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The Effects of Tetraethyl Lead on Behavior in the Rat

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AVERY, D. D., H. A. CROSS AND T. SCHROEDER. *The effects of tetraethyl lead on behavior in the rat.* PHARMAC. BIOCHEM. BEHAV. 2(4) 473–479, 1974. – The behavioral effects on rats of various doses of tetraethyl lead, administered intragastrically, were measured on the following: bar press responding for food, two-choice discrimination under negative reinforcement, and emotional responses in the open field. Bar press response rates were drastically curtailed following administration of high doses of lead. Both trials to criterion and mean latency to criterion were detrimentally affected by administration of single doses of lead prior to acquisition of the discrimination. Lead had similar effects on these same measures in reversal of the original discrimination and in retention of the reversal. The performance deficits were not attributable to the tetraethyl radical; control injections of tetraethyl silane were without effect on all behavioral measures in the discrimination task. In addition, the results did not appear to be a function of emotional factors as lead did not influence trials to avoidance criterion or open field behavior. It was concluded that lead given intragastrically can impair learning and memory in the rat.

Tetraethyl lead Discrimination learning Lead and behavior

IN VIEW of the widespread use of lead and its well documented neurological effects [9], there is a surprising paucity of information with respect to the effects of lead or other heavy metals on behavior. A search of the literature revealed only two such studies concerned with lead effects. Bullock *et al.* [2], failed to observe differences in escape time in a water T-maze between control rats and ones receiving lead; only one cumulative dose was tested and thus it may have been outside an effective range. In the second study [1] also with a water T-maze, lead was again found not to affect performance. However, the criterion was five correct choices out of fifteen trials which seems inappropriate for a simple two-choice discrimination task.

The purpose of the experiments reported here was to establish whether lead, over a broad range of doses, would have a deleterious effect on performance variables. Specifically, it was thought that lead would interfere with acquisition and/or retention of a discrimination learning task. This seems likely when one considers that tetraethyl lead in vitro inhibited active transport of amino acids [14], reduced brain glucose oxidation [4], and inhibited monoamine oxidase activity [8].

EXPERIMENT 1

The first experiment was designed to determine the feasibility of using an appetitive task in assessing the consequences of lead toxicity on learning measures. Previous dose response experiments for lethal doses of tetraethyl lead indicated that, for amounts up to 13 mg/kg, lead had little effect on food intake. Thus, in this experiment the effects of tetraethyl lead on food-rewarded bar press responses were recorded at two doses, one just below the level which the prior experiments indicated should affect food intake and a lower dose [12,13].

Method

Animals. 15 Sprague-Dawley male albino rats, ranging in weight from 350–400 g, were used. Each was individually housed in standard hanging rodent cages and maintained on ad lib food and water in a 12 hr light–12 hr dark cycled room.

Apparatus and procedure. Eight standard operant conditioning chambers (Grayson-Stadler) were employed. Each unit was enclosed in a sound resistant box, ventilated

by an exhaust fan. Schedules of reinforcement for bar pressing were programmed via standard electromechanical relay circuitry. All reinforcements were 45-mg Noyes Food pellets.

Following 24 hr of food deprivation, the animals were trained to bar press with subsequent shifts to fixed ratio (FR) schedules of reinforcement [7]. Thereafter, the animals were maintained on 23-hr food deprivation and ad lib water. After 3 days of 30 min on an FR 5 schedule, in which every fifth response was reinforced with a single food pellet, the animals were assigned, in a randomized block design, to four groups: Group I (3 animals), no treatment; Group II (4 animals), one ml of peanut oil (via intragastric administration); Group III (4 animals), 2 mg/kg of tetraethyl lead; and Group IV (4 animals), 10 mg/kg of tetraethyl lead dissolved in one ml of peanut oil. Following the lead treatment, each animal was observed for six consecutive days in 30-min FR 5 sessions.

