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Impact of air pollution on oxidative DNA damage and lipid peroxidation in mothers and their newborns

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ABSTRACT

Ambient air particulate matter (PM) represents a class of heterogeneous substances that form one component of air pollution. Oxidative stress has been implicated as an important action mechanism for PM on the human organism. Oxidative damage induced by reactive oxygen species (ROS) may affect any cellular macromolecule.

The aim of our study was to investigate the impact of air pollution on oxidative DNA damage [8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG)] and lipid peroxidation [15-F2t-isoprostane (15-F2t-IsoP)] in the urine and blood from mothers and newborns from two localities with different levels of air pollution: Ceske Budejovice (CB), a locality with a clean air, and Karvina, a locality with high air pollution. The samples from normal deliveries (38–41 week+) of nonsmoking mothers and their newborns were collected in the summer and winter seasons.

Higher PM2.5 concentrations were found in Karvina than in CB in the summer 2013 (mean ± SD: 20.41 ± 6.28 vs. 9.45 ± 3.62 μg/m^3, $P < 0.001$), and in the winter 2014 (mean ± SD: 53.67 ± 19.76 vs. 27.96 ± 12.34 μg/m^3, $P < 0.001$). We observed significant differences in 15-F2t-IsoP levels between the summer and winter seasons in Karvina for newborns (mean ± SD: 64.24 ± 26.75 vs. 104.26 ± 38.18 pg/ml plasma, respectively) ($P < 0.001$). Levels of 8-oxodG differed only in the winter season between localities, they were significantly higher ($P < 0.001$) in newborns from Karvina in comparison with CB (mean ± SD: 5.70 ± 2.94 vs. 4.23 ± 1.51 nmol/mmol creatinine, respectively). The results of multivariate regression analysis in newborns from Karvina showed PM2.5 concentrations to be a significant predictor for 8-oxodG excretion, PM2.5 and B[a]P (benzo[a]pyrene) concentrations to be a significant predictor for 15-F2t-IsoP levels. The results of multivariate regression analysis in mothers showed PM2.5 concentrations to be a significant predictor of 8-oxodG levels.

1. Introduction

Air pollution poses a serious threat to human health. Respirable particulate matter of aerodynamic diameter ≤2.5 μm (PM2.5), a significant constituent of polluted air, is being intensively studied along with the carcinogenic polycyclic aromatic hydrocarbons (PAHs) bound to it, including e.g. benzo[a]pyrene (B[a]P), the most known human carcinogen used as a surrogate for other carcinogenic PAHs. Owing to their small size, PM2.5 particles have the ability to penetrate into the human body via the airways. This is why they represent, compared to larger particles, a significant health risk (Russell and Brunekreef 2009). PAHs are produced by the incomplete combustion of organic matter. They are widely spread in the environment (WHO 2010) and some of them have genotoxic (Topinka et al., 2000; Binkova and Sram 2004), mutagenic, carcinogenic (IARC, 2012), and embryotoxic activities (Binkova et al., 1999).

Abbreviations: CB, Ceske Budejovice; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; 15-F2t-IsoP, 15-F_{2t}-isoprostane; B[a]P, benzo[a]pyrene; F2-IsoPs, F2-isoprostanes; HiVol, high volume air sampler; PM2.5, particulate matter of aerodynamic diameter <2.5 μm; PAHs, polycyclic aromatic hydrocarbons; ROS, reactive oxygen species; SPE, solid phase extraction.

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Environmental exposure to B[a]P in concentrations higher than 1 ng/m^3 presents the risk of DNA damage (WHO 2010). It has been demonstrated that after metabolic activation by cytochrome P450, PAHs covalently bind to DNA and form PAH-DNA adducts (Shimada and Fujii-Kuriyama 2004). This process can activate proto-oncogenes, or tumor suppressor genes, and cause the transformation of normal cells into tumor cells. Furthermore, evidence has been provided that the products of metabolic activation of PAHs can be transformed into PAH o-quinones by the effect of dihydrodiol dehydrogenase (Penning et al., 1999). These molecules enter redox cycles and produce reactive oxygen species (ROS), which causes oxidative damage to DNA and other macromolecules (Park et al., 2006). Thus, oxidative stress has been implicated as one of the mechanisms of PAHs carcinogenicity.

Oxidative stress results from an imbalance between the formation of reactive oxygen species (ROS) and the ability of the organism to readily detoxify the reactive intermediates or to repair the resulting damage (Mazzoli-Rocha et al., 2010). Oxidative damage to cellular macromolecules (nucleic acid, lipids and proteins) is associated with the development of cancer, respiratory tract and cardiovascular diseases (Yang and Omaye 2009), neurodegenerative diseases (Andersen 2004) as well as ageing (Evans et al., 2004). Oxidation of DNA results in incorrect base pairing and in the introduction of errors into genetic information (Cooke et al., 2003). ROS can further induce single- or double-strand DNA breaks, sugar-phosphate damage, apurinic/apyrimidinic sites, or may cause the formation of DNA-protein cross-links (Evans et al., 2004), which prevents chromatin development and blocks replication and transcription (Donkena et al., 2010). 8-Oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) is the most common product of DNA oxidation. Its levels can be measured in urine as a biomarker of whole body's oxidative stress (Loft and Poulsen 1999). Lipid peroxidation is caused by attack of ROS on lipid molecules, primarily those in plasma membranes (Montuschi et al., 2004). Their peroxidation modifies cell membranes properties, thus disrupting regular cellular functions (Niki 2009). Isoprostanes are considered to be the most reliable markers of lipid peroxidation. They include several groups, but F2-isoprostanes (F2-IsoPs), particularly 15-F_{2t}-isoprostane (15-F2t-IsoP), are the most often studied compounds (Rossner et al., 2008). F2-IsoPs are derived from arachidonic acid in membranes via a free radical-catalyzed mechanism (Morrow et al., 1990). F2-IsoPs are cleaved from the sites of their origin and then either circulate in plasma or are excreted in urine (Morrow et al., 1992). Measurement of 15-F2t-IsoP in urine or plasma has been shown to reflect the oxidative stress in a number of human diseases, including cardiovascular, pulmonary, neurological, renal, and liver diseases (Cracowski et al., 2002).

