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Behavioral Effects of Chronic Lead Ingestion on Laboratory Rats[1]

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DRISCOLL, J. W. AND S. E. STEGNER. *Behavioral effects of chronic lead ingestion on laboratory rats.* PHARMAC. BIOCHEM. BEHAV. 4(4) 411–417, 1976. – Rats continuously exposed to lead acetate solutions were tested on a visual discrimination reversal problem, on the open field and in 2 shuttle avoidance situations. High lead intake produced slower acquisition of the visual discrimination problem but had no effect on reversal performance. High lead intake reduced activity on the open field and improved performance on both shuttle avoidance problems. Results are interpreted to indicate that the effects produced by exposure to lead may involve an increase in responsiveness to aversive situations.

Lead acetate Lead and behavior Visual discrimination reversal Open field Shuttle avoidance

ALTHOUGH there is great concern over lead in the atmosphere and human ingestion of lead from other sources, until recently there have been few experimental investigations of the effects of lead exposure on behavior. Studies are now appearing at an increasing rate and seem to fall into 2 general categories: (1) Those concerned with effects of relatively short-term exposure to lead on adult or adolescent animals and (2) those concerned with developmental effects of lead occurring during prenatal or preweaning periods.

In general, lead acetate exposure in adolescent or adult animals does not appear to produce strong effects on behavior unless high dosages are used and such effects are attributable to obvious symptoms of lead poisoning such as motor impairment or anorexia. Two studies with rats reported no effect on escape or avoidance tasks [7] or on Hebb-Williams maze performance [18] produced by exposure to lead acetate. A third study using monkeys [1] also reported no behavioral effects produced by lead exposure. Two additional studies, one using rats [16] and the other sheep [21], reported increased variability of performance in lead-exposed animals but again no strong effects were produced by lead acetate exposure in adult animals. Adult exposure to tetraethyl lead has produced less consistent findings. One study reported no effect on a water maze escape task [8] while a second reported significant deficits in acquisition, reversal and retention of a negatively reinforced position discrimination as well as lower rates of food reinforced lever pressing for lead-exposed rats [3].

In contrast, exposing animals to lead during prenatal or preweaning periods has produced more dramatic effects on behavior. Three studies exposed nursing female rodents to lead carbonate or lead acetate. Increased activity, more frequent fighting [15,17] and deficits in Hebb-Williams maze performance [18] were reported in the offspring of these animals. A fourth study, giving infant rats oral doses of lead acetate [20] reported a lead-produced deficit in shuttle avoidance. Strengthening the possibility that infant mammals may be more sensitive to the effects of lead than are older animals are 2 additional studies, one demonstrating a deficit in the acquisition of visual discrimination in lambs prenatally exposed to lead acetate [10] and a second describing lead-produced changes in the behavior of infant monkeys [1] including decreased social exploration, increased clinging and increased vocalization for lead-exposed animals. It should be mentioned, however, that neither prenatal nor early postnatal exposure to lead produced effects on the performance of lambs in a modified Hebb-Williams maze [9].

It would appear from the existing literature that age of exposure is an important factor in determining the effects of exposure to lead. However, before the details of the age-dependence and its relation to dose and duration of exposure can be investigated, it is necessary to establish behavioral measures that will be sensitive and reliable enough to evaluate such effects. In addition, the investigation of a variety of behavioral measures may help to clarify the nature of the behavioral effects of lead and help to elucidate the underlying mechanisms. The experiments reported here represent an effort in this direction. In order to increase the probability of a strong lead effect to allow

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evaluation of different behavioral measures, continuous exposure to lead (prenatal, preweaning and postweaning) was used.