Results and Discussion

The mean numbers of bar presses during the 30-min FR 5 sessions are presented in Table 1 for each treatment condition on the day prior to lead administration and for 3 successive blocks of 2 30-min daily sessions following the treatment. An analysis of variance [15] indicated that there were significant differences among treatments, $F(3,11) = 5.09$, $p<0.05$, blocks of trials, $F(3,33) = 4.83$, $p<0.01$, and the interaction of treatments and blocks, $F(9,33) = 4.31$, $p<0.01$. An inspection of Table 1 reveals that mean response rates did not change significantly from pretreatment levels during the posttreatment block for either the control, p's>0.05, or the oil condition, p's>0.05, as tested by the Duncan Multiple Range Test [10]. This was also true for the low lead group, p's>0.05, whereas the high lead group had a lower mean response rate in each posttreatment block, p's<0.01.

TABLE 1

THE EFFECTS OF SINGLE DOSES OF TETRAETHYL LEAD ON RESPONSES ($\bar{X}$) MADE ON A FIXED RATIO 5 SCHEDULE OF REINFORCEMENT DURING DAILY 30 MIN. SESSIONS

	Performance Sessions			
	Pretreatment	Posttreatment (Blocks of 2 Sessions)		
Treatment Condition		1	2	3
Control	641	543	683	858
1 ml Peanut oil	552	579	533	625
2 mg/kg Tetraethyl lead	824	753	826	831
10 mg/kg Tetraethyl lead	807	305	372	359

These findings are important in two respects. First, the results indicate that, at least for the higher dose of lead, an appetitive task, such as FR, is contraindicated for a behavioral assessment which attempts to delineate learning measures without a confounding by motivational variables. Second, even though there were dramatic reductions in response rates for the high dose group, the animals still averaged over 60 reinforcements per 30-min session throughout the posttreatment test period, and lead did not affect performance in the low dose group. This would indicate that even with high levels, severe anorexia did not occur. As already indicated in the introduction, our previous experiments on lethal doses of tetraethyl lead in the rat revealed that food intake was little affected for doses up to 13 mg/kg [12,13]. Thus, not only will animals continue to ingest food following single applications of high doses of lead, but apparently they will continue to perform behaviorally to receive food reward although at much reduced response rates. Low levels, on the other hand, did not seem to affect behavioral responses for food.

EXPERIMENT 2

The results of Experiment 1 indicated that the use of food rewarded tasks may be inappropriate to assess the effects of high doses of lead on learning variables because of possible confounding by motivational variables. Thus, in the second experiment a two-choice negative reinforcement, discrimination task [11] was employed to determine if lead, administered in a wide range of doses, would disrupt discrimination learning, and/or retention.

Method

Animals. Forty-seven Sprague-Dawley male albino rats, ranging in weight from 365–425 g, were used. Each was maintained as in Experiment 1.

Apparatus. A Lafayette (Model No. A580) shuttle box was modified to provide for a simultaneous two-choice position discrimination task [11]. The dimensions of the shuttle box were 8 in. wide by 24 in. long by 8 in. high. A start box was constructed by placing a partition 6 in. from one end of the apparatus. This partition contained a guillotine door (4 in. high by 3 in. wide) which was raised to begin a trial. Just outside the start box there was a choice area 8 in. wide by 6 in. long leading to two side-by-side goal boxes each 4 in. wide and 11 in. long. The openings into these goal boxes were uncovered and measured 2 in. wide by 2 in. high. The apparatus was illuminated by overhead lights built into the apparatus cover. Shock (0.5 m amp) was supplied by a Lafayette (Model No. 9-615A) shock generator and shock scrambler (Model No. A620). A particular trial consisted of a 10-sec avoidance period which was accompanied by a Sonalert (Model SC) tone. A noncorrection procedure was followed and shock and tone or tone alone were terminated when the animal entered the correct goal box.