Negative effects of exposure to air pollutants are particularly deleterious for newborns and adolescents, in whom they may affect the development of physiological functions. Evidence has been provided that PAHs can cross the placenta and cause DNA damage in the fetus (Manchester et al., 1992). Prenatal exposure to ambient air pollution to some PAHs can increase the risk of either preterm birth or low birth weight (LBW) along with intrauterine growth restriction (IUGR) (Dejmek et al., 2000; Choi et al., 2008). As a consequence, IUGR and LBW newborns are more prone to a higher risk of delay in mental development (Van Wassenaer 2005), respiratory dysfunction (Lipsett et al., 2006), asthma symptoms in childhood (Nepomnyaschy and Reichman 2006), and cardiovascular diseases in adulthood (Baker 2006), including hypertension, arteriosclerosis and diabetes (Martin-Gronert and Ozanne 2007). It has been presumed that with various degrees of air pollution, the quality of the genome can also influence the sickness rates of children (Sram et al., 2006).

Due to the heterogeneous composition of polluted air, evaluating exposure and investigating the association between exposure to these compounds and the possible biological consequences poses a very complicated problem. Moreover, the resulting exposure of an individual is a multifactorial process that can be impacted not only by polluted air, but also by genetic predisposition, life style (i.e. smoking), socioeconomic and other environmental factors (Wild et al., 2008).

The aim of our study was to compare the levels of oxidative damage to DNA (8-oxodG) and lipids (15-F2t-IsoP) in subjects from two locations in the Czech Republic: newborns and their nonsmoking mothers living in Karvina, and Ceske Budejovice. The Ceske Budejovice group has been selected as a control group, since the levels of pollution in this locality are significantly lower when compared with Karvina. Sampling of biological material (urine, plasma) was performed at both locations in two periods with different levels of air pollution: in summer 2013 (low air pollutant levels) and in winter 2014 (high levels of air pollution). PM2.5 and PAHs exposure was assessed and the oxidative damage to DNA and lipids was analyzed. We expected elevated levels of oxidative damage in the group exposed to higher concentrations of air pollutants, i.e. in Karvina in the winter season.

2. Materials and methods

2.1. Subjects

The samples were collected in the Ceske Budejovice Hospital, Department of Obstetrics and Department of Neonatology, and in the Karvina Hospital, Department of Obstetrics and Department of Neonatology. The study was approved by the Ethics Committee of both hospitals and the Institute of Experimental Medicine AS CR in Prague. Each mother signed the written consent. The heating in the homes of mothers was usually by the central heating or gas; open fire places were not used in any house. The samples were collected from normal deliveries (38–41 week+) of nonsmoking mothers and their newborns in the summer and winter season to account for differences in air pollution. The samples included venous blood and urine from 99 mothers (summer) and 100 mothers (winter) at Ceske Budejovice, a locality with relatively clean air, and 70 mothers (summer) and 73 mothers (winter) at Karvina, a locality with high air pollution, and cord blood and urine from 99 newborns (summer) and 100 newborns (winter) at Ceske Budejovice and 71 newborns (summer) and 74 newborns (winter) at Karvina. The basic characteristics of the groups studied are shown in Table 1. Blood was collected in EDTA tubes to isolate DNA and plasma. Urine samples were collected into 50 mL tubes (Greiner Bio-one) and stored at −20 °C until transported to the Institute of Experimental Medicine. Aliquots (1–2 mL) of urine were frozen at −80 °C until analysis.

2.2. Air sampling and analysis of selected air pollutants

Particulate matter ≤2.5 μm (PM2.5) was collected by a High Volume (HiVol) 3000 Air Sampler (model ECO-HVS3000, Ecotech, Australia) on Pallflex membrane filters (EMFAB, TX40HI20-WW) in both study localities. The sampling was conducted as previously described (Topinka et al., 2011). Detailed information on air sampling, extraction of organic complex mixtures (EOM) from the filters and chemical analysis of B[a]P is given in Topinka et al. (2011). Concentrations of air pollutants was expressed in μg/m^3 (PM2.5) and ng/m^3 (B[a]P).

2.3. 8-oxodG ELISA

Solid Phase Extraction of 8-oxodG from urine samples (SPE) was performed as described by Rossner Jr. et al. (2013). Levels of 8-oxodG were analyzed by Highly Sensitive 8-OhdG Check ELISA