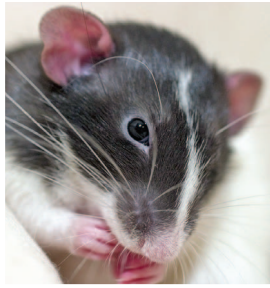
Lead and Retinal Function

Low Prenatal Exposure Suggests Future Abnormality

The harmful effects of low-level lead exposure on the development of cognitive, auditory, and visual-motor functions in children are well documented, but few studies have focused on the effects of low-level lead exposure specifically on retinal and visual functions. A rodent study reported this month provides new evidence that low levels of gestational lead exposure (GLE) can cause permanent retinal abnormalities in adult offspring and supports existing evidence that prenatal lead exposure can affect retinal development and function in humans even at blood lead levels below 10 µg/dL, the level of concern identified by the Centers for Disease Control and Prevention [***EHP* 116:618–625; Fox et al.**].

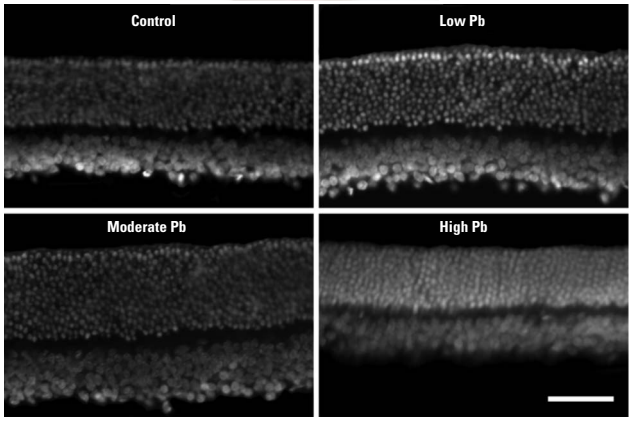


Researchers exposed two groups of female rats to lead in drinking water. A GLE group was exposed from 2 weeks before breeding through postnatal day 10 and a postnatal lead exposure (PLE) group from delivery through pup weaning. Each group was divided into four subgroups that were exposed to varying doses of lead (0 ppm [control], 27 ppm, 55 ppm, or 109 ppm). Maternal blood lead levels in the GLE rats were similar to those observed in human mothers whose children had experienced prenatal lead exposure.

The researchers included the PLE group for comparison because in previous studies PLE caused rod-selective cell death (apoptosis) and decreased retinal electrical activity as measured by an electroretinogram (ERG). Previous studies have demonstrated that postnatal blood lead levels greater than 20 µg/dL in lead-exposed humans and animals cause decreased ERG amplitudes ("subnormality"), whereas children exposed gestationally or postnatally who had blood lead levels of 6–16 µg/dL exhibited increased ERG amplitudes ("supernormality").

In the current study, when offspring in the GLE group reached adulthood, the researchers tested the animals' rod retinal function using an ERG, then counted the number of rods and cones in the rats' eyes. (Rods are photoreceptors active in low light; cones provide color vision.) Last, the researchers measured the synthesis of retinal dopamine, a neurotransmitter that regulates several retinal processes, including cell survival and eye growth.

Results from the GLE group showed an inverted dose–response curve typical of lead neurotoxicity. In adult offspring, low and moderate levels of GLE produced supernormal scoptic ERGs, increased numbers of rod cells and rod bipolar cells, and decreased dopamine synthesis and release in the absence of retinal injury, potentially heightening the likelihood of late-onset retinal degeneration. High levels of GLE produced opposite results.



Thickening of the adult rat retina following low or moderate exposure to lead reflects changes in cell numbers.

The authors note that the scotopic supernormal ERG can be a noninvasive biomarker of GLE. They also interpret the inverted dose–response curve as a sign of the retina's long-term vulnerability to low-level lead exposure during gestation. They acknowledge their data may raise complex issues for risk assessment and indicate that dose- and state-dependent effects are important in neurotoxicity risk assessment. –Valerie J. Brown

Neurotransmission on Fire?

