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Lead exposure is related to hypercortisolemic profiles and allostatic load in Brazilian older adults

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ABSTRACT

Lead levels (Pb) have been linked to both hyper- and hypo-reactivity of hypothalamic-pituitary-adrenal axis (HPA) axis to acute stress in animals and humans. Similarly, allostatic load (AL), the 'wear and tear' of chronic stress, is associated with inadequate HPA axis activity. We examined whether Pb levels would be associated with altered diurnal cortisol profile, as a primary mediator of AL, during aging. Pb levels were measured from blood samples (BPb) of 126 Brazilian individuals (105 women), between 50 and 82 years old. Six neuroendocrine, metabolic, and anthropometric biomarkers were analyzed and values were transformed into an AL index using clinical reference cut-offs. Salivary samples were collected at home over 2 days at awakening, 30-min after waking, afternoon, and evening periods to determine cortisol levels. A multiple linear regression model showed a positive association between BPb as the independent continuous variable and cortisol awakening response (R^2=0.128; B=0.791; p=0.005) and overall cortisol concentration (R^2=0.266; B=0.889; $p < 0.001$) as the outcomes. Repeated measures ANOVA showed that individuals with high BPb levels showed higher cortisol at 30 min after awakening (p=0.003), and in the afternoon (p=0.002) than those with low BPb values. Regarding AL, regression model showed that BPb was positively associated with AL index (R^2=0.100; B=0.204; p=0.032). Correlation analyzes with individual biomarkers showed that BPb was positively correlated with HDL cholesterol (p=0.02) and negatively correlated with DHEA-S (p=0.049). These findings suggest that Pb exposure, even at levels below the reference blood lead level for adults recommended by the National Institute for Occupational Safety and Health and by the Center for Disease Control and Prevention, may contribute to AL and dysregulated cortisol functioning in older adults. Considering these findings were based on cross-sectional data future research is needed to confirm our exploratory results.

1. Introduction

Environmental contaminants are of increasing interest in relation to stress pathophysiology. Heavy metals exposure, particularly lead (Pb), constitutes one of the main contaminants investigated because of their pernicious consequences over the course of life (Weiss, 2007). Although several public policies have successfully lowered blood lead (BPb) levels in many countries over the last thirty years, exposure to elevated Pb levels still poses a concern especially in emerging and low income countries where environmental regulations are fragile and at the mercy of industrial development (He et al., 2009). Indeed, the general population continues to be exposed to Pb from different resources including solder, gasoline, battery industries and consumer products such as toys, lead-based paint, cosmetic products, crayon, color pencil and even candies (Center for Disease Control and Prevention - CDC, 2009). Elderly are one of the target vulnerable

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populations to the negative effects of Pb exposure mainly because the long lifetime exposure allied to their reduced capacity to compensate for impairment (Weiss, 2007). Furthermore, the skeleton is the site of storage for around 95% of lead in the adult human body, resulting in a release of lead in blood in aging people with bone demineralization, especially during postmenopausal period (Baecklund et al., 1999; Barbosa Jr. et al., 2005).

Pb exposure has been related to several adverse health outcomes in adults including neurological and cardiovascular effects. Consistent evidence demonstrated that low-level Pb exposure as indicated by less than 10 μg/dL is associated with increased blood pressure, increased risk of hypertension, increased incidence of essential tremor and decreased cognitive function (Armstrong et al., 2014; Peters et al., 2010; Power et al., 2014; Weisskopf et al., 2007). Neuroendocrine disrupting effects have also been associated with Pb concentration (Weiss, 2012). Pb can disrupts endocrine systems via steroid hormone dysregulation affecting brain development and functioning (Weiss, 2012). In particular, elevated Pb levels disrupt the hypothalamic-pituitary-adrenal axis (HPA) axis, a stress-sensitive system that culminates in the production and release of glucocorticoid (cortisol in humans) from the adrenal glands following stress exposure (McEwen, 1998).

Studies in animals have shown that maternal Pb exposure, even at low levels, permanently alters the offspring HPA axis function, resulting in basal and stress-induced hypercortisolemism both in the neonatal and post-weaning periods (Cory-Slechta et al., 2004, 2008; Virgolini et al., 2004, 2008). Additionally, Pb exposure during rodent development leads to significant prolonged HPA axis response to acute stress (Rossi-George et al., 2009). In adulthood, rodents and the offspring exposed to Pb (before breeding, during pregnancy and after weaning) exhibit lower glucocorticoid levels than animals with no Pb exposure (Rossi-George et al., 2011). In humans, a few studies have examined the relationship between Pb exposure and stress. Children with high Pb levels exhibit heightened cortisol response following a standard cold pressor task. By contrast, no association was observed between Pb exposure and cortisol changes in basal levels (Gump et al., 2008). More recently, high prenatal BPb exposure (≥10 μg/dL) was associated with low cortisol concentration producing a downshift in the cortisol curve at 12 months-olds children (Tamayo y Ortiz et al., 2016). In adults, Fortin et al. (2012) reported a significant association between lead exposure and higher ACTH/CORT ratio in occupational-Pb exposed participants, suggesting a Pb-induced alteration of the HPA axis (Fortin et al., 2012). In non-occupational adults, pregnant women with higher BPb concentrations showed reduced cortisol awakening response that is an important predictor of adverse health outcomes (Braun et al., 2014). Given that the HPA axis functions within a multi-systemic network, it is critical that future studies of Pb in humans also assess broader physiological dysregulations.

