Unexpected findings of lead exposure may lead to treating blindness

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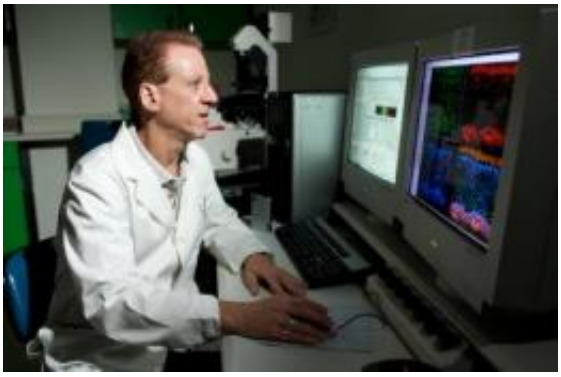

Donald Fox analyzes results from images taken with his lab's confocal microscope. Credit: Thomas Campbell

Some unexpected effects of lead exposure that may one day help prevent and reverse blindness have been uncovered by a University of Houston (UH) professor and his team.

Donald A. Fox, a professor of vision sciences in UH's College of Optometry (UHCO), described his team's findings in a paper titled "Low-Level Gestational Lead Exposure Increases Retinal Progenitor Cell Proliferation and Rod Photoreceptor and Bipolar Cell Neurogenesis in Mice," published recently online in *Environmental Health Perspectives* and soon to be published in the print edition of the prestigious peer-reviewed journal.

The study suggests that lead, or a new drug that acts like lead, could transform human embryonic retinal stem cells into neurons that would be transplanted into patients to treat retinal degenerations.

"We saw a novel change in the cellular composition of the retina in mice exposed to low levels of lead during gestation. The retina contained more cells in the rod vision pathway than normal or than we expected," said Fox, who also is a professor of biology and biochemistry, pharmacology and health and human performance. "The rod photoreceptors and bipolar cells in this pathway are responsible for contrast and light/dark detection. These new findings directly relate to the supernormal retinal electrophysiological changes seen in children, monkeys and rats with low-level gestational lead exposure."

Fox said these effects occur at blood lead levels at or below 10 micrograms per deciliter, the current low-level of concern by the Centers for Disease Control and Prevention. Because the effects occur below the "safe level," Fox says it raises more questions about what should be considered the threshold level for an adverse effect of lead on the brain and retina.

Fox has studied lead toxicity for 35 years, specifically as it relates to its effects on the brain and retina of children. His interest in gestational lead exposure started in 1999, when he and colleague Stephen Rothenberg studied a group of children in Mexico City whose mothers had lead exposure throughout their pregnancies. The study was funded to measure the adverse effects of lead poisoning on the nervous system of children born in Mexico City – a city that has elevated levels of lead in the air due to the use of leaded gasoline, as well as continued use of lead-containing pottery and glassware for food preparation. The study was funded by the U.S. Environmental Protection Agency and the Mexican government and was published in 2002 in the journal Investigative Ophthalmology and Visual Sciences.

Supported by a $1.7 million National Institutes of Health (NIH) grant, Fox and his group set out to find possible reasons for this supernormal retinal response in children. The researchers employed rat and mice models that covered the three levels of lead found in the blood of the Mexico City mothers – some below, some right at and some higher than the CDC "safe level." The researchers exposed rodents to lead throughout pregnancy and the first 10 days of life, which is a time period equivalent to human gestation.

Fox said that the early-born retinal progenitor cells give rise to four neuron types, which were not affected by lead exposure. The later-born retinal progenitor cells, he said, give rise to two types of neurons and a glial cell. Surprisingly, only the late-born neurons increased in number. The glial cells, which nurture neurons and sometimes protect them from disease, were not changed at all. The rats and mice both had "bigger, fatter retinas," according to Fox. Interestingly, the lower and moderate doses of lead produced a larger increase in cell number than the high lead dose.

"This is really a novel and highly unexpected result, because lead exposure after birth or during adulthood kills retinal and brain cells, but our study showed that low-level lead exposure during gestation caused cells to proliferate, increased neurons and did not affect glia," Fox said. "So, gestational exposure produces an exact opposite to what was previously shown by our lab and others. It also shows that the timing of chemical exposure during development is just as important as the amount of exposure."

This brought the researchers to a crossroads. On the one hand, the retina is not built to have all these extra cells and, according to unpublished data from Fox's mouse studies, the retinas will start to degenerate as the mice age. This suggests that the retinas of the children from the original Mexico City study should be examined as they might start to degenerate

when they are 40 years of age.

"This work has long-term implications in retinal degeneration and diseases where photoreceptors die. If we can figure out how low-level lead increases the number of retinal progenitor cells and selectively produces photoreceptors and bipolar cells, then perhaps a drug can be created to help those with degenerative retinal diseases that eventually cause blindness," Fox said. "Researchers may be able to use lead as tool in transforming embryonic retinal stem cells into rods and bipolar cells that could be transplanted into diseased retinas, ultimately saving sight and reversing blindness."

Fox said that more research is needed before such a potential drug could be developed to mimic the effects of lead. Ideally, this drug would induce human embryonic retinal stem cells to form rods and bipolars that could be transplanted into patients to treat early stages of retinal degeneration.

More information: A copy of the article can be found at ehp03.niehs.nih.gov/article/in … /10.1289/ehp.1002524

Provided by University of Houston