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Cognitive impairment associated with chronic lead exposure in adults

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ABSTRACT

Lead (Pb) exposure interferes with many biochemical events present in cells of the central nervous system (neurons and astrocytes) and it can produce a wide spectrum of alterations including cognitive impairment. The review summarizes the main cognitive alterations induced by chronic Pb exposure in adults/older individuals. We have focused on the current state of knowledge concerning the most vulnerable brain areas to Pb exposure that accompanied by the long-lasting neurological effects of Pb in cognitive functions. We tried to correlate the cognitive deficits induced by Pb exposure in animal models during adulthood with those reported in humans. The great interest in whether exposure to Pb can cause long-term, progressive declines in cognitive functions not only in exposed worker but also in community-dwelling individuals suggests that despite the reduction of Pb release in the environment, it's a risk factor for accelerated cognitive decline.

1. Introduction

Lead (Pb) is one of the oldest known toxicants and it affects many organ systems including central nervous system (CNS). Up to date, neurological alterations related to Pb exposure continue to be a major public health problem in many places in the world although the extent of Pb exposure significantly differ among countries (Tong, McMichael, & Baghurst, 2000). Neurological alterations related to Pb exposure have been documented even in those subjects who have been exposed to Pb several years ago, because its half-life in the body is very long (several decades) (Maret, 2017). The present review mainly focuses on recent knowledge and developments about cognitive deficits associated with chronic Pb exposure in adults. Others Pb-mediated neuro-psychiatric disturbances such as alterations of stress responses due to Pb ability to interfere with the hypothalamic-pituitary-adrenal (HPA) axis and impulsive and rewarding behaviours due to alterations of meso-cortico-limbic dopamine pathway, or of motor functions have been reviewed elsewhere (Cory-Slechta, Weiss, & Cranmer, 2008; Guilarte, Opler, & Pletnikov, 2012; Mansouri & Cauli, 2009). The review is focused on cognitive impairment associated with chronic Pb exposure in adults which had received less attention compared to the harmful effects induced by this metal during the neurodevelopment and childhood. The he main findings about the studies on the possible role of Pb exposure as an environmental factor that contribute to the pathogenesis of the Alzheimer's disease have been also summarized. Finally, We tried to correlate the cognitive deficits induced by chronic Pb exposure in humans with those reported in animal models.

2. Level of Pb-exposure in humans

In human studies, Pb exposure and its burden in the body are mainly quantified by means of the concentration of the metal in the blood and in the bone. For occupationally exposed individuals, while there is disagreement about what exposure levels needed to produce the earliest symptoms of neurotoxicity, most experts agree that overt manifested neurotoxic effects can occur at blood Pb levels of 60 μg/dL whole blood and therefore recommend a maximal cocentration in workers about 40 μg/dL (CDC, 2000). However, other studies showed association between Pb exposure and cognitive alterations in workers with blood Pb concentrations ranging 20–40 μg/dL (Barth et al., 2002; Lucchini et al., 2012; Murata, Iwata, Dakeishi, & Karita, 2009). The recommendation of the World Health Organization for community-dwelling adult individuals, is to maintain Pb concentration in blood below 10 μg/dL. However there is no exposure level below which Pb appears to be safe and concentration of 1–3 μg/dL have been associated to subtle neurotoxic effects (Kosnett et al., 2007). Pb concentration in bone is considered the measurement for cumulative exposure, and it is mainly measured by using K-shell X-ray fluorescence spectroscopy in tibia and patella which correspond to cortical and trabecular bone, respectively. Reports on the half-life of Pb in bone vary by body site as well as by factors such as age, prior exposure, and other conditions that modify bone turnover (Farooqui et al., 2017). Trabecular bone is reported to

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have an elimination half-life ($t_{1/2}$) of 8–20 years, whereas the concentration in cortical bone ranges from 10 to 50 years (Dorsey et al., 2006; Hu, Rabinowitz, & Smith, 1998; Kim, Landrigan, Mossmann, Sparrow, & Hu, 1997).

3. Cognitive alterations in adult subjects exposed to Pb

Several studies demonstrated both occupational and environmental exposure to Pb are associated with cognitive deficits (Fenga, Gangemi, Alibrandi, Costa, & Micali, 2016; Payton, Riggs, Spiro, Weiss, & Hu, 1998; Power et al., 2014; Shih et al., 2006; Wright et al., 2008). A study performed in Italy reported several neuropsychological alterations in lead-exposed workers (mean Pb concentration in blood approximately 56 μg/dL). These alterations mainly involve domains such as executive function, short time memory and different psycho-emotional variables (Fenga et al., 2016).

Several cohort studies showed that occupational exposure to Pb measured with tibia Pb levels, is associated with poor neurobehavioral test scores (Stewart et al., 1999), and with longitudinal decline in the cognitive functions (Schwartz et al., 2000; Weisskopf et al., 2007). Almost two decades after occupational exposure had ended, damage to the brain is still there, and it's characterized by white matter lesions, and decreased volumes in both larger (e.g., total brain, lobar grey and white matter) and smaller (e.g., cingulate gyrus, insula, corpus callosum) brain regions (Stewart et al., 2006). Occupational exposure to Pb is also associated, in transversal studies, with abnormalities of learning, memory and complex cognitive functions such as impairment of reaction time, visuomotor functioning, verbal memory, and dexterity (Baker et al., 1985; Campara et al., 1984; Hogstedt, Hane, Agreel, & Bodin, 1983; Valcuikas et al., 1980). Cognitive deficits are frequently accompanied by motor alterations such as ataxia, tremor and abnormal deep reflexes, and reduced motor strength (Ehle & McKee, 1990; Goldings & Stewart, 1982; Mansouri & Cauli, 2009; Pasternak et al., 1989; Schwartz et al., 1993; Stollery, Broadbent, Banks, & Lee, 1991).

