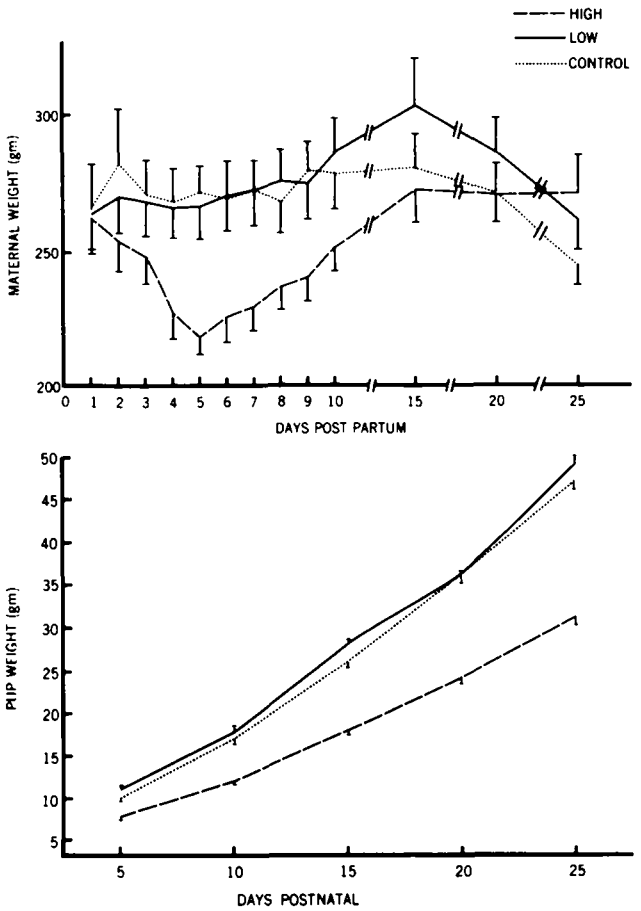

FIG. 1. Maternal weights over the first 25 days post-partum and body weights of pups over the first 25 days postnatal.

Passive Avoidance

On the first day of passive avoidance testing, animals were given a 10 min adaptation period in the passive avoidance apparatus which consisted of two compartments (each 0.305 m long, 0.254 m wide, and 0.305 m high) made of black Plexiglas separated by a black Plexiglas guillotine-type door. The floors of both compartments were made of stainless steel rods 3 mm in dia. and spaced 7 mm apart. During the adaptation period, the door between the compartments was raised and water was available in the goal compartment.

On the next day, each rat was given 10 training trials. On each trial, the time between door opening and entry into the goal compartment was recorded. Each rat was allowed to remain in the goal box for 30 sec or until the animal had drunk water for 10 sec. The animal was then returned to the start box and a new trial started after a 10 sec intertrial interval.

On the next day, five training trials were given following the procedure used on the previous day. On the sixth trial, the rat received a 10 sec 0.8 mA inescapable shock through the grid bars of the goal compartment floor. Five more test trials were given after this single shock trial. The maximum latency allowed per trial was 300 sec.

Brain Weights

Between PN 116 and PN 120 (hereafter referred to as PN 120) animals were weighed and sacrificed using chloroform inhalation. Brains were immediately removed and trimmed flush to the anterior pole of the cerebral cortex and posterior pole of the cerebellum. After whole brain weights were taken, the cerebellum, cerebral cortex and hippocampus were dissected, and along with the remaining brainstem their weights were also taken.

RESULTS

Maternal Weights

High Pb mothers showed an initial drop in body weight which reached significance by PN 4 ($p=0.005$, see Fig. 1). On PN 6 High Pb mothers began to regain their weight such that by PN 15, and continuing through to PN 25, no significant differences were found between groups. No differences in maternal weights of Controls and Low Pb mothers were observed over any of the 25 days post-partum.

Body Weights

Low Pb pups unexpectedly weighed slightly, but significantly more than Controls on PN 5 ($p=0.014$), 15 ($p=0.024$) and 25 ($p=0.006$) (see Fig. 1). However, these very small differences were not observed on PN 10 and 20. In contrast, High Pb pups weighed significantly less than the Controls on PN 5, 10, 15, 20 and 25 ($p<0.001$ on all days). Paraplegia and urinary incontinence were observed in some High Pb animals beginning around PN 22; however, these signs disappeared by PN 28.

