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Chromosomal aberrations in environmentally exposed population in relation to metabolic and DNA repair genes polymorphisms

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Abstract

The capital city of Prague is one of the most polluted localities of the Czech Republic. Therefore, the effect of exposure to carcinogenic polycyclic aromatic hydrocarbons (c-PAHs) adsorbed onto respirable air particles (<2.5 μm) on chromosomal aberrations was studied in a group of policemen (males, aged 22–50 years) working in the downtown area of Prague and spending daily >8 h outdoors ($N = 53$). Age- and sex-matched healthy volunteers spending >90% daily time indoors were chosen as controls ($N = 52$). Ambient air particles (PM10, PM2.5) and c-PAHs were monitored using versatile air pollution sampler (VAPS), and personal exposure was evaluated using personal samplers during working shift. Chromosomal aberrations were analyzed by conventional cytogenetic analysis and fluorescent in situ hybridization (FISH). Urinary cotinine plasma levels of vitamins A, E and C, folate, total cholesterol, HDL, LDL cholesterols and triglycerides were also analyzed as possible effect modifiers. Genotypes CYP1A1*2A, CYP1A1*2C, GSTM1, GSTP1, GSTT1, EPHX1, NAT2, hOGG1, XRCC1, XPD, p53 BstI, p53 MspI, MTHFR677, and MS2656 were determined by PCR-based RFLP assays. The following levels of air pollution were recorded during the study period (mean from HiVol sampling): PM10 62.6 μg/m^3, c-PAHs 24.7 ng/m^3, B[*a*]P 3.50 ng/m^3. The conventional cytogenetic analysis did not reveal any differences between the group of policemen exposed to the ambient air pollution and the control group. The cytogenetic analysis by FISH analysis used the whole chromosome painting probes for chromosomes #1 and #4 (Cambio, UK). It detected a significant increase in all studied endpoints in the policemen compared to controls (% AB.C. = 0.33 ± 0.25 versus 0.24 ± 0.18, $p < 0.05$, $F_G/100 = 1.72 \pm 1.57$ versus 1.25 ± 1.11, $p < 0.05$, AB/1000 (aberrations/1000 cells) = 5.58 ± 4.62 versus 3.90 ± 3.06, $p < 0.05$). CYP1A1*2C (Ile/Ile), XPD 23 (Lys/Lys), and XPD 6 (CC) genotypes were associated with an increase of aberrant cells by conventional method. Factors associated with an increased level of translocations by FISH included age, smoking, B[*a*]P-like DNA adducts (corresponding to the exposure of c-PAHs), folate, polymorphisms of CYP1A1*2C, GSTP1, EPHX1, p53 MspI and MTHFR. Ambient air exposure to c-PAHs significantly increased FISH cytogenetic parameters in nonsmoking policemen. We may conclude that FISH indicates that the city policemen in Prague represent a group of increased genotoxic risk. This is the first study

Abbreviations: PAHs, polycyclic aromatic hydrocarbons; c-PAHs, carcinogenic polycyclic aromatic hydrocarbons; B[*a*]P, benzo[*a*]pyrene; PM10, particulate matter < 10 μm; PM2.5, particulate matter < 2.5 μm; EXP, exposed group, policemen; CON, control group; CA, chromosomal aberrations; CCA, conventional cytogenetic analysis; FISH, fluorescence in situ hybridization; PBL, peripheral blood lymphocytes; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphisms; GSTM1, GSTP1, GSTT1, glutathione-*S*-transferase M1, P1, T1; CYP1A1, cytochrome P-450 1A1 gene; EPHX1, epoxide hydrolase1; NAT2, *N*-acetyl transferase 2; hOGG1, 8-oxoguanine DNA glycosylase; XPD, xeroderma pigmentosum D gene; XRCC1, X-ray repair cross complementing group 1; MTHFR, methylene tetrahydrofolate reductase; MS, methionine synthetase; p53, protein p53