Metabolic Activation Heightens Effect of PBDEs

Polybrominated diphenyl ethers (PBDEs) are man-made flame retardants used in a variety of consumer products, including fabrics, cushion foam, carpet pads, computers, and electronic equipment. Ubiquitous in the environment, PBDEs and their metabolites are being found in wildlife and humans, but little is known about the human health effects of these chemicals. A new study now reveals that 6-OH-BDE-47, a hydroxylated metabolite of the widely used BDE-47, induces a more potent response than the parent compound in terms of intracellular calcium concentration (denoted $[Ca^{2+}]_i$) and release of catecholamine neurotransmitters [***EHP* 116:637–643; Dingemans et al.**]. This finding suggests that metabolic activation could increase the neurotoxic potential of PBDEs.

$[Ca^{2+}]_i$ controls biological processes such as neurotransmitter release by fluctuating in response to chemical and electrical signals. In cell culture studies, high concentrations of PBDEs induced an increase in intracellular Ca^{2+}. *In vitro* endocrine studies have further revealed that 6-OH-BDE-47 interacts more strongly with hormone receptor systems than its parent compound. Preliminary evidence suggests that exposure to high concentrations of PBDEs may cause neurobehavioral alterations and affect the immune system in animals. Exposure of newborn mice to high concentrations of BDE-47 alters behavior, learning and memory, and brain protein density and enzyme activity.

The authors used cultured rat pheochromocytoma (PC12) cells, which secrete catecholamines upon stimulation, to compare the effects of 6-OH-BDE47 with those of BDE-47 on intracellular Ca^{2+} balance and catecholamine release. Members of the team had earlier measured the frequency of vesicular catecholamine release in individual cells in response to 6-OH-BDE-47 exposure and found that a high concentration of BDE-47 (20 µM) could trigger catecholamine release in PC12 cells. In the current study, they found that a lower concentration (5 µM) of 6-OH-BDE-47 caused an even stronger response. Moreover, 1 µM 6-OH-BDE-47 caused an initial transient increase in $[Ca^{2+}]_i$ that was temporally related to catecholamine release. At 6-OH-BDE-47 concentrations of 1 µM or higher, they observed a delayed, dose-dependent increase in $[Ca^{2+}]_i$. Additional experiments revealed that the initial increase originated from emptying of the endoplasmic reticulum, whereas the delayed increase originated primarily from mitochondria.

Based on these findings, the authors conclude that 6-OH-BDE-47 can disrupt intracellular Ca^{2+} levels and trigger neurotransmitter release at lower levels than its parent compound, BDE-47. This conclusion suggests the neurotoxic potential of PBDEs may be strongly enhanced by oxidative metabolism, which is especially relevant for children, who may be exposed to higher levels of PBDE than adults at a time when their brains are still developing. Given recent findings that hydroxylated PBDE metabolites, including 6-OH-BDE-47, bioaccumulate in the serum of children, further investigation of potential neurotoxicity is vital. –Julia R. Barrett

Top to bottom: Alexey Krasavin; Fox et al.

PAHs from the Inside Out

Birth Outcomes Vary among Ethnic Groups in NYC

In humans, the developmental hazards associated with exposure to urban ambient air pollution, particularly polycyclic aromatic hydrocarbons (PAHs), continue to be debated. PAHs are formed during the incomplete burning of fossil fuels, wood, and tobacco products, with high levels found in automobile exhaust and industrial emissions. This month, researchers at Columbia University report that prenatal exposure to PAHs affects birth outcomes differently in pregnant African-American and Dominican women [***EHP* 116:658–665; Choi et al.**].

Previously the same group showed that approximately 40% of the children studied had *in utero* DNA damage as a result of exposure to air pollution from fossil fuel combustion. The same group has also examined the link between prenatal exposure to airborne PAHs and intrauterine growth restriction, a condition in which the fetus is smaller than expected for the length of pregnancy, and has shown a relationship between prenatal exposure to PAHs and reduced birth weight in African Americans in New York City and whites in Krakow, Poland.

In the current prospective study, the team recruited women from local prenatal care clinics in New York City. The women lived in three neighborhoods served by Columbia's Mailman School of Public Health. The target population was limited to women aged 18–35 who did not use tobacco products or illicit drugs; did not have diabetes, hypertension, or known HIV; and had started prenatal care by the twentieth week of pregnancy.

