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Exposure to Lead During Development Alters Aggressive Behavior in Golden Hamsters

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DELVILLE, Y. *Exposure to lead during development alters aggressive behavior in golden hamsters.* NEUROTOXICOL TERATOL **21**(4) 445–449, 1999.—The present studies were designed to test the effects of early exposure to low doses of lead on aggressive behavior in male golden hamsters. Litters of hamsters were exposed to lead acetate (either 0 or 100 ppm) from embryonic day 8, through weaning on postnatal day 25 (P-25), until P-42. Play fighting behavior was tested on P-19 and P-20 around the developmental onset of the behavior. During the first day of testing, lead-exposed hamsters displayed less play fighting activity. However, this difference disappeared by P-20. Around the same time, lead-exposed animals were around 20% lighter than the controls, suggesting a delayed maturation in these hamsters. Blood lead levels assayed on P-42 ranged between 10 and 15 μg/dL. Aggressive behavior was tested in early adulthood (P-45) in a resident/intruder paradigm. Lead exposure affected aggressive behavior, because lead-exposed male hamsters were faster and more likely to attack and bite their intruders. These results support the possibility that early exposure to low doses of lead during development is capable of enhancing aggressive behavior in males. © 1999 Elsevier Inc. All rights reserved.

Lead exposure Development Aggression Play fighting Toxicology

DURING development, the nervous system is vulnerable to chemical agents present in the environment. Studies performed in children have indicated a reduction of two full-scale IQ points for an increase in plasma lead levels from 10 to 20 μg/dL (3,5,18,23,31,35). Preclinical support for these findings originates from animal models of cognition. In rats, early exposure to lead impairs performance in specific and well-characterized behavioral paradigms, such as discrimination learning or acquisition and reversal learning (2,11–13,38). Typically, these tasks are impaired by early exposure to doses of lead acetate in the drinking water resulting in plasma lead levels ranging from 15 to 40 μg/dL.

However, the effects of lead are not limited to cognition. Positive and statistically significant correlations have been established between increased lead exposure and increased aggression in children (particularly boys) ranging from 4 to 5 to 11 years old (4,32,34,36,37). For instance, in one study, boys (4–5 years old) with blood lead levels over 15 μg/dL were two to three times more likely to have aggression subscores rated in a clinical range than boys with blood lead levels below 15 μg/dL (34). The possibility that early exposure to lead affects social behavior has been addressed in several animal models. These studies have tested the effects of early lead exposure on agonistic interactions during development and in adults. In rhesus monkeys, lead-treated individuals are less likely to engage in social play during infancy (30). In rats, early exposure to lead increases rough and tumble play fighting between juveniles (27). However, experiments testing the developmental effects of lead on adult behavior led to various results ranging from increased aggressivity to decreased aggressivity. In mice, animals exposed to 2,500–5,000 ppm lead acetate in the drinking water during development were quicker to attack intruders than their control-treated counterparts (19,20). In contrast, mice exposed to 1,000 ppm lead acetate were found to be less aggressive toward conspecifics during tests in a neutral arena (14). Similarly, rats exposed to 0.1% lead acetate in their food were also found less aggressive during tests in a neutral arena (21). It is possible that the various outcomes of these studies were affected by differences in the experimental protocols. Testing conditions were varied, including aggres-

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sion against intruders (which in some cases were previously littermates; 19,20), aggression between males placed in an unfamiliar (neutral) arena (14,21), competition between cagemates for access to a limited resource (22), or shock-elicited aggression (26). Doses of lead administered to the animals ranged from 200 ppm to 5,000 ppm lead acetate in the drinking water, leading to blood levels ranging from 25 to 160 μg/dL (14,19–21,22,26). Finally, while some animals were tested when still subjected to daily lead intake (14,19,20), others were tested well after the cessation of treatment (20,21,22,26). These different conditions represent different factors that could affect aggressive behavior. Primarily, doses of lead are a critical factor. Blood lead levels observed in animal models of aggression have to be relevant to the interests of clinicians concerned about the behavioral effects associated with blood lead levels above 10 μg/dL (8).