EXPERIMENT 1

A number of experiments have reported impaired performance on both positively and negatively reinforced learning tasks [3, 10, 16, 18, 20] with at least 2 of these [3,18] attributing the impairment to deficits in learning and memory. However, it is generally accepted that performance on any learning task is determined by 2 sets of factors: (1) The acquisition and retention of information (learning) and (2) the expression of acquired information (performance). A deficit in performance could be due to inability to acquire or store information or it could be produced by a number of performance factors such as level of deprivation, level of activity or reactivity to novel stimuli. The observation that lead exposure during early development does affect activity level [15,17] suggests that the reported impairment of performance may be due to deficits in the expression of acquired information rather than learning or memory. Experiment 1 tested these possibilities by examining performance on initial acquisition and several reversals of a visual discrimination problem. Applying Bitterman's general suggestions [4] to this problem, if learning variables are involved, the pattern of performance over reversals should be different for lead-exposed and control animals. Absolute levels of performance may also differ if this is the case. If performance is affected, different absolute levels of performance will be observed but the pattern over reversals should be similar for lead-exposed and control subjects.

METHOD

Eighteen adult albino rats were obtained from Simonsen Laboratories and placed in breeding groups of 2 females and 1 male. Each group was provided with ad lib Purina chow and a single drinking solution of 10^{-2} M lead acetate (high lead), 10^{-4} M lead acetate (low lead) or sodium acetate (control). The sodium acetate solution was later replaced with a water control. The offspring of these animals were continuously maintained on the same lead solution as their parents. Pup weights were taken daily for the first 10 days of development and every other day for the next 21 days, a procedure which provided additional early stimulation. High lead pups weighed approximately 20% less than control and low lead pups ($p<0.01$ on all days). There was no difference in litter size for females on different lead concentrations. These breeding and maintenance procedures were used for all animals in the following experiments. Experiments 1 and 3 used only high lead and control subjects; Experiments 2 and 4 used high lead, low lead and control subjects. In Experiment 1, eight adult males, 4 high lead and 4 control, were used as subjects. These animals had previously been tested on the open field.

Since it was possible that the lead solutions might be aversive, fluid intakes of the original 18 animals were measured by weighing the water bottles each day for 3 days before placing the animals in breeding groups. To provide further information on long-term intake of the high lead solution, the fluid intake of 4 Simonsen albino rats (2 male, 2 female), approximately 120 days of age, was measured for 13 days of water intake and 14 days of intake of the high lead solution. These animals were not used in the behavioral experiments described. Their body weights were also recorded during the 27 day period.

In Experiment 1, animals were required to discriminate between lighted and unlighted alleys in a Y maze equipped with a food cup and light (GE #40, 6V.) mounted at the end of each alley. The alleys of the maze were joined at 120° angles. Each alley was 51 cm. long × 15 cm. wide by 14 cm. high. The entire maze was covered with a Plexiglas top. At the center of the Y, the walls of each of the alleys were slotted enabling the experimenter to insert a plexiglas door at the end of the alley that the subject occupied after each choice. This alley then served as the start lane for the next trial.

Each animal was food deprived and maintained at 90% of his ad lib weight throughout training. Each animal received one 30 trial training session each day until he met a criterion of 90% correct choices on 2 consecutive days. The problem was then reversed on the next day so that the previously negative stimulus was now positive and vice versa. The lighted alley was positive in initial training. Every animal received 5 reversals of the problem. The alley in which the positive cue was presented on each trial was randomly determined. The intertrial interval was 20 sec and the animal was reinforced with three 45 mg. Noyes pellets for each correct choice. Correction of incorrect choices was not allowed.

Results

Three days of fluid intake of the 12 original female animals (4 high lead, 4 low lead, 4 sodium acetate) were evaluated using analysis of variance. All 3 groups showed reduced fluid intake on the first 2 days of exposure to the novel solutions ($\bar{X}$ = 19.0 ml. on Day 1 and 11.8 ml. on Day 2) and a substantial increase in intake on Day 3 ($\bar{X}$ = 41.5 ml.). These changes were reflected in a highly significant Days main effect, $F(2,18) = 31.9$, $p<0.001$. There were no significant differences among the 3 groups. Since there were only 2 male animals in each fluid condition, their intakes were not subjected to statistical analysis. These intakes followed a pattern similar to that of the females.

