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Developmental lead exposure impairs contextual fear conditioning and reduces adult hippocampal neurogenesis in the rat brain

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Abstract

The effects of developmental lead exposure on the emotional reactivity, contextual fear conditioning and neurogenesis in the dentate gyrus of 60–80 days-old rats were studied. Wistar rat pups were exposed to 0.2% lead acetate via their dams' drinking water from postnatal day (PND) 1 to PND 21 and directly via drinking water from weaning until PND 30. At PND 60 and 80 the level of anxiety and contextual fear conditioning were studied, respectively. At PND 80 all animals received injections of BrdU to determine the effects of Pb on the generation of new cells in the dentate gyrus of hippocampus and on their survival and differentiation patterns. The results of the present study demonstrate that developmental lead exposure induces persistent increase in the level of anxiety and inhibition of contextual fear conditioning. Developmental lead exposure reduced generation of new cells in the dentate gyrus and altered the pattern of differentiation of BrdU-positive cells into mature neurons. A lower proportion of BrdU-positive cells co-expressed with the marker for mature neurons, calbindin. In contrast, the proportions of young not fully differentiated neurons and proportions of astroglial cells, generated from newly born cells, were increased in lead-exposed animals.

Our results demonstrate that developmental lead exposure induces persistent inhibition of neurogenesis and alters the pattern of differentiation of newly born cells in the dentate gyrus of rat hippocampus, which could, at least partly, contribute to behavioral and cognitive impairments observed in adulthood.
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1. Introduction

It has been long understood that various environmental factors like stress, pharmacological drug treatment or toxin exposure, taking place early in life, have a profound influence on brain development, producing persistent effects on its function and increasing vulnerability for psychic disorders in adulthood (Ikonomidou et al., 2000; Roceri et al., 2002). Lead is still widely distributed in the environment, and the consequences of chronic exposure to low levels of lead in childhood have been a matter for extensive research during recent years. All current evidence suggests that there is no threshold below which lead remained without effect. Exposure to low levels of lead, during early development, has been implicated in long-lasting behavioral abnormalities and cognitive deficits in children and experimental animals (Bourljeily and Suszkiw, 1997; Murphy and Regan, 1999; Finkelstein et al., 1998; Moreira et al., 2001; Canfield et al., 2003). The learning impairment, and other behavioral disturbances in affected children and laboratory animals, suggests that hippocampus might be one region adversely affected during early life. Indeed, recent findings demonstrated that early lead exposure disrupts expression and phosphorylation of the cAMP-responsible element binding protein (CREB), a transcription factor directly related to the neuronal plasticity in the hippocampus of juvenile rats (Toscano et al., 2003).

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Furthermore, early lead exposure altered the *N*-methyl-D-aspartate receptor subunit composition in favor of the prevalence NR2B receptor subunit and decreased expression of the NR 2A subunit, which might be important in hippocampal development and maturation (Toscano et al., 2002). The possible reduction of neuronal plasticity, caused by lead exposure, is also reflected by the altered hippocampal long-term potentiation (Xu et al., 1998).

In rodents, the hippocampal formation differs from other brain structures because approximately 85% of granule neurons of the dentate gyrus are produced during the post-natal period and adult neurogenesis persists through the whole life span (Altman, 1962; Cameron et al., 1993; Hastings et al., 2001). It has been hypothesized that adult hippocampal neurogenesis exists as a substrate for neuronal plasticity and is related to the memory formation, emotions and helps the brain to accommodate continued bouts of novelty (Kemperman, 2002). Several negative events occurring during early childhood, such as maternal deprivation, ethanol administration, impair cognitive functions and induce long-lasting alterations of hippocampal neurogenesis (Lemaitre et al., 2000; Jaako et al., 2003; Zharkovsky et al., 2003). The persistent disruption of hippocampal neurogenesis might diminish the plasticity of the hippocampus and finally enhance the likelihood of mood and memory disorders (Jacobs et al., 2000).

Based on the above considerations, the aim of the present investigation was to study whether low-level lead exposure, during the extended post-natal period, would induce emotional and cognitive dysfunctions and alterations in the hippocampal neurogenesis in adulthood.

2. Materials and methods

Experiments conformed to local and international guidelines regarding the ethical use of animals, and all efforts were made to minimize the number of animals used and their suffering.

Wistar rats were obtained from Kuopio Animal Research Center (Finland) and used as the parent generation. Adult female rats (70–80 days old) were individually housed in plastic cages with a 22 °C, and 12-h light:12-h dark cycle and were mated with males of the same strain. Lead administration was performed according to the protocol described by Murphy and Regan (1999), with minor modifications. In short, 1 day after parturition, litters were culled to eight pups. On the same day, water was replaced by a 0.2% solution of lead acetate. The treatment lasted during the whole lactation period until weaning (day 21). Pups were weaned at the age of 21 days and then were kept in a group of five males per cage. The animals continued to receive 0.2% lead acetate with drinking water until post-natal day 30. At post-natal day 30, lead was removed from the drinking water, and the animals were allowed to attain adulthood (post-natal day 60). The control group dams and pups remained on tap water. Pup weights, maternal and pups' fluid and food consumption were measured on a weekly basis. During the whole experiment, animals were fed with regular laboratory foodstuff.

On days 15, 30, 60 and 80 after birth, separate groups of animals (3–4 per group) were taken for lead determination in blood and brain tissue. Animals were anesthetized with chloral hydrate and blood was taken from the heart. Animals then were perfused with physiological saline and the brain was removed. The blood samples and brain tissue were immediately frozen at −70 °C. Quantitative analysis of lead levels was performed in an independent State Environmental Laboratory using a Perkin-Elmer 1100B atomic adsorption spectrometer with a Philips HGA/P3105 graphite furnace and a deuterium background corrector.

2.1. Behavioral testing

Behavioral testing was performed on male pups at the age 60 days (locomotor activity and anxiety testing) and 80 days (contextual fear conditioning).

2.1.1. General locomotor activity

General locomotor activity was determined in a rectangular wooden cage (50 cm × 50 cm × 50 cm) uniformly illuminated with dim lighting. The light sensitive video camera, connected to the computer, was mounted about 1 m above the observation cage and the locomotor activity of an animal was monitored and analyzed using VideoMot2 software (TSE Systems, Germany) during a 30-min observation period.

2.1.2. Anxiety

Anxiety was evaluated in the elevated plus-maze The elevated plus-maze behavior was assessed using an apparatus consisting of two open and two enclosed arms of equal length and width (50 cm × 10 cm). The enclosed arms are not entirely enclosed, but rather have walls that extend 40 cm high. The plus-maze was elevated 50 cm above the floor. Each rat was placed in the center of the elevated plus-maze facing one of the open arms, and the number of entries and time spent (seconds) in the open or closed arms were recorded during a 5-min test period. The elevated plus-maze was carefully cleaned with 5% ethanol before each animal was introduced. Data was quantified and presented as a % time spent in the open arms and % entries in the open arms.

2.1.3. Contextual fear conditioning

At post-natal day 80, control animals and lead-exposed animals were trained for the contextual fear conditioning. The study was performed between 09.30 a.m. and 14.00 p.m. The task was carried out during four consecutive days in the experimental chamber (220 mm × 160 mm × 160 mm; $L \times W \times H$). Three sides of the box are made of non-transparent plastic and the fourth side is made of transparent

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