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Association between heavy metal exposure and poor working memory and possible mediation effect of antioxidant defenses during aging

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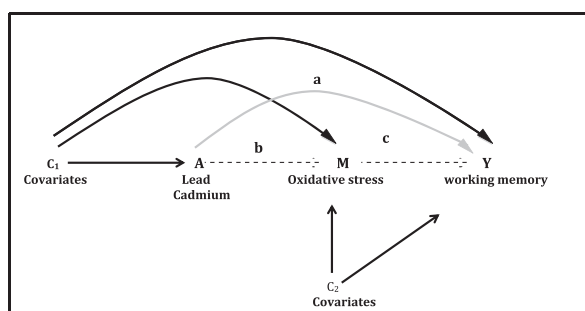
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HIGHLIGHTS

- Poor cognitive outcomes have been associated with heavy metals exposure.
- Cadmium alone and combined with lead was associated with poor working memory.
- Low antioxidant capacity was associated with both cadmium and lead.
- Cadmium and lead influence on memory may be mediated by low antioxidant defenses.
- Strategies to prevent and control exposure to heavy metals must be reinforced.

GRAPHICAL ABSTRACT



Effects of Lead and Cadmium exposure on working memory performance and the mediation role of oxidative stress.

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ABSTRACT

Background: Inverse associations have been observed between memory performance and blood concentrations of cadmium (Cd) and lead (Pb). Low antioxidant cell activity has also been linked to decline in memory due to aging. However, it has not yet been established whether the heavy metal-memory relationship is mediated by differences in antioxidant activity.

Methods: We examined Cd and Pb levels, as well as oxidative stress parameters, in blood samples from 125 older adults (age range 50–82 years). The Counting Span Test (CST) was used to evaluate working memory capacity (WMC). The Monte Carlo Method for Assessing Mediation (MCMAM) was used to analyze the mediation role of antioxidant activity in the heavy metals-memory association.

Results: High blood Cd (BCd) concentration alone, and in combination with elevated blood Pb (BPb) concentration, was associated with poor WMC ($p \leq 0.001$) and low enzymatic antioxidant defenses ($p \geq 0.006$). The

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variance in WMC accounted for by BCd or by BCd combine with BPb was 20.6% and 18.6%, respectively. The MCMAM revealed that the influence of BCd and BPb concentrations on WMC was mediated by low antioxidant capacity (confidence interval - CI: 0.072 to -0.064 for BCd; CI: -0.062 to -0.045 for BPb).

Conclusion: These findings showed Pb and Cd blood concentration in older adults, even at levels below the current recommended threshold, was negatively associated with WMC and that this relationship may be partly mediated by low antioxidant defenses. Knowledge on the environmental factors that negatively influence brain and cognition during aging can help inform public policy strategies to prevent and control the adverse effects of environmental contaminant exposure during aging.

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1. Introduction

The heavy metals cadmium (Cd) and lead (Pb) have become an environmental concern due to their toxic properties and worldwide commercial use in the manufacture of many products including batteries, plastics and pigments (CDC, 2009). Although many interventions have been implemented around the world to reduce the use of Pb and Cd in commercial products, these metals are still widely found in the environment, especially in developing countries, contaminating the air, water and soil (Fewtrell et al., 2003). Humans are exposed to Pb and Cd through dermal contact, inhalation, cigarette smoking, dietary intake and dust ingestion (CDC, 2009). The elderly are one of the most vulnerable populations to environmental contaminants given the longer exposure to these substances compared to younger populations and also because of their lower functional reserve, which is higher in younger individuals and enables them to better compensate for the physiological damage that these metals may cause (Weiss, 2012). A range of adverse health outcomes has been attributed to the toxic effects of Cd and Pb including cognitive decline (ATSDR, 2012; CDC, 2009).

Pb and Cd are capable of crossing the blood-brain barrier and reaching the brain where they can induce apoptosis, interfere with neurotransmitter storage and acetylcholinesterase activity in cognitive-related structures such as the prefrontal cortex and the hippocampus (Gonçalves et al., 2010; Sanders et al., 2009). Due to these effects, Pb and Cd have been independently associated with poor attention and perception, slow information processing and poor long-term memory performance in older adults (Ciesielski et al., 2013; Kunert et al., 2004; Schwartz and Stewart, 2009; Weisskopf et al., 2004).