At the time of sacrifice (PN 120) HE animals weighed significantly less ($p<0.001$) than CE animals, but this difference was not observed in their I counterparts (see Table 1). No effect of environmental enrichment on body weight was observed. Body weights taken on one half of the animals (one replication) on PN 60 indicated that neither environmental enrichment nor water deprivation resulted in preferential lack of nutrition in High Pb animals; weight gain PN 30–60 (High Pb, 175.6%; Low Pb, 164.6%; Control, 200.1%) PN 60–120 (High Pb, 383.3%; Low Pb, 191.0%; Control, 209.0%)

Blood Pb Determinations

On PN 25 (last day of Pb exposure) the High Pb animals had a blood Pb level of 1297 ± 47 (mean ± SEM) μg/100 ml blood (μg %). Low Pb and Control animals had blood Pb levels of 331 ± 68 μg % and 2 ± 0.2 μg %. As there was no overlap between the groups in terms of blood Pb levels, no statistical analysis was required.

Open Field

No effect of environmental experience on activity levels was observed in any of the groups (see Table 2). High Pb animals were significantly more active than the Controls in both environmental conditions (HI>CI, $p=0.010$; HE>CE, $p=0.009$). Low Pb animals demonstrated activity levels intermediate between Control and High Pb values but this increased activity in the Low Pb group did not reach significance.

Lead exposure had no significant effect on either the number of rears or boli. However, enrichment resulted in

TABLE 1

MEAN BODY, BRAIN AND BRAIN REGIONAL WEIGHTS FOR THE DIFFERENT EXPERIMENTAL GROUPS*

Group	Body Weight PN 120	Whole Brain Weight	Neocortical Weight	Hippocampal Weight	Cerebellar Weight	Brainstem Weight
CI	408.6	1.799	0.867	0.138	0.271	0.523
N=22	±25.2	±0.090	±0.043	±0.007	±0.014	±0.027
CE	446.4	1.918	0.912	0.148	0.286	0.573
N=22	±10.6	±0.018	±0.012	±0.003	±0.004	±0.011
LI	433.8	1.869	0.894	0.147	0.286	0.543
N=22	±17.0	±0.010	±0.011	±0.002	±0.005	±0.007
LE	408.1	1.816	0.868	0.139	0.276	0.533
N=22	±26.6	±0.090	±0.043	±0.007	±0.014	±0.027
HI	401.8	1.709	0.830	0.135	0.249	0.496
N=22	±13.4	±0.019	±0.009	±0.003	±0.005	±0.006
HE	362.0	1.672	0.808	0.128	0.239	0.497
N=22	±16.6	±0.019	±0.011	±0.001	±0.005	±0.008

*All weights in gm, mean ± SEM

TABLE 2

MEAN ACTIVITY, REARS AND BOLI SCORES FOR THE DIFFERENT EXPERIMENTAL GROUPS*

Group	Activity	Rears	Boli
CI	88.4	23.1	1.7
N=22	±6.9	±1.9	±0.4
CE	87.0	26.6	3.1
N=22	±5.8	±2.2	±0.5
LI	98.0	20.7	1.0
N=22	±6.9	±1.4	±0.3
LE	102.5	28.6	2.1
N=22	±6.2	±2.0	±0.4
HI	117.9	20.7	0.8
N=22	±8.6	±1.8	±0.3
HE	110.1	30.6	2.6
N=22	±6.2	±2.6	±0.5

*mean ± SEM

significant increases in boli in all groups ($p<0.05$) and increased rearing in the High Pb and Low Pb groups ($p<0.003$, see Table 2).

Passive Avoidance

An analysis of variance with repeated measures revealed strong Pb effects on passive avoidance behavior (see Fig. 2). Both High Pb and Low Pb animals in the I condition had shorter latencies compared to Controls (HI<CI, $p=0.041$; LI<CI, $p=0.050$). Enrichment resulted in non-significant increased latencies in all groups. While the effect of enrichment was not sufficient to raise High Pb latencies to Control levels (HE<CE, $p=0.031$), increased latencies due to enrichment in the Low Pb group were sufficient to result in these animals no longer differing significantly from Controls.

Symmetrical Maze

The results of symmetrical maze testing for individual maze patterns are presented in Fig. 3. In general, total errors to criterion (summed over all test problems) were found to parallel the trends found in individual test problems in that little Pb effects were observed. However, a significant reduction in errors due to enrichment within all groups was seen. Percent reduction due to enrichment was comparable in all three groups (Control, 38%; Low Pb, 35%; High Pb, 38%), indicating that a preferential reduction in errors due to enrichment did not occur in any group.

Learning curves for total errors did not indicate any obvious differences in learning patterns associated with environment or Pb exposure.

Brains Weights

Environmental enrichment had no significant effect on either whole brain or brain regional weights in any of the groups. The single Pb effect was a reduction of both whole brain and brain regional weights in HE animals ($p<0.001$, see Table 1), which was consistent with the reduced body weights in this group.

There was a reduction of 9.1% and 1.0% in the brain weights of High Pb and Low Pb animals, respectively; these differences were reduced to 4.2% and 0.2% when body weight was treated as a covariate.

