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Consequences of lead exposure, and it's emerging role as an epigenetic modifier in the aging brain

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ABSTRACT

Lead exposure has primarily been a concern during development in young children and little attention has been paid to exposure outcomes as these children age, or even to exposures in adulthood. Childhood exposures have long term consequences, and adults who have been exposed to lead as children show a host of cognitive deficits. Lead has also been shown to induce latent changes in the aging brain, and has been implicated in the pathogenesis of neurodegenerative diseases, particularly Alzheimer's Disease, and Parkinson's. Recent research has shown that lead has the ability to alter DNA methylation, histone modifications, and miRNA expression in experimental models, and in humans. These findings implicate epigenetics in lead induced toxicity, and long term changes in individuals. Epigenetic modification could potentially provide us a mechanism by which the environment, and toxic exposures contribute to the increased susceptibility of adult neurodegenerative disease.

1. Introduction

As we age our bodies grow increasingly susceptible to environmental injury and insults, the brain in particular is at great risk (Peters, 2006). Interestingly, there aren't many toxicants that are discussed in the context of age related changes and abnormalities. A classic neurotoxin, that has been studied for it's role in childhood and developmental toxicity is the environmental agent lead (Pb). Historically, the toxic effects of lead have been researched and documented extensively as related to children and adolescents, however, the impact of past exposure to lead on the aging brain was not a major concern. There have been devastating cases of lead encephalopathy involving both adults and children, which is defined as a medical emergency, and observed when individuals have blood lead levels (BLLs) over 70 μg/dL (Abadin et al., 2007). Infants who have suffered acute exposure experience sever brain damage, and impaired neurological outcomes at doses even lower than what is considered lead encephalopathy (56 μg/dL) (al Khayat et al., 1997).

A dangerous property of lead is it's ability to interact and bind to calcium (Pounds et al., 1991). Over 95% of lead stores have been found to be deposited into bone, and it is considered a primary source of exposure. Measurements of both blood and bone lead levels provide researchers with evidence on how recent and past lead exposure may have occurred. Lead has been shown to be mobilized from the bone during periods of the human lifespan in which bone resorption/growth are occurring, for example during osteoporosis and pregnancy (Silbergeld, 1991), giving lead the ability to induce toxic effects over prolonged periods of time, without recent exposure. Lead has also been shown to compete with Zinc, in a number of physiological interactions. It has a similar affinity for motifs and receptors that are typically occupied by zinc, and ultimately is able to modify transcription. The effects of lead exposure on transcription, and it's dynamics with zinc have been extensively reviewed (Zawia, 2003).

In this review, we will discuss some of the classical outcomes as a result of lead exposure, but will focus on the role of lead in neurodegenerative and adult disease. We will introduce the role lead may have in regulating gene expression by way of epigenetics, and provide compelling evidence for lead as an epigenetic modifier.

1.1. Adult consequences of childhood exposure to lead

Childhood exposure to environmental lead has been heavily implicated in cognitive dysfunction during early years. The toxicant has been identified as a clear disruptor of

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neurodevelopment in early life, shown to impair academic performance in school age children, and to negatively impact intelligence scores (Lanphear et al., 2005; Lidsky and Schneider, 2003; Lidsky and Schneider, 2006; Faust and Brown, 1987; Rosen, 1995; Bellinger et al., 1992; Dietrich et al., 1993). Furthermore, children who have unfortunately been exposed to lead during development have shown cognitive dysfunction that continues into adulthood. Early studies examined children who suffered from lead encephalopathy in the first four years of life, were found to have decreased scores on a battery of neuropsychological tests (White et al., 1993). Similar findings were reported in a group of young adults (aged 19–29), who resided nearby a lead smelter facility during childhood (Stokes et al., 1998). More recently, a study conducted in Boston MA examined young adults (mean age 29) and their cognitive function, by IQ tests. Individuals were known to have low-level (<10 μg/dL) environmental lead exposure during childhood, and had measurements of blood lead taken at 6, 12, 18, 24 and 57 months, and again at 10 years of age (Mazumdar et al., 2011). The study reported lower IQ test scores in individuals with higher levels of exposure during childhood (Mazumdar et al., 2011).

Longitudinal studies have been carried out to characterize the changes in brain development that are associated with this early exposure, namely in terms of brain volume reduction in specific regions. The Cinncinatti Lead Study (CSL) recruited a birth cohort from Cincinnati between 1979 and 1984, infants were excluded if they had low birth weight, or medical issues (Dietrich et al., 1987). The CSL reported childhood BLLs were associated with regions of brain volume reduction in adult gray matter. Specifically this loss occurred in the prefrontal cortex, in regions associated with executive function control, behavioral modulation and fine motor control (Cecil et al., 2008). Furthermore, a subset of adults were recruited to high resolution volumetric magnetic imaging, and these changes were related to mean blood levels in the first six years of life. Significant inverse associates between age, gray matter volume and BLLs were observed, with the strongest reductions in adult gray matter associated with BLLs measurements at 5 and 6 years of age (Brubaker et al., 2010). Further analysis of this cohort revealed significantly decreased levels of *N*-acetyl asparatate metabolite in gray matter as measured by proton magnetic resonance spectroscopy (Cecil et al., 2011), these findings were replicated in a similar cohort (Trope et al., 2001). These observations implicate lead in long lasting brain abnormalities that impact cognitive function negatively.

