Low Level Lead Exposure Impairs Attentional Set Shifting Task Performance Depending upon Sex and Developmental Periods of Exposure

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Introduction
Exposure to low levels of lead (Pb) impairs a variety of cognitive processes. Indeed, Pb exposure during development produces a variety of cognitive impairments that include deficits in working memory, attention, and learning and memory. The mechanisms underlying these effects are not well understood, but experimental work on Pb toxicity in rats has focused mainly on learning and memory deficits and has been on executive functions. However, detrimental effects on executive functioning could lead to or even underlie a variety of other cognitive problems attributed to Pb exposure. In this study, we examined the ability of Long-Evans rats (control and Pb-exposed) to perform a 150gms Pb-acetate in food given postnatally (gestation through weaning) or early postnatally (Pb, birth through weaning) to acquire and perform an attention set shifting task (ASST) that requires animals to locate a food reward based on distinguishing between different materials and odors. The task consisted of simple (SD) and complex (CD) discriminations, and reversals, and intradimensional (ID) and extradimensional (ED) shifts followed by reversals.

Methods

Subjects: The use of animals complied with NIH Guidelines for the Care and Use of Laboratory Animals and the study was approved by the institutional animal care and use committee at Thomas Jefferson University. Long-Evans rats (Harlan Laboratories) were fed chow (RMH 1000) with or without Pb-acetate (300 mg/kg diet) to maintain 80% body weight. Rats were housed in a standard animal colony, with 12/12 h light/dark cycle for the duration of the study. Animals exposed to Pb from gestation through weaning (i.e., postnatal day (PND) 22) comprised the postnatal (P) Pb-exposed group. Other exposure groups were exposed to the same levels of Pb but exposure started on PND 0 and continued to PND 22 (PND 0-22 Postnatal exposure group (P0-22 PE)). At PND 22 all rats were placed on regular chow (i.e. 4 week Pb exposure). At PND 60 all rats were placed on regular chow for 2 weeks (i.e., 4 week Pb exposure). Groups were housed in standard plastic cages and had ad libitum access to food and water. All procedures were approved by the Institutional Care and Use Committee (IACUC). At the time of behavioral testing, BLLs were below detection levels. Pb-acetate was administered per os in a 12g (i.e. 4 food pellets) per day to maintain 80% body weight. Food Restriction Protocol: At PND 0, rats were housed individually, baseline weights were taken and they were placed on a food restriction protocol of 12g (i.e. 4 food pellets) per day to maintain 80% body weight. Diabetes mellitus was not induced. Weights, body weight were monitored to ensure that the diet was tolerable. All animals had the same amount of food available. The remaining food was weighed at the end of each day to determine the amount of food consumed. Food and water were provided ad libitum. All animals had free access to water.

Results

Low Level Lead Exposure Impairs ASST Performance

As shown in Figure 1, Pb-exposed animals performed the task differently than controls. The Pb-exposed animals (i.e. EP0 vs. P0) produced distinctive cognitive learning deficits. The low level Pb exposure during development results in different deficits in the ability for females to learn the ASST. Males with EP0 exposure learned the task well and had no difficulty at the ED shift stage. EP0 rats did have difficulties learning with SD learning more than material and were unable to learn the ASST test. EPN females (EPN females had the most difficulty performing the ASST). All female rats that could not learn CD could not proceed through ASST. EPN males were able to complete the ASST, required more trials to reach criterion at almost every stage, compared to controls. Peri-natal exposure to low levels of Pb but exposure started on PND 0 and continued to PND 22 (PND 0-22 Postnatal exposure group (P0-22 PE)) had the least number of trials needed to learn at the ED and ED-Rev stages. Control male rats, and had the most difficulty performing the ASST (ANOVA post hoc Tukey = -3.56, p < 0.05). MD = Material Discrimination; OD = Odor Discrimination; SD = Simple Discrimination; CD = Complex Discrimination; CD-Rev = Complex Discrimination Reversal; ED = Extra-Dimensional Shift; ID = Intra-Dimensional Shift; ID-Rev = Intra-Dimensional Reversal; ID-Rec = Intra-Dimensional Reversal; ID = Intra-Dimensional Shift; ED-Rev = Extra-Dimensional Shift. Data are shown as ± SEM.

Conclusions

- Perinatally exposed males performed the test differently than controls. The Pb-exposed animals (i.e. EP0 vs. P0) produced distinctive cognitive learning deficits.
- These cognitive deficits were further differentiated based upon the rat sex.
- Males with EP0 Pb exposure were unable to learn an odor-based SD, while controls and EP0 females were able to complete all tests. All males Pb-exposed rats were able to complete all tests. Pb-exposed female rats had the most difficulty at the ED and ED-Rev stages compared to controls.
- Perinatally Pb-exposed male rats learned the odor SD but had significant numbers of errors at the CD-Rev, ID, ID-Rev, and ED-Rev stages. Perinatally Pb-exposed female rats were better at learning the ID-Rev task than controls and Pb-exposed female rats and had the most difficulty in the ED and ED-Rev stages.
- EPN males exhibit deficits in learning and perform simple discriminations and thus cannot be tested fully to assess the formation of an attention set. Pb-exposed female rats for attention sets and have deficits in extra-dimensional set shifting.
- Peri-natal male rats exhibit deficits in extra-dimensional set shifting, whereas peri-natal female rats exhibit deficits in extra-dimensional shifting.
- These data suggest that low level Pb exposure may result in attentional/ executive dysfunction and in particular, may impair the ability to form, maintain, and shift response sets resulting in potential problems with cognitive flexibility.

- Lastly, different outcomes based on developmental period of Pb exposure are seen among the potential for different critical periods during brain systems involved in different aspects of executive functioning may be affected.