Environment International 121 (2018) 308–316

Contents lists available at ScienceDirect

Environment International

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

Greater susceptibility of girls to airborne Benzo[*a*]pyrene for obesity-associated childhood asthma

Hyunok Choi[a,*], Miroslav Dostal[b], Anna Pastorkova[b], Pavel Rossner Jr[b], Radim J. Sram[b], Shuk-Mei Ho[c]

[a] Departments of Environmental Health Sciences, Epidemiology, and Biostatistics, University at Albany School of Public Health One University Place, Rm 153, Rensselaer, NY 12144-3456, USA
[b] Department of Genetic Toxicology and Nanotoxicology, Institute of Experimental Medicine, Czech Academy of Sciences, Vídeňská 1083, 142 20 Prague 4, Czech Republic
[c] Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA

ARTICLE INFO

Editor: Olga-Ioanna Kalantzi

Keywords:
Polycyclic aromatic hydrocarbon
Benzo[*a*]pyrene
Obesity
Asthma
Air pollution
Sex-dimorphic

ABSTRACT

Background: Sexually dimorphic risk of obesity-associated asthma is posited to accelerate around puberty. Yet, the role of air pollution on the lean and obese asthmatic children has never been examined.
Objective: To compare whether a unit exposure to airborne benzo[*a*]pyrene (B[*a*]P) is associated with altered risks of asthma across the overweight/obese (OV/OB) control, lean asthmatic, and OV/OB asthmatic children, respectively, compared to the lean controls, before and after adjusting for oxidant stress markers (i.e. 15-F2t-IsoP, 8-oxo-dG, and Carbonyl).
Methods: Asthmatic and healthy control children, recruited from polluted urban and rural areas, were matched to ambient concentration of B[*a*]P. A unit increase in B[*a*]P and multinomial logistic regression on OV/OB control, lean asthmatic, and OV/OB asthma were compared across the sex- and age-groups.
Results: The median B[*a*]P was associated with a linear increase among the female children, according to OV/OB and asthma, respectively, and together, compared to the lean control girls ($p = 0.001$). While B[*a*]P was associated with positive relationship with 15-F2t-IsoP level among the OV/OB boys, the same exposure-outcome association was inverse among the OV/OB girls. One natural log-unit increase in ambient B[*a*]P was associated with 10.5-times greater odds (95% CI, 2.6–39.6; $p = 0.001$) the adolescent OV/OB boys, compared to the unit odds among the lean controls. In contrast, the adolescent OV/OB girls were associated with highest adjusted odds of the asthma (aOR = 15.4; 95% CI, 2.9–29.1; $p < 0.001$) compared to the lean control girls. An adjustment for 15-F2t-IsoP, and Carbonyls was associated with greater odds of asthma per unit exposure for the adolescent OV/OB girls (aOR = 16.2; 95% CI, 1.4–181.8; $p = 0.024$).
Conclusions: B[*a*]P exposure was associated with a leap in the odds of asthma among the OV/OB adolescents, particularly the girls, after adjusting for 15-F2t-IsoP and Carbonyls.

1. Introduction

Asthma and obesity represent two diseases with grave public health burden worldwide (Asher and Pearce, 2014). The present global prevalence of 300 million life-time asthma sufferers is expected to grow to 400 million by 2025 (Masoli et al., 2004). As of 2015, an estimated 700 million adults have obesity worldwide (Arroyo-Johnson and Mincey, 2016). While these two diseases have been investigated as two separate diseases with distinct pathophysiologic features, growing number of lifetime asthma sufferers are also obese (Boulet and Boulay, 2011). A segment of the obese asthma patients is associated with most severe and poorly-controlled asthma type (Lang et al., 2013). In fact, the co-morbid condition of severe asthma among obese individuals incurs 50%–80% of the total health care costs for asthma (Accordini et al., 2013, 2008). To date, environmental origin of asthma, which is either induced by or further exacerbated by obesity, has not been extensively investigated. The prevalence of either or both conditions has risen too rapidly within the last few decades, to be adequately explained by genetic