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that has reported a relationship between DNA adducts (biomarker of exposure) and chromosomal aberrations by FISH (biomarker of effect).
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Keywords: Chromosomal aberrations; Conventional cytogenetic analysis; FISH; Genetic polymorphisms; Metabolic genes; DNA repair genes; Environmental exposure to carcinogenic polycyclic aromatic hydrocarbons

1. Introduction

Cytogenetic analysis of peripheral blood lymphocytes (PBL) has been accepted as a technique for the biological monitoring of genetic damage in somatic cells since the early 1970s. Up to the present time, it has remained the only suitable assay for biological monitoring of the genetic damage induced in somatic cells by excessive exposure [1–4] to clastogenic agents in the workplace.

Today, chromosomal aberrations (CA) in human peripheral lymphocytes are recognized as a valuable biomarker of effect, probably the only one which has been internationally standardized and validated [5–7]. Nowadays it is generally accepted that a high frequency of chromosomal aberrations in peripheral lymphocytes is predictive of an increased risk of cancer [8–10].

When the whole chromosome painting by fluorescence in situ hybridization (FISH) was introduced in the 1990s in the field of ionizing radiation research [11], the classic cytogenetic analysis of chromosomal damage was partly supplanted by FISH.

While the classic cytogenetic analysis (conventional method) is the method of choice for the determination of unstable types of aberrations, the FISH technique seems to be a rapid, sensitive, and reliable method for the detection of stable structural rearrangements not diminished in time, such as translocations. Therefore, this method is highly suitable for analyzing a low-dose radiation exposure [12,13] and has been used in several studies for biological dosimetry [14–17].

As far as exposure to chemical carcinogens is concerned, the available data are still scarce. Only few reports were published about the use of FISH painting method to detect exposures to chemical clastogens: cytostatics [18], military waste disposal [19], pesticide phosphine [20], acrylonitrile, 1,3-butadiene and ethylene benzene [21]. In general, FISH painting technique appeared to be more sensitive than the conventional technique to detect the genomic frequency of translocations induced by various chemical agents or irradiation [19,21].

Chromosome painting allows the detection of CA exclusively involving the painted chromosomes. Consequently, only a fraction of all aberrations is visible. The genomic frequency of chromosomal interchanges is thus extrapolated from the frequency observed on the painted chromosomes according to the assumption of random distribution of induced endpoints [22].

Atmospheric pollution by c-PAHs from incomplete combustion represents a relevant environmental hazard and has been associated with a considerable amount of adverse health effects in humans. c-PAHs showed, e.g. a clastogenic activity in cultured human lymphocytes [23] as well as in human studies [24]. In the EC project EXPAH [25] the cytogenetic analysis of chromosomal aberrations was simultaneously performed using conventional method and FISH to widely cover different types of CA. In our study on the impact of ambient air particulate pollution in Prague affecting city policemen and "unexposed" controls, we analyzed the relationship between chromosomal aberrations and biomarkers of susceptibility (metabolic and DNA repair genotypes), simultaneously controlling for possible modifiers and/or confounders (diet, lifestyle).

2. Materials and methods

2.1. Subjects and sampling

The study population consisted of 53 policemen (males) working in the Prague downtown and spending daily >8 h outdoors (EXP). Age- and sex-matched healthy male volunteers spending >90% of daily time indoors and working in the suburban area were chosen as controls (CON, $N = 52$). In both groups questionnaires on personal medical history and life-style (smoking, alcohol consumption, eating habits) had to be filled in by all participants. In addition, analyses of cotinine level in urine and vitamins A, C, E in plasma were done to objectify smoking status and dieting.

All participating subjects were healthy volunteers, who signed an informed consent form and could cancel their participation at any time during the study according to Helsinki II declaration. Any person with medical treatment, radiography or vaccination up to 3 months before sampling was not included in the study.

The blood and urine samples were collected at the end of working shift, by venipuncture into vacuettes containing sodium heparin, coded and transported to the laboratory. The

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