Enrichment caused a 5.2% increase in neocortical weight in Control animals, while in the Pb groups, a slight decrease in neocortical weight was associated with enrichment. The cerebral cortex of Control animals accounted for 46.8% of their whole brain weight, while in Low Pb and High Pb animals it accounted for 49.0% and 48.7% of their whole brain weights, respectively. The brainstem comprised 26.5%,

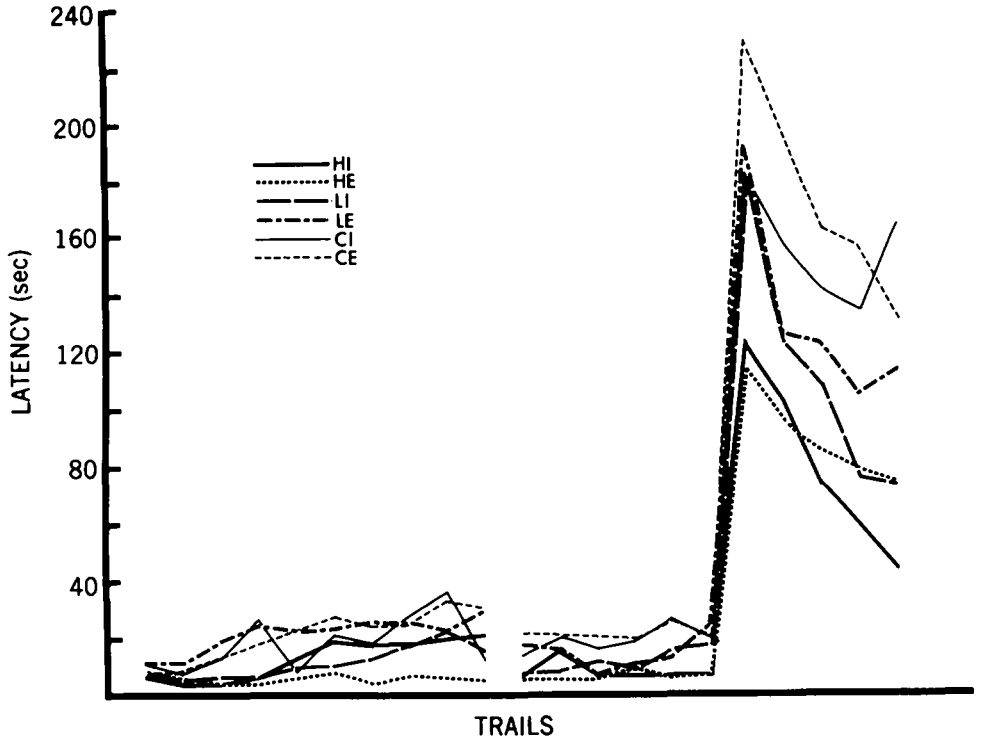

FIG. 2. Passive avoidance latencies per trial for each of the experimental groups.

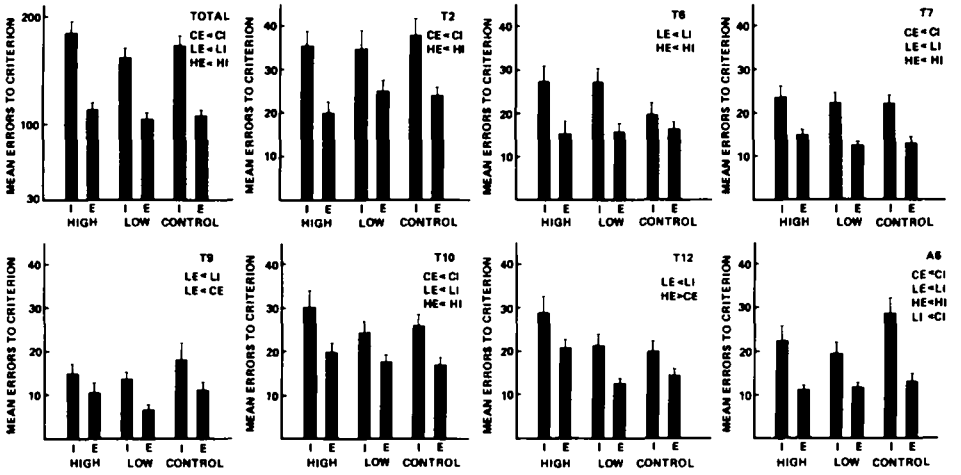

FIG. 3. Mean number of errors to criterion for each experimental group on individual maze test problems and total errors on all problems combined. Significant differences between groups ($p<0.05$) are indicated for each problem.

23.8%, and 29.4% of the whole brain weight of Control, Low Pb and High Pb animals, respectively. These data indicate little preferential effect of Pb treatment on either the cerebral cortex or brainstem.