The study by Shih et al. (2006) performed in urban-dwelling adults aged 50–70 years demonstrated that cumulative Pb (by tibia Pb concentration) is significantly associated with worse cognitive functions in several domains being the strongest association is related to visuo-construction ability. The magnitudes of the tibia Pb/cognitive function associations were moderate to large; an increase of one interquartile range of tibia Pb was approximatively equivalent to 2–6 more years of age across all domains, and the average tibia Pb effect was 36% of the age effect (Shih et al., 2006). Cumulative bone exposure seems also to influence the effect of aging on cognitive function in a study performed in community-dwelling elderly individuals (Farooqui et al., 2017; Grashow, Sparrow, Hu, & Weisskopf, 2015; Power et al., 2014; Weisskopf et al., 2007). The performance in several cognitive tasks over time worsened as bone lead increased, with the most robust effects on performance and reaction time scores on visuospatial/visuomotor tests and in men (Weisskopf et al., 2007).

The cognitive deficits associated with chronic Pb exposure in adults are accompanied by subtle brain volume reduction in some brain areas and by an altered content of the main brain metabolites determined by magnetic resonance spectroscopy both in Pb-exposed workers and in non-occupational settings (Jiang et al., 2008; Schwartz & Stewart, 2007; Weisskopf et al., 2007). At exposure levels encountered in environmental exposure, Pb bone concentration better correlates with the impairment in cognitive function compared to the level of Pb in blood (Schwartz et al., 2000; Shih et al., 2006). Similarly, in studies performed in workers with past occupational lead exposure, associations were also stronger and more consistent with cumulative dose than with recent dose (in blood) (Shih et al., 2006).

The analyses of the brain volume and measurement of cognitive functions in adult workers working in organic Pb manufactures reveal that brain atrophy is associated with lower cognitive functions in several cognitive domains (visuo-construction, processing speed, visual memory, executive functioning, and eye–hand coordination) (Schwartz & Stewart, 2007). Of the domains with the strongest evidence of longitudinal declines associated with Pb, visual memory and executive function demonstrated consistent associations with brain volumes reduction (Schwartz et al., 2007).

A cross-sectional study (Jiang et al., 2008) conducted in Pb-exposed workers (blood PB values more than 60 ug/dL) found a reduction of both right and left hippocampus volumes compared with non-exposed subjects. Reduction in brain size has been also reported for other brain regions such as prefrontal grey matter (Cecil et al., 2008), which might predispose to many psychiatric disturbances like impulsive, aggressive, or violent behaviours (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000; Yang, Coid, & Pan, 2005) in individuals chronically exposed to Pb that has been reviewed elsewhere (Cory-Slechta et al., 2008; Guilarte et al., 2012).

4. Cognitive alterations in animal models exposed to Pb during adulthood

Lead exposure in animal models produce many behavioural disturbances (Cory-Slechta et al., 2008; Guilarte et al., 2012; Winneke, Collet, & Lilienthal, 1988), however few studies have analysed the effects induced by Pb exposure on brain function during adulthood. Yun et al. (2000) exposed chronically adult rats (10-month-old) to 200 ppm Pb acetate and reported an impairment in cognitive function e.g. learning and memory processes in the hole-board spatial memory, after 1-year exposure, when the mean Pb levels in blood and brain are 18 μg/dL and 0.7 μg/g, respectively. The impairment in learning and memory was associated with a decrease in the concentration of energy-rich phosphate in parieto-temporal cortex and hippocampus (Yun, Lannert, & Hoyer, 2000). The effects of long-term Pb exposure in adult rats (50 ppm in drinking water, for 6 months) producing a blood Pb concentration as lower as 20 μg/dL, (i.e. below that associated with overt neurological deficits in occupationally exposed individuals), induced cognitive alterations in hippocampal dependent task such as spatial learning assessed in the Morris water maze test (Mansouri, Naghizadeh, López-Larrubia, & Cauli, 2013; Vazquez & Pena de Ortiz, 2004).

A magnetic resonance spectroscopy study performed in adult rats showed that exposure to Pb did not affect metabolite profile in the striatum and increase *myo*-inositol signal in the hippocampus of male rats. The increase in *myo*-inositol in hippocampus suggests early Pb-induced alteration in glial metabolism in this brain region and may represent a potential marker of early brain dysfunction during Pb exposure (Mansouri, Naghizadeh, López-Larrubia, & Cauli, 2012).

In a primate animal model, Lasky, Luck, and Parikh (2005) showed that prenatal Pb exposure could be able to decrease the inter-hemispheric white matter volume and in lateral ventricles size which reproduce some of the findings in Pb exposed workers (Lasky et al., 2005).

5. Pb exposure and Alzheimer's disease (AD)

The sporadic nature of most AD cases strongly argues for an environmental link that may drive AD pathogenesis (Zawia & Basha, 2005). The hallmark pathological features of AD (amyloidal plaques and associated proteins) are present in normal aging individuals suggesting that AD may result from the acceleration of normal age-related processes in the brain. The pathological manifestations in AD patients are presumed to result from defects of old age; however, it is unlikely that the disease process begins late in life. Production of amyloid besides being associated with AD, it can also be viewed as a pathological feature in the brain ^{during} aging; however, some of the molecular events that had induced its accumulation in the old brain may have occurred during early stages of brain development (Zawia & Basha, 2005).

Developmental exposure of rats to the metal Pb from birth to postnatal day 20 induced an overexpression of amyloid precursor