To date, the available evidence vis-a-vis Pb and stress biology in humans is scarce and limited to situations of acute stress (e.g., reactivity). This is problematic since chronic stress promotes widespread dysfunctions in numerous systems and is associated with several disorders and neurological problems (Lupien et al., 2009; Souza-Talarico et al., 2011; Virgolini et al., 2008). Based on the allostatic load (AL) framework of chronic stress (McEwen and Stellar, 1993), prolonged and repeated activation of the stress system leads to frequent recalibrations in basal body functioning in order to adapt to environmental demands. This strain produces a “domino effect” in a non-linear multi-systemic physiological dysregulations that may lead to stress-related disorders over time (McEwen and Stellar, 1993; Juster et al., 2011a, 2011b; Picard et al., 2014).

At the subcellular level, the AL “domino effect” begins with glucocorticoid dysregulations and altered glucose levels (primary mediators) induced by chronic stress exposure, followed by mitochondria damage due to oxidative stress and inflammation (primary effects) and cellular dysfunction (primary outcomes; Picard et al., 2014). Cumulatively, these primary effects perturb metabolic, cardiovascular, immunological and neural systems producing subclinical outcomes such as elevation of blood pressure and body mass index, and dyslipidemia (secondary outcomes) that consequently, throughout organ and systems failure, leads to disease (tertiary outcomes) (McEwen and Stellar, 1993; Lupien et al., 2009; Juster et al., 2011a, 2011b; Picard et al., 2014).

There is a small but growing literature linking Pb exposure to AL. In epidemiological studies, cross-sectional and longitudinal associations have been reported between Pb exposure and elevated blood pressure including development of hypertension (Schwartz, 1988; Cheng et al., 2001; Navas-Acien et al., 2008). More recently, Zota et al. (2013) showed that higher BPb is associated with elevated blood pressure among adult men with high AL those with low AL suggesting that AL may amplify the BPb and blood pressure relationship (Zota et al., 2013). Taken together, most findings linking Pb exposure and AL are based on secondary outcomes (e.g., lipids, blood pressure) as predictors of tertiary outcomes (e.g., cardiovascular disease).

Another critical aspect that weakens the understanding of the relationship between Pb and chronic stress in humans is the lack of evidence during aging. This is a matter of concern since elderly populations are especially vulnerable to the effect of Pb. Given that the world population is growing older, it is imperative to identify environmental factors that influence the aging population in order to prevent loss of life-quality and to ensure the most successful aging possible.

The current study aimed to investigate whether Pb levels are associated with altered diurnal cortisol profiles, a primary mediator of AL, during aging. Given that a failure to shut down the HPA axis is a neuroendocrine profile that characterizes pathophysiological states and AL during aging (McEwen et al., 1998), we hypothesized that older adults with higher BPb levels would exhibit hypercortisolemic profiles and higher rate of subclinical AL biomarkers and AL index.

2. Methods

2.1. Participants recruitment, selection and ethic procedures

One hundred and twenty-six older adults (n=126; 105 women and 21 men) with 65.9 (± 8.1) years of age and 9.8 (± 4.5) years of education from São Paulo, Brazil were included in the study protocol. Individuals were recruited using media advertisements (radio, television and internet) and those who contacted the Department of Psychobiology were initially screened by a standardized telephone interview. Those who did not fulfill the following criteria were excluded: neurological or psychiatric disorder, history of alcohol, drug or tobacco abuse in the last 10 years, Pb occupational exposure, individuals living in geographic areas of known for high Pb contamination, under use of psychoactive drugs, synthetic glucocorticoids or steroids medications. Recent dental treatment was also an exclusion criterion to prevent saliva contamination with blood, which in turn could influence free-cortisol levels. All female participants were post-menopausal.

Selected participants were scheduled for an individual interview at the Department of Psychobiology of UNIFESP for routine laboratory tests, anthropometric measures and neuropsychological assessment. Participants were excluded if they presented hemoglobin alterations (elevated Pb is associated with decreased levels of hematocrit and hemoglobin; Barbosa Jr. et al. 2005), cognitive decline combined with functional impairment analyzed by the Mini-Mental State Examination (MMSE) (Brucki et al., 2003; Folstein et al., 1975) and the Informant Questionnaire on Cognitive Decline (IQCODE) (Bustamante et al., 2003; Jorm and Jacomb, 1989), and if they screened for depression according to the Geriatric Depression Symptoms (Yesavage et al., 1982). Of the 136 participants who contacted the research center, eight refused to participate and two were not eligible because of dental