Environmental Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Blood lead levels and hypothalamic-pituitary-adrenal function in middle-aged individuals

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ARTICLE INFO

Keywords:
Lead exposure
Cortisol secretion
Stress responsivity
Adults

ABSTRACT

Experimental and epidemiological studies suggested that exposure to lead (Pb) may influence the hypothalamic-pituitary-adrenal (HPA) axis. However, previous studies have yielded mixed results. We evaluated changes in basal salivary cortisol levels and acute cortisol responsivity to psychological stress in relation with blood Pb levels (BPb), in Caucasian individuals 50–67 years of age. Data were collected through the Study of Genetics, Stress and Cognitive Development (2004–2006). Diurnal basal and stress-reactive salivary cortisol levels were collected and BPb levels were determined using inductively coupled plasma mass spectroscopy. A total of 65 participants were included in the current study. General linear mixed models were used to assess the association between BPb level and change in cortisol secretion over time, for diurnal basal pattern and stress-reactive pattern, respectively. The geometric mean BPb was 2.70 μg/dL (± 1.44) and two exposure groups were created based on the median value of 2.48 μg/dL. No difference in geometric mean of salivary cortisol (μg/dL) at awakening was observed between High and Low BPb groups (0.23 (± 0.11) vs 0.20 (± 0.11), p = 0.36). The overall pattern of change in both diurnal basal (from the awakening to bedtime) and reactive salivary cortisol (during the stress induction protocol) did not differ between groups. In these middle-aged and older adults, we concluded that Pb exposure, within the range observed in the current study, was associated with neither diurnal nor stress-reactive cortisol secretion. Further investigation with larger datasets are needed to confirm our observations.

1. Introduction

Animals and humans respond to stressors through different physiologic responses, including activation of the hypothalamic-pituitary-adrenal (HPA) axis, and secretion of adenocorticotropic hormones (ACTH) and glucocorticoids (GCs; cortisol in humans). Experimental studies suggest that protein kinase C (PKC) mediates the ACTH-induced cortisol secretion (Ishizuka et al., 1997; Rasmussen et al., 1995), and represent a key factor in the regulation of its secretion. The HPA axis stress response is influenced by sociodemographic (e.g. gender (Kirschbaum et al., 1992), age (Kudielka et al., 2004)), physiological factors (Federenko et al., 2006), but also environmental chemicals (Odermatt and Gumy, 2008).

Adverse effects of lead (Pb) in adults have been largely reported in the previous literature, including impaired kidney function (Navas-Acien et al., 2009; Tsaih et al., 2004), increased blood pressure and likelihood for hypertension (Almeida Lopes et al., 2017; Navas-Acien et al., 2008; Scinicariello et al., 2011), and increased cardiovascular-related mortality (Weisskopf et al., 2009). Although no significant association was found between Pb exposure and cognitive functions in U.S. adults (Krieg et al., 2005; van Wijngaarden et al., 2011), an impairment in the domain of attention was observed in relation to blood Pb levels (BPb) in several other populations of elders (Kunert et al., 2004; Weisskopf et al., 2007).

After the stress response, high levels of GCs are regulated by a negative GCs feedback mechanism (Herman et al., 2003) and it has been argued that Pb alters this retro-inhibition (Rossi-George et al., 2009),

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http://dx.doi.org/10.1016/j.envres.2017.10.032
Received 19 July 2017; Received in revised form 10 September 2017; Accepted 19 October 2017

leading to prolonged GCs secretion and high basal GCs levels. Experimental studies also suggest that at picomolar levels, Pb influences PKC similarly as calcium at nanomolar levels (Markovac and Goldstein, 1988), and alters PKC activity after chronic exposure (Chen et al., 1999). *In vitro* studies suggest that the effect of Pb on cortisol secretion is biphasic, with stimulatory effects at Pb exposure < 10 μg/dL and inhibitory effects after high-levels exposure (Chaube et al., 2010). The timing and duration of exposure seem to play a crucial role as suggested by animal studies.

Daily exposure of rat dams to 150 ppm Pb through drinking water (from 2 months before breeding to lactation) has been associated with increase of basal blood corticosterone levels (Cory-Slechta et al., 2004). However, long-term exposure of rodents to Pb (before breeding, during pregnancy and after weaning) was associated with a lower GCs levels in adulthood (Rossi-George et al., 2011). In another study, Pb exposure was initiated only at weaning and continuing into adulthood, and stress-induced responses were observed in male rats unexposed to Pb, but not in exposed groups (ingesting 50–150 ppm Pb through drinking water), and Pb decreased basal plasma corticosterone (Virgolini et al., 2005). After short-term exposure to Pb, mices (6–8 weeks of age) showed increased concentration of corticosterone in blood, when compared to control group, but the differences were not statistically significant (Nieto-Fernandez et al., 2006).

