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How lead exposure damages the brain: New research fills in the picture

June 22 2010

Effective brain function depends on the efficient signaling from one neuron to the next, a lightning-fast process that depends on a quick release of neurotransmitters at synapses. Exposure to lead during early childhood and even later in life has long been known to affect the release of these critical neurotransmitters. However, the precise mechanism by which lead ions (Pb2+) impair this process has remained unknown.

A new study led by Tomás Guilarte, PhD, chair of Environmental Health Sciences at Columbia University's Mailman School of Public Health, helps fill in the picture. Guilarte's study demonstrates that during the formation of synapses—synaptogenesis—exposure to lead alters the levels of several key proteins involved in neurotransmitter release.

Specifically, it produces a loss of the proteins synaptophysin and synaptobrevin. It also increases the number of pre-synaptic contact sites, but these sites appear to be missing these key proteins. His work suggests that these changes are mediated by the inhibition of the N-methyl-D-aspartate receptor (NMDAR), disrupting the release of the trans-synaptic signaling neurotrophin, brain-derived neurotrophic factor (BDNF).

The study, led by Dr. Guilarte and conducted by graduate student April Neal and a team at Johns Hopkins Bloomberg School of Public Health and the School of Medicine, appears in the current issue of *Toxicological Sciences*.

New synapses are formed throughout a healthy person's lifespan, but

there is an explosion of synapse formation during a child's early brain development. During development, packets of preassembled proteins arrive at presynaptic active zones (PAZ), which are highly specialized regions designed to provide fast efficient neurotransmitter release. Disruption of this normal developmental process can impair brain function throughout life—as is the case with early lead exposure.

"What this work shows is that we are beginning to understand a comprehensive mechanism by which lead exposure alters the basic molecular biology of brain synapses," says Dr. Guilarte, who is also Leon Hess Professor of Environmental Health Sciences. "Our results are the first to explain precisely how the vesicular release of neurotransmitters is impaired."

Provided by Columbia University