Science of the Total Environment 598 (2017) 289–296

Contents lists available at ScienceDirect

Science of the Total Environment

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

Exposure to fine particulate matter causes oxidative and methylated DNA damage in young adults: A longitudinal study

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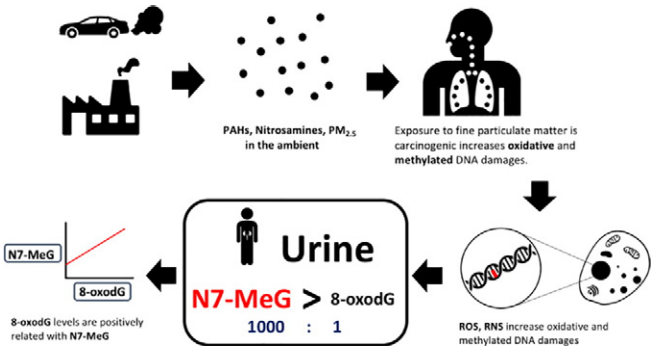
HIGHLIGHTS

- Exposure to fine particulate matter is carcinogenic.
- Limited information is available concerning the effects of $PM_{2.5}$ exposure on urinary N7-MeG levels.
- This study examined the relationships between personal exposure to $PM_{2.5}$ and oxidative and methylated DNA damage markers.
- N7-MeG is likely PAH metabolite dependent.
- Elevated levels of $PM_{2.5}$ might be associated with increases in urinary N7-MeG.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 3 January 2017
Received in revised form 24 March 2017
Accepted 11 April 2017
Available online 23 April 2017

Editor: D. Barcelo

Keywords:
Fine particulate matter
$PM_{2.5}$
1-Hydroxypyrene
N7-methylguanine (N7-MeG)

ABSTRACT

An increased understanding is needed of the physiological effects and plausible biological mechanisms that link $PM_{2.5}$ (particulate matter with an aerodynamic diameter below 2.5 μm) exposure to mortality and morbidities such as atherosclerosis and respiratory disease. $PM_{2.5}$ causes carcinogenic health effects. Biomonitoring in humans has suggested that 8-oxo-7, 8-dihydro-2-deoxyguanosine (8-oxodG) and N7-methylguanine (N7-MeG) are correlated with oxidative and methylated DNA damage. Thus, it is meaningful to explore the mechanisms of mutagenesis and carcinogenesis associated with oxidative and methylated DNA damage by simultaneously measuring these two markers. We recruited 72 participants from 2 areas (residential and commercial as well as residential and industrial) in the greater Taipei metropolitan area at baseline. Personal samplers were used to collect 24-hour $PM_{2.5}$-integrated samples. All participants completed an interview, and blood and urine samples were collected the next morning. All collection procedures were repeated twice after a two-month follow-up period. Urinary 8-oxodG and N7-MeG were assayed as biomarkers of oxidative and methylated DNA damage, respectively. Plasma superoxide dismutase (SOD) and glutathione peroxidase-1 (GPX-1) were

Abbreviations: 1-OHP, 1-hydroxypyrene; 8-oxodG, 8-oxo-7,8-dihydro-2-deoxyguanosine; GPX, glutathione peroxidase; GEE, generalized estimating equation; MNU, *N*-methyl-N-nitrosourea; N7-MeG, N7-methylguanine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NOCs, N-nitroso compounds; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase.

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http://dx.doi.org/10.1016/j.scitotenv.2017.04.079

8-Oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG)
Longitudinal study

measured as biomarkers of antioxidants. Urinary 1-hydroxypyrene (1-OHP) was used as a biomarker of exposure to polycyclic aromatic hydrocarbons (PAHs).
The mean $PM_{2.5}$ level was 37.3 μg/m^3 at baseline. $PM_{2.5}$ concentrations were higher during winter than during spring and summer. After adjusting for confounds through a generalized estimating equation (GEE) analysis, N7-MeG was significantly increased by 8.1% (β = 0.034, 95% CIs = 0.001–0.068) per 10 μg/m^3 increment in $PM_{2.5}$. 8-oxodG levels were positively correlated with N7-MeG according to both cross-sectional and longitudinal analyses, and 1-OHP was significantly associated with increasing 8-oxodG and N7-MeG concentrations.
Exposure to $PM_{2.5}$ increases methylated DNA damage. The mean level of urinary N7-MeG was 1000-fold higher than that of 8-oxodG.