Long-term intake of the high lead solution compared to a water control was observed in 2 male and 2 female rats over a 27 day period. Table 1 shows the mean daily intake of water and of lead, the mean body weight and the change in body weight for each animal during exposure to water and to lead. Change in body weight was calculated by averaging each animal's weight on the first 2 days of water exposure, the last 2 days of water exposure and the last 2 days of lead exposure. Weight change during water exposure is the difference between the weight on the first 2 days and the last 2 days of water exposure. Weight change during lead exposure is the difference between the last 2 days of water exposure and the last 2 days of lead exposure. Body weights on the first 2 days of lead exposure were not used since the substantial reduction in fluid intake which occurred during initial exposure to lead reduced body weight temporarily. All 4 rats showed lower intake of the lead solution but this reduction did not produce a loss of body weight. All rats were gaining weight during the period of water exposure. Weight gain was reduced by lead exposure in 1 male rat and eliminated in the other. Weight gain was not affected in the 2 female rats. In contrast to long-term intake, first day lead intake averaged only 62% of normal water intake. Within 2 or 3 days, however, intake had recovered to the amounts shown in Table 1.

Table 2 shows the mean errors to criterion for high lead and control animals during initial acquisition and 5 reversals of the visual discrimination problem. The high lead group made significantly more errors before reaching criterion in the initial acquisition of the discrimination problem (t = 2.30, df = 6, $p<0.05$). An analysis of variance of performance on the 5 reversals revealed no significant effects produced by lead ingestion nor did any significant improvement occur over reversals for either group.

TABLE 1

MEAN FLUID INTAKE, MEAN BODY WEIGHT AND WEIGHT CHANGE FOR WATER AND LEAD PERIODS

Rat	Sex	Mean Intake ml		Mean Body Weight g		Weight Change g	
		Water	Lead	Water	Lead	Water	Lead
1	F	30.1	23.8	227	236	+12	+11
2	F	29.3	28.1	253	262	+10	+12
3	M	36.0	28.6	384	400	+21	+14
4	M	33.1	25.6	386	386	+15	− 1

TABLE 2

MEAN ERRORS TO CRITERION FOR ORIGINAL ACQUISITION AND FIVE REVERSALS OF A LIGHT/DARK DISCRIMINATION PROBLEM

Group	Initial Acquisition	Reversals				
		1	2	3	4	5
High lead	40	85	81	58	68	62
Control	21	66	82	67	72	63

Discussion

Consistent with the findings of other investigators [19], measurement of the intake of lead solutions showed that these solutions as well as a control solution of sodium acetate can result in reduced fluid intake. In a choice situation with a more palatable solution available, this can result in permanent reduction in lead intake [19]. On the other hand, in a situation in which only 1 solution was available, intake recovered to an amount somewhat lower than normal water intake but sufficient to maintain body weight in adult rats.

The significantly poorer performance of high lead rats in initial acquisition of the visual discrimination problem is consistent with other investigators' reports of impaired performance by lead-exposed subjects on various learning tasks. However, over reversals lead-exposed animals performed as well as controls. This could indicate that high lead animals cannot acquire information as rapidly as controls although they showed no deficit in retention or transfer of information. Considering their performance over reversals, it would seem more likely that the difference in initial acquisition was due to performance factors operating only during initial acquisition, ruling out such performance variables as level of deprivation, level of activity or impaired sensory or motor capabilities which would operate throughout testing. One possibility is that high lead animals may be more responsive than controls to novel environments. This could interfere with their performance in initial acquisition but would not affect later performance after the animal had become adapted to the situation. It should also be pointed out that no improvement over reversals was observed and there was considerable variability in reversal performance. Larger numbers of subjects run for more reversals could reveal associative differences not apparent using the procedure described here.

EXPERIMENT 2

A difference in responsiveness to a novel environment is one possible interpretation of the results of Experiment 1. This possibility was further investigated in Experiment 2 by testing animals on the open field. Although there is currently some disagreement about how to interpret open field activity in relation to the emotionality construct [2], the field should still be useful in allowing the assessment of behavioral reactions to a novel environment.