Abbreviations: 8-oxo-dG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; 15-F2t-IsoP, 15-F_{2t}-isoprostane; AP, attributable proportion; B[*a*]P, benzo[*a*]pyrene; BMI, body mass index; PAH, polycyclic aromatic hydrocarbon; DEP, diesel exhaust particles; CHMI, Czech Hydrometeorological Institute; RERI, relative excess risk due to interaction; VAPS, versatile air pollution sampler

* Corresponding author.
E-mail addresses: hchoi@albany.edu (H. Choi), prossner@biomed.cas.cz (P. Rossner), sram@biomed.cas.cz (R.J. Sram), hosm@ucmail.uc.edu (S.-M. Ho).

https://doi.org/10.1016/j.envint.2018.08.061
Received 11 May 2018; Received in revised form 27 August 2018; Accepted 28 August 2018

susceptibility factors. Accordingly, there is a growing need for a deeper understanding of the environmental etiologies of obesity and asthma co-presentation.

Early-life exposure to air pollution poses risk for not only the childhood asthma onset (Tantisira et al., 2008) and exacerbation (Velická et al., 2015), but also obesity (Chu et al., 2009; Jung et al., 2014; Lang et al., 2013). Furthermore, host susceptibility to air pollution is sexually dimorphic. Excess adiposity in obese rats exacerbate the harmful effects of ozone in female rats more than the males (Gordon et al., 2016). In another study, prenatal exposure to diesel exhaust particles (DEP) predisposed the male rat offspring to heightened calorie intake, weight gain, and neuroinflammation more severely than the female progenies (Bolton et al., 2012). In addition, in utero DEP exposure subsequently induced heightened macrophage infiltration, elevated production of peripheral IL-1β response to an allergen challenge, insulin resistance, and anxiety-like behavior in male offspring, supporting an early-life "programming" towards metabolic, behavioral, and neuroinflammatory alterations (Bolton et al., 2014). In Boston, US, in utero exposure to elevated $PM_{2.5}$ during second trimester predict asthma by age 6 years in boys, but not in girls (Hsu et al., 2015).

Such growing body of evidence raises a possibility that air pollution exposure among the overweight individuals contributes to asthma onset and/or exacerbation in gender-dimorphic fashion. In support of such hypothesis, adiponectin is observed at a higher absolute concentration in women, than men (Peake et al., 2005). Furthermore, low plasma adiponectin was associated with higher risk for asthma among adolescent girls than boys (Nagel et al., 2009). Accordingly, Sood and Shore (2013) postulated that the loss of the anti-inflammatory effects of adiponectin among obese girls might differ from obese boys, thereby contributing to the difference in asthma susceptibility.

Within Czech Republic, we have been examining early-life exposure to PAHs and their risk on multiple health endpoints by taking advantage of one-of-a-kind routine PAH monitoring program in historically industrial city of Ostrava and rural towns in Southern Bohemia (Dejmek et al., 2000; Sram et al., 2005). Ambient PAH concentrations within Ostrava remain one of the highest observed concentrations within Europe (Sram et al., 2013b). Furthermore, spatial as well as the temporal gradient of ambient B[*a*]P could vary by > 10-fold (Sram et al., 2013b), thereby allowing us to investigate asthma with relatively modest sample sizes. Within the present case-control study, we investigate air-pollution associated risks of childhood asthma among lean, overweight, and obese children within a heavily polluted city (i.e. Ostrava) vs. background air quality region (i.e. Southern Bohemia) in Czech Republic (Sram et al., 2013a). We postulate that: 1) airborne PAHs are correlated with biomarkers of systemic oxidant stress (i.e. 15-F2t-IsoP, 8-oxo-dG, and Carbonyl) in a sexually dimorphic fashion; 2) PAH exposures pose different risk of asthma among the OV/OB girls than the boys; and 3) the oxidant stress biomarkers are associated with sexually dimorphic susceptibility to asthma per unit PAH exposure.