The following studies were designed to address some of these concerns in golden hamsters. First, the animals were exposed to low doses of lead acetate (100 ppm). Second, the animals were tested for aggressive behavior in a resident/intruder paradigm where the subjects are kept in their home cages and exposed to a smaller intruder. This paradigm is used to characterize offensive aggression, as the residents approach and initiate attacks against the intruder (1,6,7).

MATERIALS AND METHODS

Animals and Treatment

Female golden hamsters (n = 18) were purchased from Harlan Sprague Dawley (Indianapolis, IN), and mated. The animals were individually housed and kept in a reverse photoperiod (14 light:10 dark; lights on at 1900). They received food and water *ad libitum.* The females were separated into two treatment groups (n = 9 per group) according to the dose of lead acetate (lead acetate trihydrate, Sigma Chemical Co., St. Louis, MO) in their drinking water. The doses of lead acetate were 0 ppm (0%) and 100 ppm (0.01%, 30.7 μM). In rats, exposure to a slightly lower dose results in blood lead levels well below 25 μg/dL (2). The drinking water was prepared from distilled water purified through a filtering system (NANOpure, Barnstead/Thermolyne, Dubuque, IA). Water bottles were replaced daily to minimize the effects of precipitation and to monitor the volumes drunk. Exposure to lead started on embryonic day 8 (E-8; one week before parturition) and continued through lactation. The litters were culled to six to eight pups per litter a few days after parturition (once maternal behavior was stabilized and infanticide ended). Each litter contained both males and females. The ratios of males to females per litter were similar between the groups until weaning. Similar numbers of pups per litter were kept in both groups until weaning. The pups (two to four per litter, six litters per group, randomly selected) were weaned on postnatal day 25 (P-25), isolated in single cages, and kept on their respective treatment groups receiving the same concentrations of lead in their drinking water as their mothers did. Exposure to lead ended on P-42. After P-42, all animals received regular tap water. The experiment was performed with two separate sets of animals. The first set of animals (six litters per group) was not tested for blood lead level. These animals were used for play fighting behavior. Only half of the litters were kept for testing aggressive behavior. The selection was based on the birth dates to limit behavioral testing to a 2-day period. The second set of animals (three litters per group) was used for blood lead levels and aggressive behavior testing. These animals were not tested for play fighting behavior. The animals were housed in the Department of Animal Medicine at the University of Massachusetts Medical Center, an AAALAC-accredited facility. The protocol used during the experiment was approved by the Institutional Animal Care and Use Committee in compliance with the requirements of the Animal Welfare Act and adherence to the US PHS Policy and the NIH Guide.

Blood lead levels were assayed as follows on male golden hamsters. On P-42, animals (three per treatment group, one per litter) were killed, their blood collected into EDTA-treated tubes, kept at 4°C, and assayed for lead content by graphite furnace atomic absorption spectrometry (Hospital Laboratories, University of Massachusetts Medical Center, Worcester, MA). Additional animals (six per treatment group, two per litter) were killed on P-55, and their blood collected and assayed for lead content. The animals tested for blood lead on P-42 were littermates of animals tested for aggressive behavior. The animals tested for blood lead on P-55 were tested for aggression on P-45 and were the littermates of the animals tested for blood lead in P-42.

Behavioral Testing

Play fighting behavior. Juvenile golden hamsters initiate play fighting activity around P-20 (25). At that time, the pups become more active within the litters and initiate play fighting activity with their littermates. The litters (n = 6 per group) were observed inside their home cage for two 5-min periods per day on P-19 and P-20 to ascertain the effects of early lead exposure on behavioral development. Effects of early lead exposure on behavioral development could help explain possible effects on aggressive behavior tested during early adulthood. The number of pins performed between littermates was counted in each litter during the observations. The results were expressed as the cumulative number of pins per litter observed during each testing day.

Aggressive behavior. Males (two to four per litter, six litters per group) were tested for offensive aggression against an unknown intruder (of smaller or equal size) on P-45. The testing period lasted for 10 min. The behavior of the resident was observed during the testing period. The measures of aggressive behavior recorded during this period included the latency to attack, latency to bite, contact time, number of bites, number of attacks, and number of retreats.

Data Analysis

Parametric data (body weights, water intake, latencies) were compared between groups with Student's t-tests (two-tailed). Nonparametric data (number of behaviors) were compared between groups with Mann–Whitney U-tests (two-tailed). The litter (means or medians of individual data) was used as the statistical unit.