The mechanism by which Cd and Pb compromise cognitive performance has not been fully elucidated. One hypothesis is that these effects relate to oxidative stress-induced neuronal damage. Pb and Cd lead, directly or indirectly, to accumulation of reactive oxygen species (ROS) and to an imbalance between pro- and antioxidant elements (ATSDR, 2012; CDC, 2009). The major ROS generated during cell metabolism are the superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($\bullet OH$). Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) are crucial for maintaining intracellular ROS within physiological levels in order to avoid cell damage, since oxidative stress leads to protein, lipid and nucleic acid damage resulting in cellular dysfunction and disease (Matés et al., 2006). A recent review demonstrated the ability of Pb and Cd to trigger oxidative stress (Milnerowicz et al., 2015). More specifically, Pb and Cd are associated with lipid peroxidation, reduced activity of the antioxidant enzymes SOD, CAT and GPx and with impaired brain functioning (Liu et al., 2009; Matés et al., 2010; Milnerowicz et al., 2015). These metals have also been linked to low levels of glutathione (GSH), which plays an essential role in the removal of H_2O_2 from cells (Milnerowicz et al., 2015). Interestingly, decreased antioxidant defenses and increased lipid peroxidation have also been associated with impaired learning in middle-aged rats and poor cognitive performance in older patients with mild cognitive impairment and Alzheimer's disease (Lee et al., 2014; Torres et al., 2011; Salmon et al., 2010).

The evidence presented so far raises the question whether Pb and Cd can adversely affect cognition and whether the negative impact of heavy metals on cognitive performance is mediated by decreased antioxidant defenses during aging. We investigated whether an important cognitive construct, working memory capacity (WMC), was affected by concentrations of these heavy metals. WMC plays a central role in several complex behaviors such as comprehension, reasoning, planning and decision-making and is closely associated with long-term memory and fluid intelligence (Conway et al., 2005; Köstering et al., 2016; Wilhelm et al., 2013) and decreases throughout the lifespan (Conway et al., 2005; Köstering et al., 2016; Wilhelm et al., 2013). Therefore, any factors that increases this decline in our aging society should be known in order to ensure healthy aging, prevent poor quality of life and to extend the ability of elderly individuals to live independently for as long as possible. In the present study, we tested the mediator role of antioxidant defenses in the negative effect of blood Pb (BPb) and blood Cd (BCd) on WMC in older adults. We hypothesized that older adults exposed to BPb and BCd exhibit poorer WMC and that this association may be mediated by antioxidant defenses.

2. Methods

2.1. Participants

One hundred and twenty-five (104 women and 21 men) healthy older adults between 50 and 82 years of age ($M = 65.9$, $SD = 8.0$ years) were included in this study. All participants were recruited from the metropolitan community of São Paulo city, Brazil, using media advertisements (radio, internet and television) and previously screened by questionnaires, routine laboratory tests, anthropometric measures and neuropsychological assessment. Sample characteristics proved similar to those of the Brazilian general population (predominantly female and retired, low-to-middle socioeconomic status and educational level of up to 9 years, Instituto Brasileiro de Geografia e Estatística – IBGE, 2010).

Exclusion criteria were reports of neurological or psychiatric disorders, a history of alcohol or drug abuse, smoking in the last 10 years, heavy metal occupational exposure in lifetime, use of antidepressants, benzodiazepines, synthetic glucocorticoids or steroid medications at the time of assessment. Cognitive and functional impairments were ruled out by applying the Mini-Mental State Examination - MMSE (Folstein et al., 1975) and the Informant Questionnaire on Cognitive Decline - IQCODE (Jorm and Jacomb, 1989), respectively, both adapted for local use. The Geriatric Depression Scale (GDS) was applied to assess symptoms of depression (Almeida and Almeida, 1999). One hundred and thirty participants were initially recruited, five of which were subsequently excluded as follows: four had MMSE scores below the cut-off for educational level (Brucki et al., 2003) while one participant exhibited dental problems during the study protocol compromising saliva sampling. The study was approved by the Ethics Committee of the UNIFESP, São Paulo, Brazil (permit no. 0823/09) and all participants provided informed consent.

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