Procedure. The 47 animals were randomly assigned to two groups of 23 and 24 animals each. The first group, 23 animals, constituted the tetraethyl lead pool and the animals were assigned to six treatment groups as follows: Group I (3 animals), received 10 mg/kg of tetraethyl lead; Group II (4 animals), 8 mg/kg; Group III (4 animals), 6 mg/kg; Group IV (4 animals), 4 mg/kg; Group V (4 animals), 2 mg/kg; and Group VI (4 animals), one ml of pure peanut oil. The lead was obtained from Ventor Corporation, Beverly, Mass., and, as measured by gas chromatography, was 98.7% pure tetraethyl lead. The lead was dissolved in peanut oil and all doses were adjusted to one ml and were adminstered via intragastric intubation.

The second group, 24 animals, was assigned to the tetraethyl silane subject pool with four animals in each group.

This substance was chosen as a control for potential effects associated with the tetraethyl radical. Doses were chosen so that there were the same number of tetraethyl radicals in each treatment group as in each of the tetraethyl lead groups as follows: 4.46 mg/kg, 3.57 mg/kg, 2.68 mg/kg, 1.78 mg/kg, 0.78 mg/kg, and one ml peanut oil. Again the solvent was peanut oil and each dose was adjusted to one ml.

The behavioral test procedures for all animals were the same. Each animal received the appropriate injection 72 hr prior to initiation of behavioral testing. Administration was via the intragastric route. Prior to discrimination training each animal was taught to avoid shock to one side (50% animals assigned to right side, 50% to left side). This was accomplished by blocking the opening to the inappropriate goal box, opening the start box door, and terminating the shock and tone, or tone alone after the animal entered the goal box. Each trial was separated by a 30-sec intertrial interval. When the animal had successfully avoided 5 out of 6 successive trials, discrimination training was initiated by removing the partition covering the other goal box and terminating shock and tone or tone alone only when the animal entered the correct goal box. Each animal was run to a criterion of 9 out of 10 correct trials. Latencies to reach the correct side were recorded on all trials. The measures made were trials to avoidance criterion, trials to discrimination criterion, and average latency to discrimination criterion.

Reversal of the discrimination was started five days following the injections. The procedure was the same as was used during acquisition of the original discrimination except that the opposite side of the chamber was the correct goal box for each animal. If an animal failed to enter the correct goal box on ten consecutive trials, the entrance to the incorrect goal was blocked for one trial. Animals were run to a criterion of four consecutive correct choices. The measures evaluated statistically were trials to criterion and mean latency to criterion.

Retention for the reversal learning was tested three days after the criterion sessions. Each animal was run ten trials with the reversed side being the correct choice. Number of incorrect choices and mean latency of responses were recorded.

Results and Discussion

Considering only the tetraethyl lead animals, there was no difference, $F(5,17) = 1.90$, among the dosage groups in the number of trials they required to reach the avoidance criterion. There were, however, differences $F(5,17) = 7.81$, $p<0.01$, among the groups in their trials to the acquisition criterion. Subsequent tests, Newman-Keuls with $\alpha = 0.05$, revealed that while the two highest dosage groups did not differ from each other ($\bar{x} = 25.30$ versus $\bar{x} = 25.80$) in trials required to reach criterion they did require significantly more trials to acquisition than the control group and the two lowest dosage groups. No other significant differences

TABLE 2

THE EFFECTS OF SINGLE DOSES OF TETRAETHYL LEAD ON PERFORMANCE MEASURES ($\bar{X}$) IN A TWO-CHOICE, NEGATIVE REINFORCEMENT DISCRIMINATION TASK

