Science of the Total Environment 626 (2018) 147–155

Contents lists available at ScienceDirect

Science of the Total Environment

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

Seasonal variations in fine particle composition from Beijing prompt oxidative stress response in mouse lung and liver

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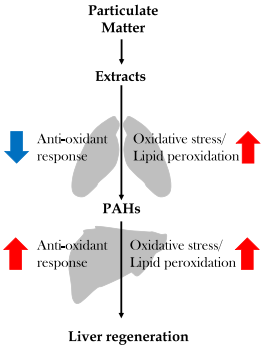
HIGHLIGHTS

- Extracts from PM collected in Beijing harm the lung and liver.
- Extracts of collected heating season (HS)-PM contained higher levels of metals and Poly aromatic hydrocarbons (PAH) than the non-HS extracts.
- In the lungs, the organic extracts increased oxidative damage and reduced protection mechanisms.
- In the liver, exposure to organic extracts increased Nrf2 protection genes.
- PAH from coal and biomass burning may lead to observed damage in the liver.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 14 September 2017
Received in revised form 3 January 2018
Accepted 3 January 2018
Available online xxxx

Editor: Jianmin Chen

Keywords:
Air pollution
Beijing
Inflammation
Nrf2 transcription factor
Antioxidant response
PAHs

ABSTRACT

Exposure to air pollution can induce oxidative stress, inflammation and adverse health effects. To understand how seasonal and chemical variations drive health impacts, we investigated indications for oxidative stress and inflammation in mice exposed to water and organic extracts from urban fine particles/$PM_{2.5}$ (particles with aerodynamic diameter ≤ 2.5 μm) collected in Beijing, China. Higher levels of pollution components were detected in heating season (HS, winter and part of spring) $PM_{2.5}$ than in the non-heating season (NHS, summer and part of spring and autumn) $PM_{2.5}$. HS samples were high in metals for the water extraction and high in polycyclic aromatic hydrocarbons (PAHs) for the organic extraction compared to their controls. An increased inflammatory response was detected in the lung and liver following exposure to the organic extracts compared to the water extracts, and mostly in the HS $PM_{2.5}$. While reduced antioxidant response was observed in the lung, it was activated in the liver, again, more in the HS extracts. Nrf2 transcription factor, a master regulator of stress response that controls the basal oxidative capacity and induces the expression of antioxidant response, and its related genes were induced. In the liver, elevated levels of lipid peroxidation adducts were measured, correlated with histologic analysis that revealed morphologic features of cell damage and proliferation, indicating oxidative and toxic damage. In addition, expression of genes related to detoxification of PAHs was observed. Altogether, the study suggests that the acute effects of $PM_{2.5}$ can vary seasonally with stronger health effects in the HS than in the NHS in Beijing, China and that some secondary organs may be susceptible for the exposure damage. Specifically, the liver is a potential organ influenced by exposure to organic components such as PAHs from coal or biomass burning and heating.

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https://doi.org/10.1016/j.scitotenv.2018.01.017
0048-9697/

1. Introduction

China's recent rapid urbanization and economic growth are accompanied by increased emissions of air pollutants (He et al., 2002). The urban air pollution affects large regions in Eastern China but also global pollution levels, as gases and aerosols can be transported over long distances (Liu and Diamond, 2005). The Global Burden of Disease assessment (GBD) (Collaborators, 2016) in 2010, and Lelieveld et al. (2015) in 2015, estimated that fine particles ($PM_{2.5}$, particles with aerodynamic diameter ≤ 2.5 μm) has become one of the largest environmental global public health problem. The estimated annual premature mortality due to $PM_{2.5}$ exposure in China is estimated to be million (Liu et al., 2016), out of which 79% accounts for strokes and ischemic heart disease (Maji et al., 2017). The premature mortality in large cities such as Beijing, Shanghai or Chongqing is estimated to be high (Maji et al., 2017).

The sources and the chemical composition of the PM in Beijing (China) vary between seasons (Lu et al., 2017; Qi et al., 2016), reflecting varying emission sources. This suggests possible seasonal differences in the PM composition and possibly also in the resulting health effects (Chen et al., 2013; Lu et al., 2017; Qi et al., 2016). In China, health effects such as cardiovascular diseases, respiratory diseases and lung cancer due to high PM exposure were observed in the winter and autumn (Chen et al., 2013; Chen et al., 2016; Lu et al., 2017; Qi et al., 2016; Rohde and Muller, 2015). These effects were associated with increased use of fuel and coal for heating in the winter. The associated emissions worsen air quality. In contrast, other studies showed larger effects in summer (Ma et al., 2011), that are attributed to pollution from vehicular emissions (Y. Chen et al., 2017b).

