

Developmental Lead Exposure: Mechanisms of Sleep and Metabolic Disturbances

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Abstract

Lead (Pb) is a well-established neurotoxicant; yet, despite dramatic reductions in Pb exposure within the United States over the past few decades, Pb exposure persists as an unresolved health problem. Exposure to Pb during fetal and early postnatal development is associated with decreased fetal and childhood growth, cognitive defects, attention deficit hyperactivity disorders, and auditory and language impairments. Recently, Dr. Jianghong Liu (a member of the CEET) made the novel observation that blood Pb levels predict long-term sleep disturbances in children. Persistent sleep disruption and attention deficit disorders are consistent with injury to locus coeruleus neurons (LCn). In preliminary studies in mice exposed to Pb during adulthood, we found sleep disturbances and injury to and loss of LCn. Intriguingly, derangements in sleep also affect glucose homeostasis and appetite control and may contribute to the increased risk of metabolic dysfunction in children exposed to Pb. Previous studies in an animal model of gestational Pb exposure show that offspring have altered food intake, increased adiposity, and insulin resistance later in life. The epigenetic machinery plays a fundamental role in regulation of gene expression during early development and provides a mechanism by which environmental exposures can alter the phenotype to induce a disease state or allow for adaptation to an adverse environment. The human brain undergoes epigenetic changes throughout life and alterations in epigenetic determinants are linked to neurodevelopmental disorders. Thus, we hypothesize *that early life exposure to Pb induces epigenetic changes at key genes essential for neuronal connectivity in the LCn, which in turn result in permanent sleep and metabolic disorders.*