RESULTS

Body Weights and Water Intake

Water intake was monitored during pregnancy and the first weeks after parturition. During this period, daily water intake rose from about 20 mL for all animals. On the day of birth, water consumption ranged between 20 and 30 mL. No statistically significant difference was observed between treatment groups on that day. One week after parturition, water consumption ranged around 50 mL per day and rose further to around 100 mL per day by P-20. Body weights were compared between litters on P-21, a few days before weaning (Fig.

1). Lead exposure had significant effects on body weights [$t(10) = 3.50, p < 0.01$]. The average weight of the pups in the control litters was 20% heavier than for litters exposed to 100 ppm lead acetate. Body weights were also recorded on P-50 after testing for aggression (Fig. 1). By then, control animals were less than 10% heavier than lead-exposed animals. This difference was not statistically significant [$t(10) = 1.02, p > 0.10$].

Blood Lead Levels

Blood lead levels were assayed in animals exposed to 0 ppm and 100 ppm lead acetate on P-42 and P-55. On P-42, animals exposed to 100 ppm lead acetate ranged between 10 and 15 μg/dL (mean ± SD; 13 ± 0.9 μg/dL), while the controls were below 2 μg/dL (below the range of detection). On P-55, after the end of lead exposure, experimental animals had blood lead levels between 2 and 5 μg/dL (mean ± SD; 3.5 ± 0.4 μg/dL).

Behavior

Play fighting. Litters were observed for play fighting behavior on P-19 and P-20. The results were compared between the groups (Fig. 2). The comparison shows that lead exposure affected the cumulative number of pins observed in the litters on P-19 but not on P-20 (respectively: $U1 = 0.5$, $U2 = 35.5$, $p < 0.01$; $U1 = 17.5$, $U2 = 18.5$, $p > 0.10$). On P-19, fewer pins were observed in the litters exposed to 100-ppm lead acetate and in the controls.

Aggressive behavior. The animals were tested for aggressive behavior in the presence of a smaller intruder on P-45. Hamsters exposed to 0-ppm lead acetate were not particularly aggressive. Animals in three out of six litters spent most of their time avoiding the intruders. Attacks were consistently performed by animals in only three out six litters. Bites were consistently performed by animals in only one litter. In contrast, animals exposed to 100 ppm lead acetate appeared to be more aggressive (Fig. 3). In this group, every litter contained individuals that attacked readily and bit their intruders. These differences were statistically significant. Litters of lead-exposed animals were faster to bite ($t(10) = 3.73, p < 0.01$) their intruders and tended to be faster to attack them ($t(10) = 2.2$, $p < 0.1$). Lead-exposed hamsters were also more likely to attack and bite the intruders (respectively: $U1 = 32.5$, $U2 = 3.5$, $p < 0.05$; $U1 = 32$, $U2 = 4$, $p < 0.05$). Lead-exposed hamsters also appeared to retreat less from the intruders and spend more time in contact with them (Fig. 3). However, these later differences were not statistically significant.

DISCUSSION

The present experiments produced observations recorded before and after weaning. The former observations were recorded around P-20. This preweaning period is characterized by the developmental onset of play fighting in golden hamsters (25). The animals were observed at that time to determine whether early lead exposure can affect behavioral development which, in turn, could help explain effects on aggressive behavior tested during early adulthood. In the present experiments, lead exposure had a temporary effect on play fighting behavior. Lead-exposed hamsters were less likely to engage in play fighting activity on P-19 but not on P-20. This observation combined with a 20% decrement in body weight suggests that early exposure to 100 ppm lead acetate retards growth and behavioral development before weaning. However, this effect was reduced later in development. At the end of puberty, body weights in lead-exposed animals were just under 10% lower that in the controls. This difference, 8 days after the cessation of lead exposure, is interesting. Nevertheless, at the same time, lead-exposed animals were at least equally capable of attacking an intruder as their controls. The present observations on play fighting behavior inside the home cages are not in agreement with previous observations of rats (22,27). In one study, early lead exposure enhanced play fighting activity (27), while in the other lead exposure had no effect on play fighting activity (22). However, these studies had different experimental protocols. In one study (27), lead exposure (670 ppm lead chloride) started at birth, and continued through weaning until the end of the experiment. In the other study, the period of exposure was similar, but the animals were exposed to lead acetate (350 ppm). In both studies, testing was performed later in development and after weaning. It is likely that different lead-exposure protocols resulted in different effects on the development of the nervous