Method

Three groups of 31 day old rats of both sexes (high lead (N = 30), low lead (N = 29) and control (N = 23)) were reared as described in Experiment 1. All animals were experimentally naive. Each animal was tested individually for 2 minutes on a 1.3 meter square open field divided into 16 squares. The number of squares that an animal entered in the 2 min test was recorded. Defecation scores were also recorded.

Results

The mean number of squares entered in a 2 min test for the 3 groups was as follows: Control = 15.2 squares; low lead = 17.5 squares; and high lead = 9.2 squares. An initial statistical analysis demonstrated that sex differences did not occur at this age and the data were pooled for both sexes. An analysis of variance revealed a significant difference among the groups, $F(2,79) = 6.73$, $p<0.01$. Duncan's Multiple Range Test was used to further analyze the differences, showing that the control and low lead groups entered significantly more squares than the high lead group ($p<0.01$) but were not significantly different from one another. Defecation scores showed no significant differences among the groups. The frequency of defecation was low for all animals.

Discussion

The lower activity of the high lead animals on the open field supports the conclusion that the difference found in Experiment 1 might have been produced by differential reactions to the novel test environment. One possible explanation of this effect is that high lead animals are more responsive to the aversive aspects of the novel environment. In a recent reinterpretation of the avoidance learning literature, Bolles [6] has suggested that animals respond to aversive situations with characteristic species-specific defense reactions (SSDRs). In the rat, these SSDRs are usually running away or freezing, depending upon the situation. In a large, brightly lit open field, where running away is prevented, freezing in a corner would be a very probable response. If high lead rats are more responsive to the aversive aspects of the open field, they would be more likely to show specific SSDRs. In fact, high lead rats were frequently observed to freeze in a corner and generally showed ambulation scores that were lower than those of low lead or control rats.

The finding of lower activity in rats exposed to lead is not consistent with several recent investigations. Two studies, one using rats [15] and the other mice [17], have reported higher activity for lead-exposed animals tested in small test environments similar to standard laboratory cages for long test periods (3 and 24 hr). A third study [20] reported no differences in activity produced by lead exposure as measured in a photocelled device with a larger area, different from the home cage, and a shorter test duration (30 min). The open field used in Experiment 2 was considerably larger than the activity measuring devices used in these studies and was brightly lit. The test period was also much shorter. The differences in results suggest that the effects of lead on activity may depend upon the situation in which the activity is measured. It may be that the hyperactivity reported by some investigators [15,17] occurs only in specific situations, depending upon the responses elicited in those situations.

EXPERIMENT 3

If, as suggested by Experiment 2, lead ingestion produces an increase in responsiveness to aversive stimuli, one might expect even greater differences to occur in aversive learning tasks using electric shock as compared to tasks using positive reinforcement such as that in Experiment 1. Experiment 3 explored this possibility in a 2-way shuttle avoidance situation.

Interpretation of 2-way shuttle avoidance performance in SSDR terms is complicated by the fact that running, an SSDR, does not produce a complete escape from the aversive stimuli present in the situation as would a 1-way procedure. After the first trial, stimuli associated with shock are present in the compartment to which the animal must run to avoid subsequent shock. On the other hand, 1-way avoidance is typically acquired in relatively few trials and perhaps would not be as sensitive to the experimental conditions as the 2-way procedure. In the 2-way shuttle procedure, even though the running SSDR does not produce complete escape from the situation, running responses are never punished with shock as freezing responses are. Consequently, running should be more strongly maintained in this situation than freezing and the elicitation of a strong running SSDR should facilitate acquisition. If high lead animals are more responsive to the aversive aspects of this procedure than control animals, a stronger elicitation of the running SSDR should occur, producing faster acquisition of the avoidance response by high lead animals. This is directly opposite to the prediction that would be made if it is assumed that lead ingestion causes deficits in associative processes which would interfere with the association of the conditioned stimulus and shock.

Method

Two groups of 5 male rats (high lead and control), reared using the procedures described in Experiment 1, were used in this experiment. They were approximately 70 days old when testing began and had previously been tested on the open field.