	Dosage of Tetraethyl Lead (mg/kg)					
	Control (1 ml peanut oil)	2	4	6	8	10
Avoidance						
Trials to Criterion	19.5	21.3	21.3	15.3	23.0	16.3
Acquisition of Discrimination						
Trials to Criterion	12.0	13.75	15.00	22.30	25.80	25.30
Mean Latency to Criterion (sec.)	8.1	9.0	9.2	10.4	9.5	11.3
Reversal of Discrimination						
Trials to Criterion	12.25	18.25	25.50	32.50	20.25	16.30
Mean Latency to Criterion (sec.)	19.6	17.6	17.9	18.7	22.8	24.6
Retention of Reversal						
Errors	2.8	3.7	3.7	5.0	7.2	6.0
Mean Latency (sec.)	6.6	6.6	8.2	11.2	9.9	11.8

were observed among the means. A similar pattern of results was observed in mean latency to discrimination criterion where significant differences, $F(5,17) = 16.26$, $p<0.01$, among groups were observed. Subsequent tests indicated that the control latency (8.1 sec) was significantly below all dosage levels. The only inter-group comparison of the fifteen possible which was not significant was that between the two lowest drug groups (9.0 sec versus 9.2 sec). See Table 2.

The reversal trials to criterion also showed significance, $F(5,17) = 5.46$, $p<0.05$, among groups but only the 6 mg/kg group ($\bar{x} = 32.50$) took significantly more trials to criterion than did the control animals ($\bar{x} = 12.25$). The only other difference observed was between the middle dosage group, 6 mg/kg group ($\bar{x} = 32.50$), and the highest dosage group, 10 mg/kg ($\bar{x} = 16.30$), $p<0.05$.

In the analysis of the retention data there was no difference of significance among groups in number of errors, $F(5,17) = 0.84$. The groups did differ, $F(5,17) = 9.56$, $p<0.01$, in their mean latency during the retention task (see Table 2) and subsequent tests indicated differences between the control group (6.6 sec) and both the 6 mg/kg (11.2 sec) and the 10 mg/kg (11.8 sec) groups. These two high-dosage groups also were significantly slower than the low-dosage group (6.6 sec).

In general these data argue for no basic difference in ability to avoid but they do show an impairment, which is dose-related, in the rat's ability to discriminate in the various measures employed. However, the reversal and retention data present an uneven picture.

The parallel means for the tetraethyl silane animals are given in Table 3. In the nondiscriminated avoidance test there was again no difference, $F(5,18) = 0.30$, among the five dosage groups and the controls.

With respect to the trials to discrimination criterion measure, there was no significant difference, $F(5,18) = 0.73$, among all groups (see Table 3 for means). This is in marked contrast to the previously discussed results of the tetraethyl lead animals given exactly the same test.

Another, and parallel measure, in the discrimination task was that of mean latency to acquisition criterion. Again, in contrast to the tetraethyl lead animals, there was no significant difference, $F(5,18) = 1.14$, observed among groups (see Table 3 for means). With respect to reversal data, there were no reliable differences, $F(5,18) = 0.24$, among the groups. The retention data also provided no basis for rejecting the notion that all groups were drawn from the same population of animals in either the number of errors, $F(5,18) = 0.18$, or in the mean latency, $F(5,18) = 0.02$.

EXPERIMENT 3

In view of the dramatic effects that lead had on performance variables in the previous experiment it was

TABLE 3

THE EFFECTS OF SINGLE DOSES OF TETRAETHYL SILANE ON PERFORMANCE MEASURES ($\bar{X}$) IN A TWO-CHOICE, NEGATIVE REINFORCEMENT DISCRIMINATION TASK