2. Material and methods

Target sites, enrollment, and methods have been described. Briefly, 100 asthmatic and 100 healthy control children were enrolled from the city with heavy air pollution (i.e. Ostrava) as well as the background region (i.e. semi-rural towns in Southern Bohemia) in Czech Republic (Sram et al., 2013a). The Ostrava children were enrolled from the primary care clinics within the most polluted districts within Ostrava. According to one estimate, the childhood asthma prevalence in such district was ~30% during 2007 (Sram et al., 2013a). In contrast, the rural background region is marked by overall low annual mean B[*a*]P concentration in ambient air, comparable to the urban centers in western and northern Europe (Sram et al., 2013a).

2.1. Case definition

We conducted a comprehensive medical record review for each child, which contains records from the primary care physician and allergy specialist. A child was defined as positive case for asthma, if he/she met all of the following conditions: 1) positive diagnosis of 'current' asthma using *International Classification of Diseases* (ICD)*, Tenth Revision* (National Center for Health Statistics, 2016) codes within their medical record; 2) currently take asthma medication; 3) positive record of impaired lung function, based on spirometry within the past 12 months; 4) positive record of bronchial hyperresponsiveness in the last 12 months; and 5) positive on allergy skin tests (PhadiatopH, Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) for airborne allergens – timothy, mugwort, birch, cat, horse, dog, feathers, pollen, trees, grass, house dust mites (*D. pteronyssinus* and *D. farinae*), and two molds (Penicillium and Cladosporium). Diagnostic reliability across the physicians has been validated (Hertz-Picciotto et al., 2007). The control was free from all of the above conditions. Each case was matched with one healhy control by geographic location, age group, and gender. In addition, all parents answered questionnaire on the children's medical history and life-style choices. The ethics committee of the Institute of Experimental Medicine, Czech Academy of Sciences, approved the study. The parents of the children signed an informed consent.

2.2. Air pollution monitoring of polycyclic aromatic hydrocarbons

We obtained the ambient benzo[*a*]pyrene data from the Czech Hydrometeorological Institute (CHMI) website. CHMI manages and monitors eight airborne PAHs and $PM_{2.5}$ using Versatile Air Pollution Sampler (VAPS) since 1990s (Pinto et al., 1998). Based on the CHMI protocol, the mean daily level is measured once every three days for total of 10 days/month in southern Bohemia; once every six days for total of 5 days/month in Ostrava. Additional details on quality assurance and control have been described (Choi et al., 2017; Ghosh et al., 2016; Hertz-Picciotto et al., 2007).

2.3. Urinary 8-oxo-dG

The analysis of urinary 8-oxo-dG, using competitive ELISA, has been described (Rossner Jr et al., 2012). Briefly, urine samples were incubated with 50 μL of 8-oxo-dG standards (concentration range, 1.25–40 ng/mL), 50 μL of primary antibody (JaICA, Japan, clone N45.1, concentration 0.2 μg/mL) as well as 100 μL of secondary antibody conjugated with alkaline phosphatase. The urine samples were repeatedly incubated for 1.5 h at 37 °C and were washed with PBS/Tween and with 0.01% diethanolamine in water. The color absorbance was measured with a microplate reader at 405 nm. Any samples, which demonstrated inhibition < 20% or > 80% were again analyzed with or without further dilution. Urinary 8-oxo-dG concentration was measured as nmol 8-oxo-dG/mmol creatinine. The interassay coefficient of variability was calculated among the triplicate samples as 5.7%.

2.4. 15-F2t-IsoP immunoassay

Plasma concentrations of 15-F2t-IsoP were analyzed using immunoassay kits as described (Rossner Jr et al., 2012).

2.5. Protein carbonyl assay

Plasma concentration of carbonyl was analyzed using a non-competitive ELISA, as described (Rossner Jr et al., 2012). The concentration was expressed as nmol carbonyl/mL plasma. The interassay coefficient of variability was 3.1%.