The researchers interviewed each woman in the last trimester of pregnancy, in her home, to obtain information on health, lifestyle, and exposure history. They also gave each woman a small backpack containing an air monitor for measuring PAH exposure. The personal air monitor operated continuously over a 48-hour period at 4 L per minute to simulate normal lung capacity, collecting particulate and semivolatile vapor and aerosol PAHs. Filters were replaced every 48 hours and analyzed for pyrene and carcinogenic PAHs, including benzo[*a*]pyrene (BaP), which has been associated with adverse reproductive and developmental effects in laboratory animals and humans.

The investigators collected birth outcome information from medical records, including gestational age, which was estimated by attending clinicians and validated by sonogram. The analysis included 616 mother–child pairs. The results showed universal and variable personal exposure to PAHs, with a mean exposure to BaP (0.368 ng/m^3) consistent with the ambient BaP level in New York City.

Among African Americans, prenatal PAH exposure increased the risk of preterm delivery and the likelihood of infants being born small for gestational age (SGA; meaning birth weight is below the tenth percentile of babies of the same gestational age). As prenatal PAH exposure increased, so did cephalization index, a ratio of head circumference to birth weight that can presage developmental problems later in childhood.

Among Dominicans, there was no association between airborne PAH exposure and significant increase in risk of SGA, reduced birth weight ratio, increased cephalization index, or preterm delivery. This could reflect healthful cultural practices among recent Dominican immigrants such as more nutritious diets and more supportive social networks. The possible health-protective effects of the Dominicans' cultural habits and the specific factors underlying the greater vulnerability of the African-American subjects warrant further study. –David A. Taylor

Hold that Thought

Organochlorines May Alter Infant Attention Skills

From the mid-1940s on, a group of synthetic chemicals known as organochlorines (OCs) were used in industry and as pesticides. Because of evidence of human and environmental risks from exposure to some of these chemicals, the Environmental Protection Agency in the 1970s banned the use of two—the pesticide DDT and a class of industrial chemicals known as polychlorinated biphenyls (PCBs). Despite the ban of more than 30 years, residues of these persistent, bioaccumulative chemicals are still found in human tissue. Now researchers have found evidence of an association between poor attention skills in early infancy and low-level prenatal exposure to PCBs and *p,p′*-DDE, the chief metabolite of DDT [***EHP* 116:666–673; Sagiv et al.**].

Previous studies have shown associations between PCB exposure and attention deficits in adults and school-age children. In the current study, the authors sought to investigate whether these associations could be detected in early infancy using the Neonatal Behavioral Assessment Scale (NBAS) to assess infants' visual and auditory stimuli responses, motor tone and motor activity levels, and ability to regulate crying, alert, and sleep states. These behavioral items identify the infant's capacity for attention as well as abilities potentially associated with attention, such as state regulation and motor maturity.

Soothability can predict later attention skills

Hilary Brodey/Stockphoto

The present study included infants born between 1993 and 1998 to mothers who lived near a PCB-contaminated harbor in New Bedford, Massachusetts. The NBAS was administered to infants twice: between 1 and 3 days after birth and between 5 and 22 days after birth. The researchers also administered questionnaires to mothers of the infants to collect demographic data on household income; medical and reproductive histories; drug, alcohol, and tobacco use; race and ethnicity; and occupational and exposure histories pertinent to outcomes of interest.

To determine OC levels in the infants, the researchers analyzed infant cord serum samples, taken at birth, for 51 PCB congeners and *p,p′*-DDE. Of the total serum samples, 96% had detectable DDE levels; depending on the PCB congener, anywhere from fewer than 1% to 91% of the infants had detectable serum levels. For the 542 infants that completed both exams, statistical analysis revealed a decline in scores of attention with increased serum levels of DDE and of PCBs. The exposure-associated declines were less pronounced for abilities associated with attention, including state- and motor-associated outcomes.

The authors acknowledge the uncertainty of the NBAS in accurately predicting attention behaviors that may occur later in childhood. Future studies should examine whether the attention deficits observed in the current study in association with organochlorine exposure persist into childhood. –Tanya Tillett