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In what ways does lead damage the brain?

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Exposure to lead wreaks havoc in the brain, with consequences that include lower IQ and reduced potential for learning. But the precise mechanism by which lead alters nerve cells in the brain has largely remained unknown.

New research led by Tomás R. Guilarte, PhD, Leon Hess Professor and Chair of Environmental Health Sciences at Columbia University Mailman School of Public Health, and post-doctoral research scientist Kirstie H. Stansfield, PhD, used high-powered fluorescent microscopy and other advanced techniques to painstakingly chart the varied ways lead inflicts its damage. They focused on signaling pathways involved in the production of brain-derived neurotropic factor, or BDNF, a chemical critical to the creation of new synapses in the hippocampus, the brain's center for memory and learning.

The study appears online in the journal *Toxicological Sciences*.

Once BDNF is produced in the nucleus, explains Dr. Stansfield, it is transported as cargo in a railroad-car-like vesicle along a track called a microtubule toward sites of release in the axon and dendritic spines. Vesicle navigation is controlled in part through activation (phosphorylation) of the huntingtin protein, which as its name suggests, was first identified through research into Huntington's disease. By looking at huntingtin expression, the researchers found that lead exposure, even in small amounts, is likely to impede or reverse the train by altering phosphorylation at a specific amino acid.

The BDNF vesicle transport slowdown is just one of a variety of ways that lead impedes BDNF's function. The researchers also explored how lead curbs production of BDNF in the cell nucleus. One factor, they say, may be a protein called methyl CpG binding protein 2, or MeCP2, which has been linked with RETT syndrome and autism spectrum disorders and acts to "silence" BDNF gene transcription.

The paper provides the first comprehensive working model of the ways by which lead exposure impairs synapse development and function. "Lead attacks the most fundamental aspect of the brain—the synapse. But by better understanding the numerous and complex ways this happens we will be better able to develop therapies that ameliorate the damage," says Dr. Guilarte.

Provided by Columbia University