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Short review

Both physiology and epidemiology support zero tolerable blood lead levels

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ABSTRACT

Inorganic lead is one of the most common causes of environmental metal poisonings, and its adverse effects on multiple body systems are of great concern. The brain, along with the kidneys, are critically susceptible to lead toxicity for their hosting of high affinity lead binding proteins, and very sensitive physiology. Prolonged low-lead exposure frequently remains unrecognized, causes subtle changes in these organ systems, and manifests later at an irreversible stage. With the repeated documentation of "no safe blood lead level", the pernicious effects of lead at any measurable concentration need to be emphasized. In this review, we surveyed articles on chronic low-level lead exposures with a blood lead concentrations < 10 μg/dL and the development of neurobehavioral or renal disorders. The negative impacts of lead on both nervous and renal systems were obvious at a blood lead concentration of 2 μg/dL, with the absence of any detectable threshold. The deleterious effect of lead on two different organ systems at such low concentrations drew our attention to the various extracellular and intracellular events that might be affected by minimal concentration of body lead, especially blood lead. Is there a true common ground between low-level lead toxicity in both the nervous system and the kidney?

1. Introduction

In developed countries, efforts to control lead exposure has lowered the prevalence of high blood lead levels, but low-level lead poisoning remains a matter of concern (Flora et al., 2012). Chronic environmental lead exposures can damage various organs like the brain and the kidneys insidiously (Public Health Service, 2007). Low-level lead exposures impact multiple domains of the nervous system, specifically intelligence quotient (IQ) and memory (Bandeen-Roche et al., 2009; Lidsky and Schneider, 2003; Public Health Service, 2007). The lost opportunity cost for each 1 point decrease in IQ is 2.4% (World Health Organization, 2010) and below 10 μg/dL, each 1 μg/dL increase in the lifetime average blood lead concentration (PbBs) is associated with a 1.37 points decline in IQ (Canfield et al., 2003).

Alongside the nervous system, the kidneys also appear to be very sensitive to lead poisoning. Although the toxicity patterns change with decreased exposure levels, the relation between levels of lead and various kidney functions has repeatedly been documented. The availability of newer, sophisticated pathology techniques has aided the recognition of a link between lead and renal functions at much lower levels than previously possible.

The average blood lead level (BLL) in US children is 1.3 μg/dL (Centers for Diesease Control and Prevention, 2013). Despite this recent decrease in lead exposure, lead related neurobehavioral abnormality and impaired kidney functions are still a real problem among children, particularly of low socioeconomic status (World Health Organization, 2010).

2. Low-level lead toxicity observed in various epidemiological and experimental studies

2.1. Neurotoxicity

The effects of low lead on the central nervous system (CNS) are predominantly manifested as neurobehavioral impairments, including mental retardation and cognitive deficit (Mason et al., 2014; Public Health Service, 2007). In this review of both epidemiological and experimental studies, lead has been associated with various neurobehavioral impairments at BLLs below 10 μg/dL. Most recently, the Centers for Disease Control and Prevention recommended a reference value of 5 μg/dL in accordance with the 97.5th percentile of the National Health and Nutrition Examination Survey (NHANES)'s blood lead distribution among children (Centers for Diesease Control and Prevention, 2013). Advanced studies have shown that BLLs < 5 μg/dL have a negative impact on the nervous system. The dose-response slope correlating PbBs and children's mental development index (MDI) was steeper at PbBs levels < 5 μg/dL compared with PbBs levels > 5 μg/dL (Tellez-Rojo et al., 2006).

Epidemiological studies have shown that children exposed to environmental lead during their early life suffered from reduced IQ

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(Canfield et al., 2003; Chiodo et al., 2004; Lanphear et al., 2000; Mason et al., 2014). Early childhood is very important for the development of the central nervous system (Lanphear et al., 2000). In experimental studies, BLLs of 1.98 μg/dL to 2.02 μg/dL were associated with neurobehavioral problems such as reduced olfactory recognition and exploratory activity, as well as reduced memory, learning capabilities and intelligence in mice (Flores-Montoya et al., 2015; Flores-Montoya and Sobin, 2015). A depletion in the number of microglia and dentate gyri was found in mice with BLLs 2.48–20.31 μg/dL. Another group of mice with BLLs 2.48–4.65 μg/dL showed broad variability in their mean microglial cell volume. In response to a CNS lead insult, microglial cells developed altered cellular morphology, mostly enlargement of cell sizes (hypertrophy) (Perry et al., 2010). These phenomena indicate that some adverse effects of lead depend on duration of exposure, rather than on lead concentration (Sobin et al., 2013), and different BLLs may use different mechanisms for inducing toxicity.

In the assessment of academic performance in children, PbBs were strongly associated with attention deficit and decreases in reading and math composite scores. Reading skill was more deeply affected. BLLs ≥ 5 μg/dL were associated with a 25% increase in academic failure, and in the range of 2–9 μg/dL, a 5 μg/dL rise in BLL was associated with a 32% increase in failure in reading and math (Evens et al., 2015). The odds of ADHD were 2.8 times higher among children with BLL > 2.18 μg/dL compared to those with BLL < 2.18 μg/dL (Kim et al., 2010). At BLLs < 5 μg/dL, each unit increase in blood lead concentration lowered 1 point in reading and 0.7 in math scores (Lanphear et al., 2000), and PbBs below this level showed an inverse relation with cognitive or academic function, without detection of any threshold point (Chiodo et al., 2004; Lanphear et al., 2000). In children, a linear relationship between blood lead concentration and neurobehavior with 15 end points was identified without detection of any threshold level for lead neurotoxicity (Chiodo et al., 2004). The negative impact of lead on children's intelligence became conspicuous when study samples were dichotomized at BLLs of 2 μg/dL or 3 μg/dL (Chiodo et al., 2004; Evens et al., 2015; Kim et al., 2010; Lanphear et al., 2000). The associations present below this level were not significant, probably due to small sample size, imprecision of the association of very low doses of lead with neurobehavioral outcomes, and difficulty in assessing younger children in all domains of IQ with reliability (Lanphear et al., 2000).