The apparatus was a 2-way shuttle box divided into 2 compartments by a door 12 cm wide × 15 cm high. Each compartment was 19 cm long × 20 cm wide × 19 cm high. The signal (CS) which preceded the onset of the electric shock (UCS) was a light mounted in the top of each side of the shuttle box. A Lafayette Master Shocker (#82404) delivered a 0.6 mA scrambled shock through the grid floor.

A signalled avoidance procedure with a 5 sec signal-shock interval and a variable intertrial interval averaging 15 sec was used. Each animal was run 40 trials each day for 4 consecutive days. Responses during the intertrial interval were not punished and each trial was initiated in the side of the shuttle box occupied by the animal at the end of the intertrial interval.

Results

The mean percent of shocks avoided in 10 trial blocks is shown in Fig. 1. A 2-way analysis of variance with one repeated measure (Lead (2) × Blocks (16)) showed a significant main effect of Blocks, F(15,120) = 3.97, $p<0.001$, reflecting improvement with training; a significant main effect of Lead, F(1,8) = 5.91, $p<0.05$ produced by the superior performance of high lead animals; and a significant lead × Blocks interaction, F(15,120) = 2.69, $p<0.005$ resulting from differences in the rate of acquisition of the problem by the 2 groups.

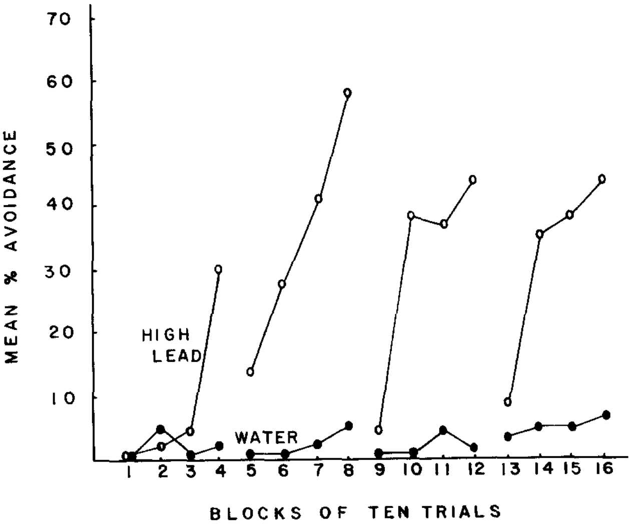

FIG. 1. Mean % shocks avoided in 4 sessions of 40 trials by high lead and control rats in 2-way shuttle avoidance.

Discussion

The performance of high lead animals in shuttle avoidance supports the conclusion drawn in Experiment 1 that deficits in discrimination learning were produced by performance factors rather than interference with the acquisition of information. It is also consistent with the conclusion of Experiment 2 suggesting that one effect of high lead intake may be an increase in responsiveness to aversive stimuli which in this case could result in stronger elicitation of an SSDR of running.

The poor performance of control animals is not unusual in this experimental situation. As mentioned earlier, all animals in these experiments were weighed frequently during their first month of life, a procedure which provided them with considerable stimulation during early developmental periods [11]. Denenberg and Karas [12] reported similar poor performance for animals with extensive early handling (Day 1 through Day 20) in a 1-way avoidance task. They attributed the poor performance to low motivation. Also contributing to the poor performance of control animals was the use of a light signal, frequently correlated with slow acquisition in signalled avoidance [14], and a relatively low shock intensity (0.6 mA). The short intertrial interval may also have contributed to the effect. The fact that the high lead group as well as the control group showed relatively poor performance in this situation is probably due to these signal and shock parameters in combination with the effects of early handling.

EXPERIMENT 4

The interpretation of Experiment 3 is somewhat complicated by the poor performance of the control group. Experiment 4 was conducted first, to modify signal and shock parameters to allow acquisition of the problem by the control group; second, to allow the evaluation of intertrial responses by increasing the opportunity for their occurrence; and third, to extend the investigation to include a low lead group and an additional avoidance procedure in which intertrial responses were punished. The first 2 of these objectives were accomplished by: (1) Using a 2-component serial compound signal (light and tone) which has been demonstrated to facilitate acquisition of shuttle avoidance [13] rather than a light signal alone; (2) increasing the shock intensity; and (3) increasing the length of the intertrial interval.