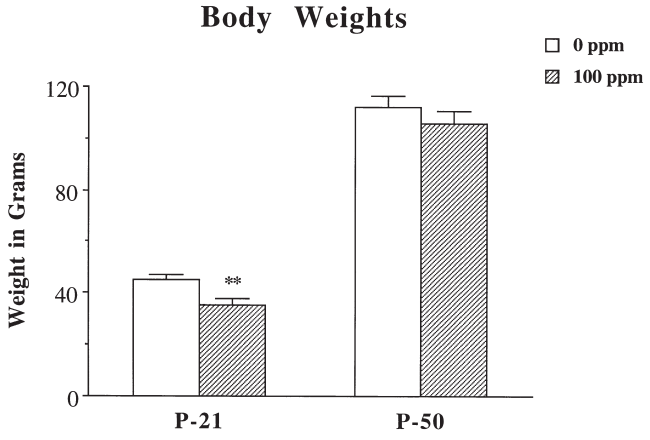

FIG. 1. Comparison of body weights (mean ± SEM) on P-21 and P-50. The animals (six litters per group) were exposed to either 0 ppm or 100 ppm lead acetate through their drinking water from embryonic day 8 until P-42. The comparisons of P-21 and P-50 were based on average weights per litter (**, $p < 0.01$).

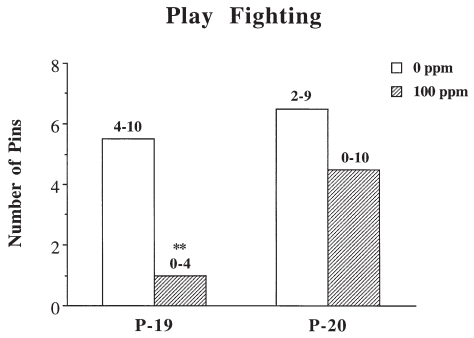

FIG 2. Play fighting behavior (median number of pins, range) tested on P-19 and P-20. The animals (six litters per group) were exposed to either 0 ppm or 100 ppm lead acetate through their drinking water from embryonic day 8 until P-42. The litters were observed twice per day, and the cumulative number of pins observed per day within each litter were kept for data analysis. (**, $p < 0.01$).

