Environment International 101 (2017) 89–95

Contents lists available at ScienceDirect

Environment International

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

Influence of exposure to coarse, fine and ultrafine urban particulate matter and their biological constituents on neural biomarkers in a randomized controlled crossover study

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ARTICLE INFO

Article history:
Received 18 November 2016
Received in revised form 9 January 2017
Accepted 12 January 2017
Available online 20 January 2017

Keywords:
Air pollution
Particulate matter
Endotoxin
β-1,3-D-glucan
Neural biomarker
Randomized controlled crossover trial

ABSTRACT

Background: Epidemiological studies have reported associations between air pollution and neuro-psychological conditions. Biological mechanisms behind these findings are still not clear.
Objectives: We examined changes in blood and urinary neural biomarkers following exposure to concentrated ambient coarse, fine and ultrafine particles.
Methods: Fifty healthy non-smoking volunteers, mean age 28 years, were exposed to coarse (2.5–10 μm, mean 213 μg/m^3) and fine (0.15–2.5 μm, mean 238 μg/m^3) concentrated ambient particles (CAPs), and filtered ambient and/or medical air. Twenty-five participants were exposed to ultrafine CAP (mean size 59.6 nm, range 47.0–69.8 nm), mean (136 μg/m^3) and filtered medical air. Exposures lasted 130 min, separated by ≥2 weeks, and the biological constituents endotoxin and β-1,3-D-glucan of each particle size fraction were measured. Blood and urine samples were collected pre-exposure, and 1-hour and 21-hour post-exposure to determine neural biomarker levels. Mixed-model regressions assessed associations between exposures and changes in biomarker levels.
Results: Results were expressed as percent change from daily pre-exposure biomarker levels. Exposure to coarse CAP was significantly associated with increased urinary levels of the stress-related biomarkers vanillylmandelic acid (VMA) and cortisol when compared with exposure to filtered medical air [20% (95% confidence interval: 1.0%, 38%) and 64% (0.2%, 127%), respectively] 21 hours post-exposure. However exposure to coarse CAP was significantly associated with decreases in blood cortisol [−26.0% (−42.4%, −9.6%) and −22.4% (−43.7%, −1.1%) at 1 h and 21 h post-exposure, respectively]. Biological molecules present in coarse CAP were significantly associated with blood biomarkers indicative of blood brain barrier integrity. Endotoxin content was significantly associated with increased blood ubiquitin C-terminal hydrolase L1 [UCHL1, 11% (5.3%, 16%) per ln(ng/m^3 + 1)] 1-hour post-exposure, while β-1,3-D-glucan was significantly associated with increased blood S100B [6.3% (3.2%, 9.4%) per ln(ng/m^3 + 1)], as well as UCHL1 [3.1% (0.4%, 5.9%) per ln(ng/m^3 + 1)], one-hour post-exposure. Fine CAP was marginally associated with increased blood UCHL1 when compared with exposure to filtered medical air [17.7% (−1.7%, 37.2%), $p = 0.07$] 21 hours post-exposure. Ultrafine CAP was not significantly associated with changes in any blood and urinary neural biomarkers examined.
Conclusion: Ambient coarse particulate matter and its biological constituents may influence neural biomarker levels that reflect perturbations of blood-brain barrier integrity and systemic stress response.

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http://dx.doi.org/10.1016/j.envint.2017.01.010

1. Introduction

Extensive epidemiological evidence has shown that daily increased particulate air pollution is associated with elevated risk of cardiovascular and respiratory mortality and hospital admissions (World Health Organization, 2013). However, the effects of urban air pollution on nervous systems are not as well studied. This has been recognized by the US National Institute of Environmental Health Sciences/National Institute of Health as a priority for scientific research (Block et al., 2012). In recent years, epidemiological studies have reported associations between daily air pollution and hospital admissions or emergency room visits for Parkinson's disease (Zanobetti et al., 2014) and neuro-psychological responses such as depression and suicide attempt/mortality (Bakian et al., 2015; Kim et al., 2010; Szyszkowicz et al., 2009; Szyszkowicz et al., 2010; Yackerson et al., 2014). Long-term exposure to elevated air pollution in urban centres has been associated with hospital admissions for dementia, Parkinson's and Alzheimer's diseases (Kioumourtzoglou et al., 2016; Ritz et al., 2016).

The biological mechanisms behind these neuro-psychological responses are not well understood. Air pollution-induced systemic inflammation and oxidative stress have been implicated in field epidemiological and controlled human exposure studies (Behbod et al., 2013; Chuang et al., 2007; Delfino et al., 2009; Liu et al., 2015; Rückerl et al., 2007). Evidence from toxicological studies has contributed to the hypothesis that particulate matter (PM)-induced systemic inflammation and oxidative stress may damage cerebral vasculature, and compromise the tight junctions of the blood-brain barrier that controls the influx of neurotoxins and release of some neural mediators into the peripheral blood stream (Hartz et al., 2016). Thomson et al. observed that short-term exposure of rats to PM and ozone induced redox/glucocorticoid-sensitive gene responses and increased plasma levels of adrenocorticotropic hormone and the glucocorticoid corticosterone (Thomson et al., 2013). These observations led to the hypothesis that exposure to these air pollutants may activate the hypothalamic-pituitary-adrenal stress response axis, resulting in various metabolic and neurobehavioral changes (Thomson, 2014). There is also evidence that long-term exposure to high levels of air pollution is associated with increased inflammatory gene expressions and disruption of the blood brain barrier in human brain autopsy samples (Calderón–Garcidueñas et al., 2008). Controlled human exposure studies examining neural biomarkers in blood and urine may contribute to evidence to elucidate how exposure to pollutants in ambient air may result in adverse neuro-psychological responses in human population.