1. Introduction

Fine particulate matter is generated directly by combustion or through secondary formation with precursor gases in the atmosphere (Lighty et al., 2000). Until recently, motor vehicle emissions remained the major source of ambient fine particulate pollution in urban areas (Schwela, 2000). Fine particles emitted from traffic exhaust can absorb polycyclic aromatic hydrocarbons (PAHs), and certain PAHs are known or suspected human carcinogens (Merlo et al., 1998; Strickland and Kang, 1999). Furthermore, emission particles from traffic exhaust contain large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Studies have shown that ROS and RNS are involved in carcinogenesis, mutagenesis and aging (Valavanidis et al., 2013; Waris and Ahsan, 2006). ROS can interact with RNS to form more potent oxidants that can directly induce DNA damage. The molecule 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) is an important DNA lesion because of its abundant and mutagenic potential. Two main groups of N-nitroso compounds (NOCs), nitrosamines or nitrosamides, are further formed through the reaction between RNS and dimethylamine or *N*-methylurea. These NOCs can cause methylated nucleobases and form DNA lesions such as N7-methylguanine (N7-MeG) (Chao et al., 2015; Chao et al., 2008).

Previous studies have explored the health effects and plausible biological mechanisms that link short- and long-term exposure to $PM_{2.5}$ (particulate matter with an aerodynamic diameter below 2.5 μm) with mortality and morbidities such as atherosclerosis and respiratory disease (Dockery, 2001; Dominici et al., 2006; Kaufman et al., 2016). In addition, $PM_{2.5}$ causes carcinogenic health effects. The International Agency for Research on Cancer (IARC) recently announced that exposure to outdoor air pollution causes lung cancer and classified outdoor air pollution as carcinogenic to humans (Hamra et al., 2014; Loomis et al., 2013). The evidence above indicates that DNA is a susceptible molecular target for oxidative damage and carcinogenic insult. Biomonitoring in humans has suggested that 8-oxodG and N7-MeG is correlated with oxidative and methylated damage to DNA (Chao et al., 2015; Chao et al., 2008; Lai et al., 2005; Tamae et al., 2009). Limited information exists regarding the effects of $PM_{2.5}$ exposure on urinary N7-MeG levels, and few studies have available data concerning personal $PM_{2.5}$ exposure. Thus, it is meaningful to explore personal $PM_{2.5}$ exposure as well as the mechanisms of mutagenesis and carcinogenesis attributed to oxidative and methylated DNA damage by simultaneously measuring these two markers. Therefore, we conducted a longitudinal study among healthy young adults to examine the associations of personal exposure to $PM_{2.5}$ using oxidative, methylated DNA damage biomarkers and antioxidant enzymes.

2. Methods

2.1. Participants

The present study employed a longitudinal design. The study participants included 72 healthy students aged 20 to 35 years old from the Nei-Hu and Xin-Zhuang districts of Taipei at baseline. All participants were non-smokers and free of disease. We collected $PM_{2.5}$, blood and urine samples from each participant three times between February and June 2014. Each participant was repeatedly measured, and the samples were collected every two months. All participants used personal monitors to assess their exposure to $PM_{2.5}$ over at least 24 h. The participants also completed an interview, and blood and urine samples were collected the next morning. During each visit, the participants completed a self-administered questionnaire and a daily diary. Not all 72 participants completed the three follow-up assessments; thus, new participants were recruited at different follow-up times. In all, 67 participants volunteered for all 3 activities, 14 participants volunteered for 2 activities, and 4 participants volunteered for one activity. A total of 233 measurements were collected and included in the subsequent statistical analyses. The Institutional Review Board of Tri-Service General Hospital and the National Health Research Institutes in Taiwan approved the present study. Written informed consent from all participants was obtained prior to study enrollment.

2.2. Questionnaire

The questionnaire contained examined the demographic characteristics, lifestyle information, and medical histories of the participants. In addition, the daily diary collected information regarding cigarettes smoked, environmental tobacco smoke exposure, ingestion of grilled or smoked foods, time spent in transit, and time spent indoors/outdoors over the past 24 h prior to specimen collection. All data were collected during the week for all three activities.

2.3. $PM_{2.5}$ personal air sampling

Personal breathing-zone air samples were collected from all participants over at least 24 h (beginning and ending at 8:00 AM) prior to blood and urine collection. The sampling train included a personal sampler designed for a 2.5-μm impactor (PEM; SKC Inc., PA, USA) and a pump (Gilian Gilair, Sensidyne Inc., FL, USA), with the sampling flow rate specified at 2 L/min. $PM_{2.5}$ samples were collected on a Quartz fiber filter (2500 QAT-UP, Purtram, Conn., USA). The air-sampling pump was placed in a nylon bag. A PEM connected to a tube to the pump was hung on the bag strap within the breathing zone of each participant during sampling. Except when participants were inconveniently sampled (e.g., during sleeping or showing), the pump functioned in the same space. A weight analysis used a microbalance (Mettler-Toledo, MT5, Greifensee, Switzerland) with 1-μg reading conducted in a lab at a constant temperature and 60% relative humidity. All filters were conditioned for at least 24 h and passed over a static neutralizer before weighing. The mean field blank weight change for the filters was 0.4 μg (n = 20; SD = 2.09 μg). The detection limit was 2.11 μg/m^3, which was measured as 3 times the standard deviation of the field blanks divided by the sampled volume of 2.88 m^3.