The better performance of high lead animals relative to controls in Experiment 3 was attributed to greater responsiveness to the aversive situation in high lead animals, producing stronger elicitation of an SSDR of running. The additional procedure used in this experiment, punishment of intertrial responses, should reduce the effectiveness of the running SSDR over the freezing SSDR and consequently reduce the differences between high lead, low lead and control animals' performance.

Method

Three groups of 12 adult male albino rats (high lead, low lead and control) were reared using the procedures described in Experiment 1. They were between 120 and 180 days of age when tested and had previously been run on the open field. Six animals within each lead group were randomly assigned to 1 of 2 intertrial response conditions. In the first intertrial response condition (free ITRs), intertrial responses were not punished. In the second condition (punished ITRs), intertrial responses resulted in the delivery of a 1.0 mA shock.

The apparatus was an automated 2-way shuttle box (53 cm long × 17 cm wide × 23 cm high) divided into 2 compartments which were separated by a wall with a 17 cm high × 10 cm wide opening. The box, centered on a rod, tilted approximately 7 mm when the animal shuttled, depressing a microswitch mounted on one end of the box. A light (CS-1) was mounted on the end wall of each compartment and a Sonalert tone generator (CS-2) was wired externally. The intensity of the 4400 Hz. tone, measured inside the box, was 90 db. A Lafayette Master Shocker delivered a 1.0 mA scrambled shock (UCS) through the grid floor.

The light (CS-1) preceded the onset of the tone (CS-2) by 4 sec and the onset of the shock (UCS) by 6 sec. Each stimulus (CS-1, CS-2 and UCS) remained on until the animal shuttled. A fixed intertrial interval of 60 sec was used. Each animal was run 50 trials each day for 3 consecutive days. In the free ITR condition, responses made during the intertrial interval produced no change in procedure and the next trial following an intertrial response was signalled in the compartment that the subject occupied. In the punished ITR condition, responses during the intertrial interval produced a 1.0 mA shock which continued until the animal returned to the original compartment. The next trial was signalled in that compartment.

At the conclusion of avoidance training, thirty of the animals were killed with CO_2. Their livers and kidneys were removed, preserved by freezing and subsequently analyzed for their lead content by atomic absorption.

Results

The mean percent of shocks avoided in 10 trial blocks over 3 days of training for the 3 lead groups and 2 intertrial response conditions is shown in Fig. 2. A 3-way analysis of variance with 1 repeated measure (Lead (3) × ITR condition (2) × Blocks (15)) revealed the following main effects: Blocks, F(14,420) = 54.2, $p<0.001$ indicating simply that all groups improved their performance over trials and Lead, F(2,30) = 6.91, $p<0.005$ reflecting the better performance of the high lead group under both conditions. The ITR condition main effect was not significant. Significant interactions included Blocks × Lead, F(28,420) = 2.34, $p<0.001$ reflecting the more rapid acquisition of avoidance by the high lead animals and Blocks × ITR condition, F(14,420) = 2.67, $p<0.005$ indicating more rapid acquisition of avoidance by all three groups in the free ITR condition. Neither the Lead × ITR condition nor the Lead × ITR condition × Blocks interaction was significant.

In order to examine the effects of lead and ITR condition in the absence of the effects of improvement with training which occurred across all groups, an analysis of variance was performed on final performance (Blocks 14 and 15 pooled) alone. This analysis revealed a significant main effect of Lead, F(2,30) = 11.47, $p<0.005$ once again reflecting differences produced by lead level and a significant main effect of ITR condition, F(1,30) = 5.16, $p<0.05$ which was masked in the previous analysis by the highly significant effect of Blocks. The Lead × ITR condition interaction was once again nonsignificant. Duncan's Multiple Range Test was used to further analyze the differences in final performance. In the free condition, the final performance of both high lead and control animals differed from that of low lead animals ($p<0.05$) for both comparisons) but these groups did not differ significantly from one another. In the punished condition, high lead animals performed significantly better than low lead animals ($p<0.05$) while the difference between control and low lead animals approached significance ($p<0.10$) and the performance of high lead and control animals did not differ significantly.