1.2. Exposures in adult populations

Evidence that exposure to lead is associated with cognitive decline is present from several longitudinal and cross-sectional epidemiological studies in the elderly. The onset of cognitive decline is an important intermediary for the development of neurodegenerative diseases, specifically Alzheimer's disease. The Baltimore Memory Study (BMS) was conducted to investigate determinants of cognitive decline while taking into account variables such as socioeconomic status, and environmental exposures (Shih et al., 2006; Schwartz et al., 2004). The cohort included individuals aged between 50 and 70 years, who lived in neighborhoods near Baltimore MD, and measured both blood and tibia lead levels (Shih et al., 2006; Schwartz et al., 2004). Results from the BMS indicated mean tibia levels were inversely correlated with cognitive function in all six domains tested, such as executive functioning, processing speed, and verbal memory and learning (Shih et al., 2006; Bandeen-Roche et al., 2009). Similar findings were reported by the Normative Aging Study (NAS) which began in 1963 and was conducted at the Veterans Affairs outpatient clinic in Boston, MA (Bell et al., 1972). NAS enrolled 2000 male veterans with the goal of investigating processes behind normal aging. They examined lead bone levels and results of the mini-mental state examination within this cohort, and reported higher bone levels are associated with worsened cognition (Weisskopf et al., 2004; Wright et al., 2003). These findings were expanded in subsequent years, and the cohort was examined using a battery of cognitive tests, such as the Wechler Adult Intelligence Scale- Revised results indicated a further decline in cognitive scores across all domains (Weisskopf et al., 2007).

While most of the studies performed have focused on examining cognitive function in males, there are a small number that have contributed to our understanding of the effects of lead primarily on women. The Nurse's Health Study established in 1976 began to collect health information from registered nurses in the United States, the study has continued to monitor health outcome changes every two years until the present day, and has a participation of >90% of individuals since its establishment (Colditz and Hankinson, 2005). Weuve et al., reported on a subset of the Nurse's study, and examined blood, tibia, and patella levels of lead in relation to current cognitive function in community dwelling women. The study identified the three biomarkers of lead exposure were associated with worsened cognitive function in women, however only tibia levels were significantly higher (Weuve et al., 2009). These studies were replicated by others, where tibia levels were significantly associated with cognitive decline (Power et al., 2014).

1.3. Occupational exposures

Due to our increased knowledge and awareness of the dangers of lead toxicity, exposures have been relatively controlled for most community dwelling individuals, while those exposed to lead in the workplace remain at risk. Both cross-sectional and longitudinal studies have been conducted in workers exposed to lead, with studies occurring both in the United States and abroad. The Lead Occupational Study originally began in 1982, and examined 288 male workers with exposure to lead for a minimum of one year, while working at a lead battery plant in Pennsylvania. Cognitive functions were analyzed using the Pittsburg Occupational Exposures Tests (POET) (Parkinson et al., 1986). POET results of this initial analysis found only significant associations between bone and BLLs and psychomotor speed (Ryan et al., 1987a; Ryan et al., 1987b). Members of this cohort were analyzed again to examine longitudinal changes in cognitive function. Khalil et al., reported that individuals who were reexamined had lower cognitive performance compared to control, as well as lower cognitive performance longitudinally. Unlike the initial study, the cognitive disruptions were observed between peak tibia lead levels, spatial ability, learning and memory and overall cognitive scores as determined by the POET battery test. Furthermore, when these results were examined by age it was determined that older individuals (>55 years) had more severe cognitive declines and dysfunctions than their younger counterparts (Khalil et al., 2009).

These findings were also observed in the Organolead study, which began in 1994 to examine the effects of tetraethyllead manufacturing on cognitive functioning, based on earlier efforts from researchers at Johns Hopkins (Schwartz et al., 1993). The cohorts last known lead exposure was 16 years prior, results indicated mean tibia lead levels were inversely correlated with neurobehavioral tests scores in the domains of manual dexterity, executive functioning, intelligence and memory (Stewart et al., 1999). Individuals were examined again two years later, with further associations of cognitive decline in relation to tibia lead levels in all areas (Schwartz et al., 2000). Studies abroad have also focused on studying the effects of lead exposure in the workplace. The Korea Lead Study began in 1997 and examined both current

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