Health effects from exposure to PM may include breathing difficulties, asthma-like symptoms (Chowdhury et al., 2017), lung function abnormalities, decreased immune functions, cataract, kidney and liver damage (e.g. Jaundice) (Rengarajan et al., 2015), and lung cancer (Wang et al., 2017; Zhang et al., 2009). However, respiratory exposure and lung cancer risk assessment from PM are still limited in China (Chen et al., 2016). The above examples suggest that exposure to PM through breathing is a significant hazard to human health. Different PM components have been suggested to cause health effects: organics (Barraza-Villarreal et al., 2014; Chen et al., 2016; Kondraganti et al., 2003; Moorthy et al., 2015; Oh et al., 2011), ultrafine particles (Han et al., 2016), biologic materials (Pardo et al., 2017), black carbon (Lin et al., 2011), and transition metals (Choi et al., 2016; Pardo et al., 2015; Qi et al., 2016). For example, organic extracts containing mainly aliphatic hydrocarbons, polycyclic aromatic hydrocarbons (PAHs) and nitro-PAH, ketones and quinones generated significant DNA breakage and micronucleus formation (Oh et al., 2011). In addition, organic components from urban dust and diesel exhaust particles produced comparable levels of DNA damage in MEFs cells, assessed by alkaline comet assay (Dumax-Vorzet et al., 2015). Soluble components in inhaled PM may dissolve in tissues or in the blood and may reach and concentrate in other remote organs (Cassee et al., 2013; Deng et al., 2017; Kim et al., 2014; Wu et al., 2013). The particles, or their dissolved components, may induce chemical reactions that produce reactive oxygen species (ROS) (Lakey et al., 2016), or exert their toxicity by other means. Increasing evidence (Gurgueira et al., 2002; Lakey et al., 2016) suggest that enhanced ROS or reactive nitrogen species (RNS) are the mediators that induce both pulmonary and systemic inflammation and increase oxidative stress (Li et al., 2017; Pardo et al., 2016; Pardo et al., 2015). However, the mechanism of action of pollution PM is still not fully understood.

The objectives of this study are to understand how seasonal variations influence possible health effects of PM from Beijing and to investigate which fractions of the PM drive the major effects. Model mice were exposed to aqueous and organic extracts from collected PM using intra tracheal installations. The oxidative and anti-oxidative status in the lung and liver were evaluated in order to investigate the possible effects on primary and secondary organs and how solubility of the PM components affects these reactions.

2. Materials and methods

2.1. Particulate matter (PM) collection and extracts characterization

$PM_{2.5}$ was collected at the Peking University Urban Atmosphere Environmental Monitoring Station (about 30 m above ground level) in Beijing, China. Thirty seven samples collected from November 15 to March 15, 2012 represent the "heating season (HS)", while 29 samples collected from March 16 to November 14, 2012 represent the "non-heating season (NHS)". $PM_{2.5}$ samples (24 h) were collected on quartz fiber filters using a high-volume sampler (HIVOL-CABLD, ThermoFisher Scientific, Waltham, MA, USA) regularly every six days. A previously developed extraction method was applied in this study with slight modification (Heo et al., 2015). Briefly, two sets of filters were extracted with pierce water and dichloromethane, respectively. After sonication for 10 min and vortex for 15 s, samples were extracted at 200 rpm for 16 hr. After filtered through a 0.45 μm filter, water extract was freeze-dried, while the organic extract was rotary evaporated. 20 mg/mL stock solutions in sterile ultrapure water for the water extract and in DMSO/sterile ultrapure water (final concentration of DMSO was <5‰) for the organic extract were prepared. Accordingly, we obtained water and organic extracts from the non-heating season (NHS) and from heating season (HS). All the stock solutions were stored at −80 °C. Filters were divided into several parts and subjected to analysis by different analytical techniques. Daily mass concentrations of $PM_{2.5}$ (daily $PM_{2.5}$ samples on Teflon filter, determined by gravimetric method) and black carbon (BC, multi angle absorption photometer (MAAP, model 5012; Thermo Scientific, USA)) were concurrently measured at the same sampling site. The concentrations of OC and EC were measured by NIOSH thermal optical method using an EC/OC analyzer (Sunset Laboratory Inc., Hillsborough, NC, USA). Metals were measured with inductively coupled plasma mass spectrometry (ICPMS, Agilent7500a; Leeman Labs Inc., Hudson, NH, USA), and PAHs and their derivatives were determined with gas chromatography-mass spectrometer (GC–MS, Agilent 7890A-5975C; Santa Clara, CA, USA) coupled with electron ionization (EI) and electron-capture negative ionization (ECNI) ion sources (Lin et al., 2015). In addition, gas phase pollutants such as SO_2, NOx, O_3, CO, etc. and meteorological parameters were monitored at the same site continuously (data not presented).

2.2. Mice and exposure

The study was approved by The Institutional Animal Care and Use Committee (IACUC) at the Weizmann institute of science. Five weeks old male C57BL/6 mice were purchased from Harlan laboratories (Rehovot, Israel). After a week of acclimation, mice were exposed to water and organic extracts of the collected PM or to a blank extract using our previously-published protocol (Pardo et al., 2016). Briefly, mice were exposed every other day for a total of 5 times, using intra-tracheal (IT) model (Pardo et al., 2016). The mice received a dose of 20 μg of extract in 50 μL volume, each time, for 5 successive exposures. The overall dose is equivalent for 21 micrograms per cubic meter ($\mu g/m^3$) of PM in humans. Such concentrations are in the lower limit of PM pollution in Asia (Rohde and Muller, 2015). Twenty-four hours after the last instillation, mice were anesthetized again with ketamine/xylazin (20 mg/kg and 10 mg/kg body weight, respectively), and whole-body perfusion with phosphate buffer solution (PBS) was performed. The lungs and tracheas were exposed by dissection, and tracheal cannula was inserted. Lungs were lavaged with PBS solution twice. Cells were separated from the broncho-alveolar lavage fluid (BALF) by centrifugation (500 ×*g*, 5 min). The supernatant was removed and the cells were re-suspended in 100 μL of sterile saline. Lungs and liver were extracted.