Young Brains on Lead: Adult Neurological Consequences?

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Gilbert and colleagues examine the effect of chronic low-level lead exposure, occurring during development, on hippocampal neurogenesis and spatial learning in adulthood. The effects of lead exposure on cognitive and behavioral deficits in children leading to learning and memory impairments is well established, whereas there is little information on the long-term (adult) consequences of gestationally initiated lead exposure. One important issue that Gilbert and colleagues assess is the long-term consequences of chronic developmental low-level lead exposure in adult offspring. Secondly, Gilbert and colleagues are the first to report the effect of lead exposure on hippocampal neurogenesis.

The work by Gilbert and colleagues is intriguing, in view of the fact that this paper attempts to integrate the consequences of developmental exposure to lead, known for its ability to impair cognitive functions, such as learning and memory, with a dysfunction in adult hippocampal neurogenesis. Chronic lead exposure initiated during development and continuing through adulthood (E16–PND75) resulted in a reduced survival of newly generated neurons in the dentate gyrus, but no effects on spatial learning and memory as assessed by the Morris water maze (MWM). As in other studies, discontinuation of lead at weaning did not result in observable differences from control animals in the chosen endpoint. Generally, the effects of developmental lead exposure on neurobehavioral deficits may or may not persist, and may be subtly manifested, but this paper emphasizes that lead exposure does have neurological consequences in the long term.

Up until the early 1900s, lead poisoning was viewed largely as a disease of adults due to occupational exposure. However, the particular sensitivity of children to lead exposure quickly became recognized. In combination with higher rates of gastrointestinal tract absorption, the nervous systems of children are more vulnerable to the toxic effects of lead, making childhood exposure a great concern. Thus, much effort has been put into public awareness campaigns and government interventions to reduce the level of this environmental toxicant.

Although mean national blood lead levels have decreased dramatically over the past 30 years in the United States, elevated levels are still found in specific areas, affecting mainly low-income, urban children and those living in older housing (Meyer et al., 2005). The most significant sources of lead continue to be old paint in homes built before 1978, lead pipes placed before the 1930s, and soil along highways and heavily traveled roads. A bimodal distribution of elevated blood lead levels in humans shows a peak for children (1–5 years of age) and a second one for adults >50 years of age (Pirkle et al., 1998). Therefore, despite intensive efforts to reduce lead use, exposure continues to be a major public health problem.

Due to lead’s effects on children, the major focus of the literature has been on the acute effects of lead exposure in developing animals. Although there is considerable consensus about the toxic effects of high levels of lead, the effects of low-level lead exposure are less clear. Human epidemiological studies have consistently found a strong association between lead and IQ. However, there is still considerable debate on these manifestations, due to highly confounding variables such as socioeconomic status and quality of parenting. Animal studies have confirmed a significant interaction between developmental lead exposure and the nature and persistence of neurotoxic effects manifested in cognitive defects such as learning and memory, although these effects are highly age- and dose-dependent (Finkelstein et al., 1998).

Numerous investigations focusing on the mechanism of lead neurotoxicity have found a wide array of effects, including apoptosis, excitotoxicity, interference with neurotransmitter storage and release mechanisms, alterations in second messengers, and damage to mitochondria (Lidsky and Schneider, 2003). Although there is no unifying mechanism, lead’s ability to substitute for calcium, and possibly zinc, is a factor common to many of its toxic actions. The disruption of dopaminergic functioning, which is involved in motor control and attention, as well as memory and executive functioning, can produce a host of behavioral problems, including attention deficit hyperactivity disorder and alterations in cognition (Brown et al., 1997). Also, lead has effects on glutamatergic transmission, which is a major player in both development and...
neuronal plasticity and is related to learning and memory impairments (Nihei and Guilarte, 2001). The effects of lead on the development of the nervous system establish the basis for cognitive impairments in lead-exposed children.