Lead disrupts synapse formation and plasticity in developing neurons, impairs neurotransmitter release, and alters the function of GABAergic, dopaminergic, and cholinergic systems (Mason et al., 2014; Public Health Service, 2007). BLL 2–3 μg/dL adversely affect the developing brain, and calculations point to a non-threshold dependence. Children exposed to any amount of lead are at risk for various neurobehavioral problems, mostly learning difficulties and low intelligence.

2.2. Nephrotoxicity

For many years, chronic high-lead exposure was known to be associated with development of lead nephropathy. In this review, we found a convincing relation between abnormal renal function and BLLs < 10 μg/dL (Fadrowski et al., 2010; Lai et al., 2008; Muntner et al., 2003; Osman et al., 1999; Spector et al., 2011; Tsaih et al., 2004). Most of the studies revealed significant changes in kidney functions notably low glomerular filtration rate (GFR) around BLLs 2–3 μg/dL (Basgen and Sobin, 2014; Fadrowski et al., 2010; Muntner et al., 2003; Osman et al., 1999; Spector et al., 2011; Tsaih et al., 2004). At BLLs > 1 μg/dL, cystatin C estimated GFR was −1.4 ml/ min/1.73 m^2 (95% CI: −7.4 to 4.5) less compared to GFR at BLL < 1 μg/dL in US adolescents. Above Pb concentrations of 2.9 μg/dL, it decreased by 6.6 ml/ min/1.73 m^2 (95% CI: −12.6 to −0.7, p = 0.009) compared to GFRs at BLL < 1 μg/dL (Fadrowski et al., 2010). In a sample of 3941 subjects from a US population with geometric mean blood lead of 1.7 μg/dL, rising blood lead concentrations were inversely related to the GFR level estimated with all types of equations (Spector et al., 2011). In a lab study, mice with BLLs from 2.4 μg/dL to 4.7 μg/dL developed glomerular hypertrophy due to increase in mesangium and capillary volumes (Basgen and Sobin, 2014), ultimately resulting in glomerular hyperfiltration. This outcome is consistent with the findings of an epidemiological study showing an increase in GFR and decreases in serum levels of creatinine, cystatin C and β_2 microglobulin at low BLL (> 5.5 μg/dL) concentrations, without detection of a threshold point (de Burbure et al., 2006). BLLs > 7 μg/dL were associated with increased urinary protein HC secretion and hyperuricemia, indicating impaired tubular function (Lai et al., 2008; Osman et al., 1999). In experimental studies, a 4-month ingestion of 0.06% lead acetate by rats caused alteration of both glomerular and tubular basement membrane structure, including modified laminine-1 and fibronectin expression. Thinning of the glomerular basement membrane (GBM) and alteration of filtration units resulted in microalbuminuria (Perkins et al., 2007). Mice exposed to low dose lead for 14 weeks developed focal areas of tubular dilatation and disruption, and loss of tubular cell brush border (Rodríguez-Iturbe et al., 2005). In studies of adult populations, lead at very low dose was associated with significant impairment of renal function among people having other comorbidities such as hypertension, diabetes, and age > 60 (Muntner et al., 2003; Spector et al., 2011; Tsaih et al., 2004). Among hypertensive people with a blood lead level ranging from 2.5 μg/dL to 3.8 μg/dL, prevalence of lead associated elevated Scr and chronic kidney disease were 12.1% and 10.4% respectively (Muntner et al., 2003). Chronic exposure to low-dose lead was associated with elevation of systolic blood pressure and enhancement of contractility in the rat aorta (Silveira et al., 2014).

Several studies proclaimed significant inverse relationship between kidney function and blood lead below 5 μg/dL (Fadrowski et al., 2010; Muntner et al., 2003; Spector et al., 2011; Tsaih et al., 2004). The dose-dependent inverse linear relationship persisted without discontinuation from linearity or detection of any threshold point (Fadrowski et al., 2010).

Low-lead exposure alters glomerular and tubular structures and glomerular capillary pressure. This may result in renal tubular dysfunction and altered glomerular filtration rate (GFR), which signal decreased kidney function. Individuals exposed to chronic low-levels of lead are likely to exhibit worse prognosis in the potential for progressive renal decline.

Very few studies have been carried out on nephrotoxicity due to low-level lead exposure. More studies are required, especially on children, because of their sensitivity to lower doses. Moreover, as children are free from various adverse effects of aging, a more precise association can be established between lead and kidney diseases (Tables 1 and 2).

3. Mechanisms involved in the development of neurotoxicity and nephrotoxicity at very low doses of lead

Lead induces cellular toxicity through multiple pathways. Because calcium changes are linked with all pathways it is difficult to identify a single one as dominant. They couple with each other in altering cellular homeostasis and produce toxicity.

3.1. Ionic mimicry/ionic substitution

Lead mimics or replaces calcium, iron, magnesium, and zinc. It enters into cells through multiple channels or pumps traveled by these ions (Bressler et al., 2007) and acts like them in numerous biologically significant events with greater affinity. Elevated intracellular calcium concentration and calcium-regulated events have been considered as primary mechanisms of lead toxicity (Garza et al., 2006).

3.1.1. Ca^{2+} mimicry/Ca^{2+} substitution

Lead enters cells by mimicking/substituting calcium in various ion