Comparing punished and free ITR conditions within

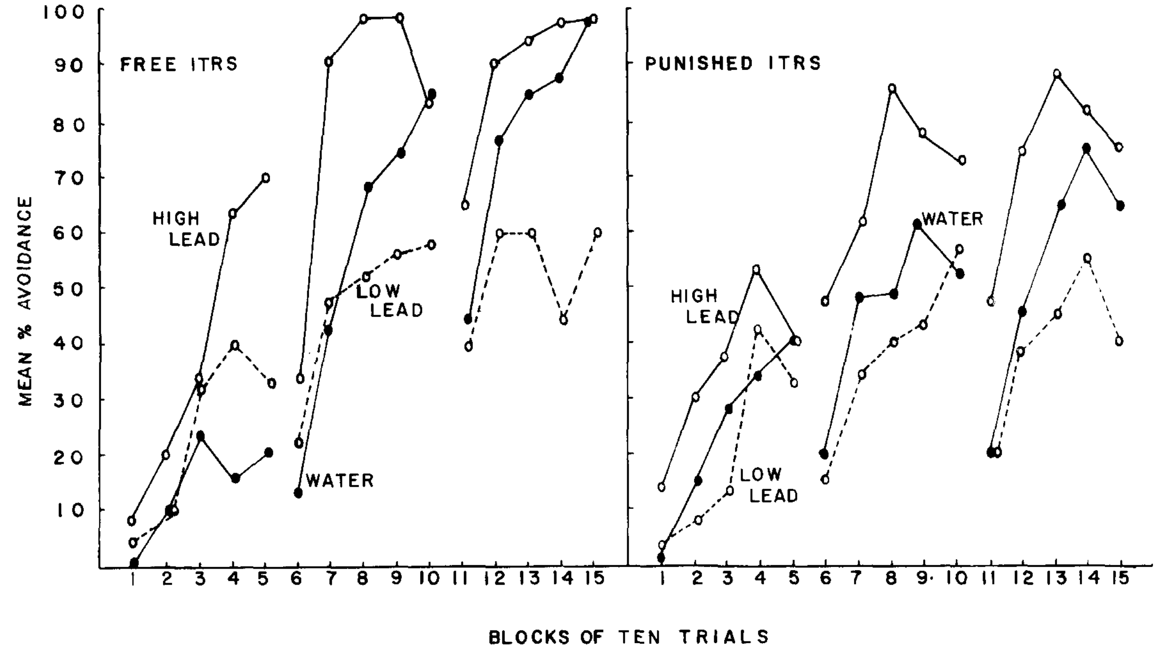

FIG. 2. Mean % shocks avoided in 3 sessions of 50 trials by high lead, low lead and control rats under conditions of free or punished intertrial responses.

each lead level, the performance of neither high lead nor low lead groups was changed significantly by punishment of intertrial responses. The performance of controls may have been somewhat suppressed by punishing intertrial responses but the difference only approached significance ($p<0.10$). Given the significant Blocks x ITR condition interaction in the original analysis of variance and the significant ITR condition main effect in the analysis of final performance, it would appear that punishment of ITRs did suppress performance in this situation but that the effect was not strong.