Gilbert and colleagues are the first to report a study relating lead exposure with hippocampal neurogenesis. In mammals, one germinial region where neurons are born is the subgranular zone (SGZ) of the hippocampal formation. In the SGZ, the stem cells involved in adult neurogenesis are believed to be a subset of astrocytes, which give rise to intermediate progenitors, which then mature locally into granule neurons of the dentate gyrus. Many of these newly generated neurons integrate into the existing circuitry of the hippocampus (Van Praag et al., 2002).

Gilbert and colleagues report that, despite the fact that developmental lead exposure reduced the viability of newly generated neurons in the dentate gyrus, developmental lead exposure did not subsequently alter spatial learning and memory in adult rats tested in the MWM. Designed over 20 years ago to evaluate spatial localization in rats (Morris, 1984), the MWM is one of the most commonly used behavioral assays in behavioral neuroscience (D’Hooge and De Deyn, 2001). The hippocampus, cerebellum, striatum, basal forebrain, and neocortex have been linked to successful performance in this assay (for a review, see D’Hooge and De Deyn, 2001). The glutamatergic and cholinergic systems play critical roles in performance (for a review, see McNamara and Skelton, 1993), although other systems also appear to be involved. Thus, we would predict that, if lead influences neurogenesis in the hippocampus, effects should be evident in MWM performance. So, why didn’t Gilbert and colleagues see impaired performance on this task? There are a number of possible explanations. Perhaps, as the authors suggest, neurogenesis in the adult dentate gyrus granule cell layer of the hippocampal formation has little to do with MWM performance. It is also possible that other learning and memory assays (e.g., fear conditioning, inhibitory avoidance) might have revealed deficits. Furthermore, the MWM has almost as many protocols as there are researchers using it. Perhaps a more challenging version of the maze would have uncovered subtle cognitive differences. These factors and others, require more study.

Other researchers who have attempted to assess the functional significance of adult hippocampal neurogenesis on behavior have relied on various ablation strategies, such as use of the methylation agent methylazoxymethanol (MAM) or selective irradiation of hippocampus that kills dividing cells. When these techniques were used, followed by examination for abnormalities in the MWM, no deficits could be found (Shors et al., 2002). Instead, effects on hippocampal-dependent fear-learning and a lack of response to antidepressants were seen (Santarelli et al., 2003; Shors et al., 2002). These findings emphasize an emerging role for the hippocampus in modulating emotional responses. The specific function of the dentate gyrus within the hippocampal circuitry still needs further elucidation.

While much of the research on lead exposure has focused on declines in learning and memory, there is a substantial amount of evidence showing that lead influences other behaviors such as mood (depression), anxiety, and violence/aggression. Needleman and colleagues (Needleman, 2004) have found associations between lead exposure and juvenile delinquency and criminal behavior. Relatedly, an emerging theory termed the fetal basis of adult disease, was recently put forth by David Barker (Barker et al., 2002). This theory posits that several adult diseases have developmental origins. Interestingly, relationships between early exposure to lead and neuropsychological abnormalities have been observed throughout the course of life, and chronic exposure to lead has been associated with the development of neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease (Prince, 1998; Winkel et al., 1995). Schizophrenia is also a plausible candidate, given that some of its premorbid features such as reduced attention, neurocognitive impairment, and diminished educational attainment strongly resemble the behavioral deficits associated with lead exposure (Jones, 1993). These findings suggest that developmental lead exposure can play a role in adult-onset neuropsychiatric or degenerative disorders. Furthermore, adult neurogenesis has been proposed as a key to understanding and even treating such phenomena as Alzheimer’s, depression, and schizophrenia (Mitchell et al., 2004).

While continued efforts are made to reduce lead exposure in humans, recent animal studies, including that by Gilbert and colleagues, have shown that low levels of lead have the potential to harm not only the young, but mature adults as well. The highlighted study emphasizes the need for further investigation of the behavioral consequences of modulating hippocampal neurogenesis by a toxicant. Obviously, efforts will continue to monitor children who are at risk for lead exposure, but there is also clearly a need to evaluate adults, who have had longer and more numerous exposures to lead.

REFERENCES