Results from epidemiological studies have yielded conflicting results. In a longitudinal birth cohort study, neither prenatal nor postnatal Pb exposure (both mean BPb < 10 μg/dL) was associated with basal cortisol levels, but authors found a positive association with cortisol levels after a cold pressor task in children 9.5 years of age (Gump et al., 2008). In a previous study, high-level Pb exposure (mean BPb of 49 μg/dl) was associated with lower basal serum cortisol levels in male adults (Gustafson et al., 1989). Among workers, Fortin et al. (2012) found that both higher Pb levels (greater than 4 μg/dl) and tibia Pb were associated with lower basal serum cortisol levels but higher serum ACTH levels in response to stress (which could be interpreted as increased HPA activity). More recently, Souza-Talarico and co-workers found increased cortisol awakening response in older adults with increased BPb (Souza-Talarico et al., 2017).

Based on previous animal studies, suggesting that timing of Pb exposure may affect the direction of the association between Pb exposure and GCs levels (with the negative association when post-lactation exposure is prolonged), we postulated that the relation of salivary cortisol secretion with Pb status in this aging population may be different to what is observed in other age groups. Aging population is characterized by a high body burden of Pb (Bjermo et al., 2013) and an increased release of Pb from bones in postmenopausal women (Garrido Latorre et al., 2003). We suspected that long-term exposure to Pb would associate with decreased HPA activity in elderly. To test this hypothesis, we examined whether BPb levels associate with basal and stress-reactive cortisol salivary levels in individuals 50–67 years of age.

2. Methods

2.1. Study participants

Participants (n = 132) were recruited in the context of a study of genetics, stress and cognitive development. The recruitment process has been described in details in a previous study (Fiocco et al., 2008). For the purpose of this study, participants were recontacted in 2010 and asked whether they were willing to have their BPb measured. From the 132 participants in the original study, 28 could not be reached and 34 refused to participate, leaving 70 participants. Sufficient blood volume was available from 65 participants and acquired blood samples were stored at −20 °C. They were not reassessed for the presence of acute conditions that could affect HPA activity. The waist-to-hip ratio in included participants varied between 0.67 and 1.11, with a mean of 0.84 (± 0.08). Based on the threshold from World Health Organization for defining abdominal obesity (World Health Organization, 2008), 57.14% of participants were obese. This proportion was 26.5% if we consider the cut-off from the U.S. Department of Health and Human Services (U.S. Department of Agriculture, 1990). This study was approved by the Ethics Board of the Douglas Hospital Research Centre (#03/40) and by the Ethics Board of the Research Centre of the Montreal Mental Health University Institute (#03/22). All participants signed an informed consent before the start of the study protocol.

2.2. Data collection

In the original study, all participants were recruited using media advertisement (newspaper, public-sac and internet) and were evaluated according to the following experimental protocol. Exclusion criteria included: any current Axis I psychiatric disorders (DSM-IV criteria), diabetes, thyroid dysfunction, major medical illness that would interfere with endocrine or cognitive measures, exposure to general anesthesia in the last year, use of medications that interact with endocrine measures (e.g. antidepressants, anti-anxiolytics, cortisone), and lack of proficiency in either French or English. All female participants were postmenopausal, and not under hormone replacement therapy, which was an exclusion criterion. Cognitive and functional impairments were ruled out by administering the Mini Mental State Examination (Folstein et al., 1975).

Participants were invited to the Centre for Studies on Human Stress (Douglas Hospital, Montreal, Canada) for two separate visits. The first morning visit to place between 8:00 AM and 10:00 AM in the morning, following 24-h fasting period. Over a two-hour testing session, participants provided informed consent, underwent blood draw for biological analysis and clinical evaluation, and completed a battery of cognitive tests and psychological questionnaires. Participants were also provided with detailed instructions baseline cortisol sampling at home. After one week, participants returned with their salivary samples for a second visit in the afternoon between 1:00 PM and 3:00 PM and were exposed to a psychosocial stress-induction protocol, the Trier Social Stress Task (TSST), after which participants were debriefed.

2.3. Assessment of basal cortisol

Participants were asked to collect saliva samples at home to characterize basal cortisol levels. Salivary samples were collected by placing a polyester-coated cotton swab (Salivette, Sarstedt) in the mouth for two minutes to saturate the cotton. The cotton swab was then placed in a plastic tube and stored in the participant's freezer until the second visit, at which point it was stored in a −20 °C freezer until subsequent analysis. Participants were instructed to collect saliva five times per day during three consecutive week days: upon awakening, 30 min after awakening, at 2:00 PM, at 4:00 PM, and at bedtime (See Fig. 1). These sampling times have been previously described to be reliable markers of the diurnal cycle of cortisol secretion (Smyth et al., 1997). For assessing compliance regarding timing of saliva collection, participants were asked to log the exact time when each salivette was sampled using self-report sampling log book. Samples for each sample time were averaged over three days. Compliant samples were considered for the individuals who collected the first sample within 10 min of awakening and the second sample 30 ± 7 min after awakening. In addition, compliance for the remaining three samples was defined as ± 1 h of the targeted time as recommended elsewhere (Kudielka et al., 2003).

2.4. Assessment of stress reactivity

Psychosocial stress was induced using the TSST, an established and highly effective stress induction protocol that has been found to consistently activate the HPA axis (Kirschbaum et al., 1993). The TSST consisted of a 10-min anticipatory period, followed by a 5-min public speech task and a 5-min mental arithmetic task (See Fiocco et al. for