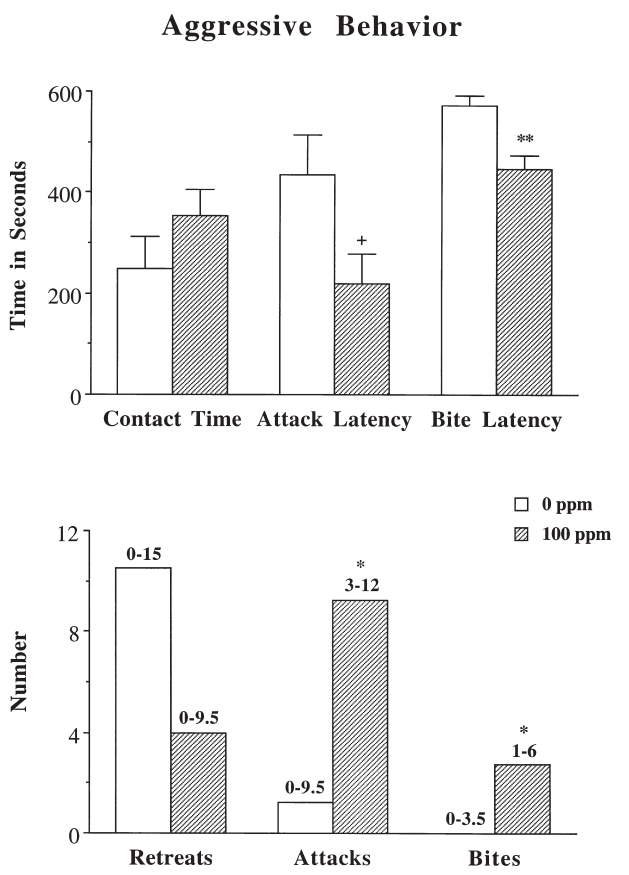

FIG. 3. Offensive aggression tested in a resident/intruder paradigm. The animals (six litters per group) were exposed to either 0 ppm or 100 ppm lead acetate through their drinking water from embryonic day 8 to P-42. The animals (two to four per litter) were tested on P-45. The latencies to attack (Attack Latency), latencies to bite (Bite Latency), contact times (Contact Time), number of attacks (Attacks), number of bites (Bites), and number of retreats (Retreats) were compared between the groups with the litter as the statistical unit. The means (± SEM, for latencies and durations) and medians (and ranges, for number of behaviors) are represented in the figure (+,*, and **: $p < 0.10$, $p < 0.05$, and $p < 0.01$, respectively).

system. It is also possible that the different testing conditions would also have affected the outcome of the studies. For instance, it is possible that the effect of lead exposure on play fighting differs after weaning and once the behavior is well established.

The observations recorded at the end of puberty on P-45 indicate a clear effect of lead exposure on aggressive behavior tested in a resident/intruder model. Litters of male hamsters exposed to 100 ppm lead acetate were faster to initiate aggressive actions and more likely to perform them. Their littermates had blood lead levels between 10 and 15 μg/dL 3 days before testing, and it is likely that blood lead levels were similar at the time of the aggression tests. In humans, this level of exposure has been associated with a cognitive deficit (3,5,18,23,31,35), and is suspected to be associated with an enhanced frequency of aggressive individuals, particularly boys (32,34,36). The present data in male hamsters are compatible with the possibility that early exposure to low doses of lead enhances aggressive behavior in boys. Of course, it is unlikely that offensive aggression as tested through a resident/intruder paradigm in golden hamsters is analogous to delinquent behavior and aggression scores in children. It is likely that the stimuli and social conditions affecting aggression differ between humans and hamsters. Nevertheless, a number of parallels have been observed between hamsters and humans. The same neurochemical signals that control aggressive behavior in hamsters have been implicated in the regulation of aggressive behavior in humans. In golden hamsters, aggressive behavior toward intruders is facilitated by vasopressin and inhibited by serotonin (15,16,24,28). Moreover, because exposure to social stress during development alters aggressive behavior in hamsters, it also changes the activity of the vasopressin and serotonin systems within the forebrain (17). The data reported in hamsters are consistent with correlations established with vasopressin and serotonin in humans. In humans, decreased serotonin release or sensitivity within the brain has been associated with increased aggression (29,33). Impulsive aggression in patients is reduced by treatment with fluoxetine, a serotonin reuptake inhibitor (9). Finally, increased vasopressin release has been associated with enhanced aggression (10). Therefore, it is likely that common traits exist in the limbic mechanisms controlling aggression in both humans and animals. As such, the present data are valuable for the establishment of an animal model testing the effects of early exposure to low doses of lead on aggressive behavior.

During the present experiments, the level of lead exposure was not examined in detail. While some measurements of water intake were taken during pregnancy and lactation, these measurements do not indicate a level of exposure to the pups. As a result it is difficult to estimate blood lead levels in the pups during lactation. Blood lead levels were assayed in animals on P-42 at the end of the exposure to lead. It is likely that blood lead levels were higher at earlier periods, especially early after birth. This could explain the suspected delay in the developmental onset of play fighting behavior on P-19 and the lower body weights at this period. Nevertheless, the present data on golden hamsters are comparable to previous reports presented on rats under similar levels of exposure to lead (2,11–13). Furthermore, the animals were tested for offensive aggression against an intruder on P-45. These tests were performed after the cessation of lead exposure. The data on blood lead levels were collected from animals on P-42 and P-55. Between these days, blood lead levels decreased from 10–15 to 2–5 μg/dL in animals previously exposed to 100 ppm lead acetate. It is likely that blood lead levels on P-45 were rather similar to those tested on P-42.

In conclusion, the present observations made on male hamsters are consistent with earlier reports on children (particularly boys) pointing to early exposure to low doses of lead as a risk factor for aggressive and delinquent behavior (32,34,36). Although this conclusion may only apply to males, the present results provide preclinical support for these observations in children. Future studies will be focused on the toxicology and neurobiology of early lead exposure.

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