Examining intertrial responses directly, punishment suppressed such responses almost completely. The overall mean number of intertrial responses which occurred under the punished condition in a 10 trial block was 1.0 responses compared to an overall mean of 4.5 intertrial responses for the free condition. Since all 3 groups showed similar suppression of intertrial responding under the punished condition, an analysis of variance was performed on data from the free ITR condition only. A 2-way analysis of variance with a repeated measure (Lead (3) x Blocks (15)) showed a significant main effect of Blocks, $F(14,210) = 6.37$, $p<0.001$ reflecting the increase in intertrial responding that occurred in all 3 groups with training, and a significant Lead x Blocks interaction, $F(28,210) = 1.90$, $p<0.01$ indicating differential changes for the three lead groups. The Lead main effect was not significant. To further clarify these effects for the 3 lead groups, intertrial responses made by each animal were summed for the 5 blocks of each day of training and these were analyzed separately. Significant effects on intertrial responding were produced only on the first day of training as revealed by a 1-way analysis of variance ($F(1,15) = 4.17$, $p<0.05$). Both high and low lead groups made more intertrial responses than did controls. The mean number of intertrial responses made during the first day of training follow: High lead = 9.1; low lead = 14.5; and control = 4.8.

The liver and kidney tissues of 30 of the animals (10 control, 8 low lead and 12 high lead) were analyzed for their lead content by atomic absorption. Mean lead content of the kidneys was: Control = 0.26 ppm; low lead = 0.56 ppm; and high lead = 44.70 ppm. The control and low lead groups did not differ significantly while there was no overlap in the range of these animals and the high lead group. High lead values ranged from a low value of 32.99 ppm to a high value of 63.60 ppm. Liver tissue contained less lead in the high lead group. Mean liver lead content was: Control = 0.22 ppm; low lead = 0.80 ppm; and high lead = 2.42 ppm. The differences were highly significant, $F(2,27) = 28.41$, $p<0.001$, an effect mainly attributable to the high lead group.

Discussion

Consistent with the results of Experiment 3, the avoidance performance of high lead animals was superior to that of controls. However, the fact that the performance of control animals fell between that of high lead and low lead animals indicated that the relationship between lead intake and performance in shuttle avoidance may not be simple. The variance in methods of administration and dosages of lead used in the literature will not yet allow an interpretation of the form of the dose-response function for lead. The results of Experiment 4 suggest that this function may be nonmonotonic at least when measured in avoidance learning situations. The performance of lead-exposed animals seemed to be mediated by a high level of activity which increased running and decreased freezing responses early in training. This is consistent with an analysis in terms of SSDRs. The SSDR hypothesis is also supported by the analysis of intertrial responding in which lead-exposed animals made more intertrial responses early in training. However, final performance and performance under the punished ITR condition are less consistent with a simple interpretation in terms of SSDRs.

Punishment of intertrial responses was introduced in this study in the hope that this procedure would further clarify differences in the performance of lead-exposed and control subjects. While there is a suggestion that lead-exposed animals' performance may have been affected less by this procedure than that of controls, the effect produced on controls was not pronounced. The suppression of avoidance performance which is frequently produced when intertrial responses are punished [5] was probably reduced by the use of the double CS (light and tone). The predicted reduction of differences in avoidance performance between high lead and control animals may occur only if the association between the signal and the shock is more difficult.

In contrast to our results in Experiments 3 and 4, one study exposing infant rats to lead acetate reported a deficit in the shuttle avoidance performance of lead-exposed rats [20]. However, the procedure involved a short CS-UCS interval (3 sec), a short intertrial interval (14 sec) and a UCS (3 sec) which apparently terminated whether the animal shuttled or not. This procedure could result in shock termination during freezing responses as well as running responses. If other aspects of the situation tended to produce freezing rather than running, these results would not be inconsistent with the interpretation suggested here. The fact that the observed deficit was eliminated with amphetamine injections could indicate that it was produced by freezing in lead-exposed animals.

In summary, the following conclusions seem reasonable from these studies and the available literature. First, exposure to lead acetate during early development (prenatal, preweaning) produces effects on a wide variety of behavioral measures, although such effects may be quite complex depending upon the dosage and the specific characteristics of the behavioral measures used to assess them. Second, while the studies reported here do not exclude direct effects on associative processes (learning and memory), they do suggest that other effects, some of which may involve differential reactions to aversive stimuli, are produced by lead exposure and may change performance independently of associative factors.

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