The cerebellum comprised 16.9% of the whole brain weight in Controls, 17.2% in Low Pb and only 14.4% in High Pb animals. This difference in percent brain weight indicates a preferential reduction of the cerebellum in High Pb animals of 14.7%. The hippocampus of Control and Low Pb animals accounted for 9.8% and 9.9% of their whole brain weight, respectively, while it accounted for only 6.8% of the brain weight of High Pb animals. This difference in percent brain weight indicates a preferential reduction of the hippocampus in High Pb brains of 20.7%.

DISCUSSION

Developmental Pb exposure in rats resulted in increased activity levels and decreased latencies in passive avoidance behavior, but had minimal effects on symmetrical maze performance. Environmental enrichment caused an increase in both rears and boli, decreased errors in the symmetrical maze, but had no effect on activity or passive avoidance performance. Environmental enrichment was, however, capable of raising passive avoidance latencies in Low Pb animals to Control values.

Investigations into the effects of Pb have generally exposed rats to Pb either directly through injection or esophogeal intubation [30,43] or indirectly via the maternal milk supply [12, 16, 33], both methods having associated disadvantages. The problem with direct intubation or injection is the stress being inflicted on the pup; stress itself is known to effect brain and behavioral development. The problem with the maternal route is the confounding effect of possible malnutrition through deficiencies in either the quality or quantity of maternal milk [4]. The reduction of litter size in this study to less than half normal was undertaken in an effort to compensate for these effects. While it remains a possibility that malnutrition augmented the effects of Pb in the High Pb group, these animals did not appear undernourished or disadvantaged in terms of overall state of health prior to PN 20.

Developmental Pb exposure resulted in elevated activity levels which were associated with the degree of Pb exposure. It would appear from our results that while High Pb results in hyperactivity in rats, lower levels of Pb results in marginal or equivocal increases in activity levels. With very low levels of Pb we (unpublished observations) and others have observed reduced activity levels [17]. Consequently, the inconsistent changes in activity levels observed following developmental Pb administration may be due to varying doses of Pb used in these studies.

Deficits in maze performance were not observed in Low Pb treated animals and inconsistently seen in animals following High Pb exposure. This relationship between Pb exposure and maze performance is in agreement with other reports where Pb has been found to cause maze deficits by some researchers [41] but not others [30].

Behavioral effects of developmental Pb exposure appear to parallel those of hippocampal damage in several ways. Hippocampal damage has been reported to result in hyperactivity as well as deficits in passive avoidance, DRL performance, operant extinction, discrimination reversal and spontaneous alternation [2,19]. One of the more interesting findings of this study was the deficit in passive avoidance performance observed in Pb treated animals. Results of passive avoidance testing and the observed increase in activity levels are consistent with deficient hippocampal function. In keeping with this, other researchers have reported deficits in DRL performance [30], spontaneous alternation [20], operant extinction and discrimination reversal problems [30,43] following developmental Pb exposure. Finally, the hippocampus showed the greatest percent weight reduction of any brain structure examined here. These results are even more interesting when one considers that the concentration of Pb in the hippocampus is 10 times higher than that of the rest of the brain [13]. Thus, several lines of evidence suggest that the hippocampus may be a major site of Pb action during development. The sensitivity of this brain area is not unexpected since regions of the hippocampal formation are still experiencing rapid cellular proliferation postnatally [1].

In this investigation, environmental enrichment did not alter the activity level of the Controls nor reduce the hyperactivity of the Pb exposed animals. While enrichment did result in a marked reduction in the number of errors in the symmetrical maze, the Pb exposed animals were neither deficient in this task nor did environmental enrichment preferentially benefit these animals.

While some researchers have reported almost complete recovery of brain damaged animals following environmental enrichment, these improvements may depend on two factors. One, the task employed and two, the degree of brain damage in the treated animals [8,46]. In this study enrichment was capable of increasing passive avoidance latencies to Control values only in the Low Pb group. Environmental enrichment was not capable of normalizing passive avoidance behavior in the High Pb group.

It has been documented [4] that an increase in Pb exposure occurs when pups begin eating a Pb contaminated solid diet around PN 16, and a decrease following the animal's removal from the diet on PN 25. Consequently, our reported blood levels probably represent the highest blood Pb levels to which these animals were exposed. Even so, these levels are extremely high when compared to levels tolerated by children. Greengard and co-workers [15] and Pentschew [32] have observed mean blood Pb levels of 316 μg percent (range: 90–825 μg percent, n=20) and 257 μg percent (range: 83–470 μg percent, n=8), respectively, in cases of severe Pb encephalopathy in children that resulted in death. These levels are very similar to those of our Low Pb animals (331 μg percent) and drastically lower than our High Pb animals (1297 μg percent). From these findings it becomes apparent that caution must be used in extrapolating from the rat to the human in terms of blood Pb levels. Species differences in the reaction to Pb may enable the rat to tolerate much higher blood Pb levels before displaying symptoms analogous to those observed in humans.

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