Urban PM in ambient air is generally categorized into coarse [mass median aerodynamic diameter (MMAD) 2.5–10 μm, $PM_{10-2.5}$], fine (MMAD ≤ 2.5 μm, $PM_{2.5}$) and ultrafine (MMAD ≤ 0.1 μm) particles. Studies suggest that various particle size fractions may affect systemic inflammation and oxidative stress in a different manner, which might be explained by differences in particle delivery rate, route and deposition location in the body and by the presence of chemical and biological components of varying toxic potency [including neurotoxicity, (Lucchini et al., 2012)] in different PM size fractions. For example, Samet et al. reported that controlled exposures to concentrated ambient $PM_{2.5}$ and $PM_{10-2.5}$ were associated with increased airway inflammation and a trend of increased blood coagulation markers such as fibrinogen and plasminogen in human volunteers, but exposure to ultrafine particles had no such effects (Samet et al., 2007). Our findings in a controlled exposure study suggest that among the three size fractions, coarse concentrated ambient particles (CAP) had a stronger association with vascular endothelial growth factor (VEGF) in blood, fine CAP a stronger association with urinary marker of lipid peroxidation, and ultrafine CAP a stronger association with urinary marker of DNA oxidative damage (Liu et al., 2015). PM often carries biological components such as endotoxin, a major constituent of the outer membrane of the cell wall of Gram-negative bacteria, and β-1,3-D-glucan (β-glucan), a constituent of the cell wall of fungi and plants. They both are known to be associated with respiratory illness in children and adults (Dales et al., 2006; Douwes et al., 2000; Thorne et al., 2015). We have observed that endotoxin contained in coarse and fine CAPs were significantly associated with blood leukocytes (Behbod et al., 2013) and blood pressure (Zhong et al., 2015), as well as systemic changes in vasodilatory inflammatory marker VEGF and biomarkers of DNA and lipid oxidation (Liu et al., 2015), suggesting that endotoxin plays a role in the effects of coarse and fine CAPs on human health.

In this study, we tested the hypotheses that (1) a short-term exposure to concentrated ambient coarse, fine or ultrafine PM in a controlled environment is associated with changes in systemic neural biomarkers in the blood and urine of healthy individuals; and (2) endotoxin and β-glucan in these particles might play a role in the perturbation of these biomarkers. The neural biomarkers examined in this study are those that have been reported to be associated with: a) oxidative stress [brain-derived neurotrophic factor (BDNF) in blood] (Moylan et al., 2013); b) traumatic brain injury or degeneration [neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), and ubiquitin C-terminal hydrolase L1 (UCHL1) in blood] (Arent et al., 2014; Lewis et al., 2010; Zetterberg et al., 2013); and c) systemic stress [cortisol in blood and urine, and urinary metabolites of dopamine and norepinephrine: homovanillic acid (HVA) and vanillylmandelic acid (VMA), respectively](Frankenhaeuser et al., 1986; Fukuda et al., 1996; Sapolsky et al., 2000).

2. Materials and methods

The study design was a single-blind randomized cross-over trial. Detailed methods of participant recruitment were described by Liu et al. (2015). Briefly, participants were non-smokers, 18–60 years of age, without history of coronary artery disease, myocardial infarction, peripheral vascular disease, angina, heart failure, hypertension or diabetes mellitus, and free of lipid abnormalities and respiratory tract infections. We excluded participants with baseline spirometry < 75% of predicted normal values (forced vital capacity and forced expiratory 1-second volume), having clinically significant abnormalities in their resting electrocardiogram, as well as those who were pregnant or breast-feeding. All participants provided informed written consent prior to participating in the study. The Research Ethics Boards of Health Canada and Public Health Agency of Canada, St. Michael's Hospital, and the University of Toronto approved the study protocol.

2.1. Exposure facility

Details of the coarse, fine and ultrafine particle concentrator facility were described elsewhere (Rastogi et al., 2012). The controlled exposures to CAPs drew air from breathing height (1.8 m) adjacent to a downtown street in Toronto, Canada. We used the Harvard Ambient Fine and Coarse Particle Concentrators and an enclosed temperature-controlled exposure chamber for the study participants. Ambient aerosols were drawn through a size-selective inlet where particles > 10 μm were removed. The fine PM concentrator delivered CAP 0.15–2.5 μm in MMAD (fine CAP), while the coarse PM concentrator delivered CAP 2.5–10 μm in MMAD (coarse CAP). Particle-free filtered ambient air (FA) was used as a control by inserting a high-efficiency particulate absorption (HEPA) filter inline downstream of the particle concentrator. For the study on coarse and fine CAPs, we enrolled 50 participants. Forty-one participants also had exposure to HEPA-filtered cylinder medical air as control that was particle- and ambient gas-free; the remaining 9 participants only had filtered ambient air as control. The study for the coarse and fine CAPs included up to five exposures for each participant when he or she was available: two exposures to coarse CAP, and one exposure to fine CAP, HEPA-filtered ambient air, and/or filtered medical air. Details on the regime of exposures were described elsewhere (Liu et al., 2015).