	Control (1 ml peanut oil)	Dosage of Tetraethyl Silane (mg/kg) 2	4	6	8	10
Avoidance						
Trials to Criterion	20.50	19.50	16.00	16.50	17.75	15.75
Acquisition of Discrimination						
Trials to Criterion	11.00	16.25	18.50	15.00	20.00	13.25
Mean Latency to Criterion (sec.)	7.60	8.08	8.45	8.53	9.75	9.48
Reversal of Discrimination						
Trials to Criterion	17.75	11.70	22.50	22.50	19.75	24.00
Mean Latency to Criterion (sec.)	17.9	23.4	21.4	19.1	17.0	20.8
Retention of Discrimination						
Errors	2.75	2.25	2.75	3.25	3.00	1.50
Mean Latency (sec.)	6.00	7.00	5.80	7.00	7.50	6.60

deemed important to see if similar disruptions in the learning of a discrimination would occur following cumulative doses. This is an important question when one considers that it may be possible for lead in small doses to be excreted over time [9] and the fact that many environmental exposures to lead compounds occur in a cumulative way. Thus, Experiment 3 was designed to see if administering smaller doses of lead over several days prior to discrimination training would disrupt performance in a similar fashion to what was observed in Experiment 2.

Method

Animals. Twenty-four Sprague-Dawley male albino rats, ranging in weight from 375–410 g, were used. They were maintained as in Experiments 1 and 2.

Apparatus and procedure. The same test situation and behavioral procedures used in Experiment 2 were again applied. Prior to testing, the animals were randomly assigned to six treatment groups. Each group (4 animals) received a comparable administration of lead to the tetraethyl lead groups in Experiment 2; however, the doses were cumulative. Nine days prior to initiation of behavioral training each animal received 0.20 of its appropriate dose, this procedure was replicated on days seven, five, three, and one prior to training. Thus, each animal received 0.20 of its total dose on each of five pretraining days, each injection day separated by 48 hr. As in Experiment 2, the total doses for each group were: 10 mg/kg, 8 mg/kg, 6 mg/kg, 4 mg/kg, 2 mg/kg and one ml peanut oil. All doses were in one ml peanut oil.

Again the measures evaluated were: (1) trials to avoidance criterion; (2) acquisition-trials to discrimination criterion and mean latency to discrimination criterion; (3) reversal of discrimination-trials to criterion and mean latency to criterion; (4) retention of reversal-number of incorrect choices and mean latency of responses.

Results and Discussion

Table 4 summarizes the basic data which parallel the information obtained in the two major groups in Experiment 2. The statistical analyses can be briefly summarized by indicating that there were no reliable differences in trials to avoidance criterion, $F(5,17) = 0.98$. Beyond that, in the discrimination data, there was no observed difference in acquisition trials to criterion $F(5,17) = 0.88$. This was true even though the mean number of trials for all dosage groups was higher than for the control group. In the measure of mean latency to acquisition criterion a similar, but nonsignificant, $F(5,17) = 2.81$, result was observed.

The reversal trials to criterion demonstrated no statistical differences among the various groups: number of trials to criterion, $F(5,17) = 0.41$, and mean latency, $F(5,17) = 3.79$. As was the case in acquisition, however, these measures were elevated in the dosage groups.

TABLE 4

THE EFFECTS OF CUMULATIVE DOSES OF TETRAETHYL LEAD ON PERFORMANCE MEASURES ($\bar{X}$) IN A TWO-CHOICE, NEGATIVE REINFORCEMENT DISCRIMINATION TASK

	Cumulative Total Dosage of Tetraethyl Lead (mg/kg)					
	Control (1 ml peanut oil)	2	4	6	8	10
Avoidance						
Trials to Criterion	19.5	20.3	15.5	16.3	16.8	18.0
Acquisition of Discrimination						
Trials to Criterion	12.00	18.3	18.0	22.3	19.0	21.5
Mean Latency to Criterion (sec.)	8.1	8.7	8.1	10.0	9.5	9.9
Reversal of Discrimination						
Trials to Criterion	12.3	27.0	15.0	24.0	30.5	22.3
Mean Latency to Criterion (sec.)	17.9	17.9	18.1	20.5	14.7	21.9
Retention						
Errors	2.8	2.0	6.7	2.3	4.3	3.5
Mean Latency (sec.)	6.6	7.9	9.8	9.3	10.9	13.2

EXPERIMENT 4

Evidence that emotionality can have a powerful influence on performance in tasks involving aversive stimuli is well documented [6]. That lead did not affect avoidance learning in our experiments suggests that emotionality did not play a role in the performance decrements in the discrimination task. Even so, we thought a broader test of possible influences of lead on emotionality was desirable. The fourth experiment was designed to test such a possibility; pre- and postmeasures associated with multiple doses of lead were taken in the open field test [5].

Method

Animals. Twenty-four Sprague-Dawley male, albino rats, ranging in weight from 375–425 g were used. Each was maintained as in Experiments 1, 2 and 3.

Apparatus and procedure. The open-field test space, as described by Denenberg [5] was used. The chamber was a 4 ft. square black box with open top. The floor of the box was partitioned off into 9-in. squares by painting parallel white lines, 0.25 in. wide. The measure of interest was number of squares entered, an entrance being defined as all four feet within a square.

Each animal was assigned to one of six treatment groups comparable to the tetraethyl lead groups in Experiment 2. Each animal was tested for 3 min, 24 hr prior to receiving tetraethyl lead, and subsequently tested for 3 min, 24 hr after lead intubation. The dose groups were: 10 mg/kg, 8 mg/kg, 6 mg/kg, 4 mg/kg, 2 mg/kg and one ml peanut oil. As in the other experiments, all doses were adjusted to one ml.

Results and Discussion

The activity levels of the animals were statistically equated, by analysis of covariance, on the basis of a predosage open field test. The mean number of squares traversed (unadjusted) in the open field was 61.75 for the control animals and was as follows for the dosage groups (in ascending order of dosage): 29.75, 37.75, 77.00, 57.50, and 58.75. These means, when adjusted, did not differ, $F(5,17) = 2.38$, $p<0.05$, in the analysis of covariance and consequently, no subsequent tests were indicated.

DISCUSSION

Several features of the results of these experiments deserve further discussion. First, it is apparent from Experiment 1 that tetraethyl lead, at least at the highest dose we used, has a deleterious effect on food motivated operant behavior. After the administration of lead, animals in the high dosage group reduced their bar press rates for food. Whether this effect was a consequence of gastrointestinal involvement or was related to a more general motivational decrement is not discernable from our results. However, there can be no doubt that such findings should be a major consideration for any future experiments designed to test the effects of lead on behavior.

Second, Experiment 2 clearly indicated that single doses of tetraethyl lead affected discrimination performance. This was evidenced in higher trials to criterion and longer mean latencies to criterion in acquisition; higher trials to criterion and longer mean latencies to criterion in reversal; and in greater error frequency and mean latencies in retention tests. That these effects were not correlated with the ethyl radical, but can be directly attributed to lead, is evident from the results obtained following administration of tetraethyl silane. In addition, the performance decrements can not be explained on the basis of either increased tolerance to the shock or to an emotionality factor. Recall that there were no differences among any groups in avoidance learning, and that lead had no effect on open field test performance. Thus, it seems reasonable to conlude that lead, in sufficient amounts, can cause a reduction in an organism's ability to both learn and retain a discrimination problem.

From the results of Experiment 3 it would seem that lower, cumulative doses may not affect performance variables. Even though animals in this experiment received the same total amount as the acute doses administered to those animals in Experiment 2, there were no differences in any measures. These data are consistent with the observations of Bullock *et al.* [2] and are of particular importance because ingestion is the major source of lead in man and daily amounts are typically quite small [3]. Our failure to observe a significant effect on performance variables following cumulative doses, as well as the Bullock *et al.* results, may reflect the animal's ability to dispose of lead through fecal and urinary secretion. Even so, caution is necessary in interpretation of these results. Had we extended the application of lead in the cumulative experiments, at some critical level of lead, performance decrements probably would have become evident. Thus, these results have obvious implication for future experiments. Studies are called for which relate chronic long term lead exposure to learning variables.

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