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Genetic variability in the system of natriuretic B peptide and principal toxicological parameters in workers exposed to lead

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ABSTRACT

The study was aimed at evaluating the influence of selected polymorphisms of natriuretic peptide B precursor (NPPB) and natriuretic peptide receptor C (NPR3) genes on blood lead concentration (Pb-B) and blood zinc protoporphyrin concentration (ZnPP) in persons occupationally exposed to lead. Investigations were conducted on 360 persons (mean age: 44.49 ± 9.62 years), workers exposed to lead compounds. The analysis examined four polymorphisms of BNP gene, i.e.,: rs198388, rs198389, rs632793, and rs6676300; as well as one polymorphism of receptor C for natriuretic peptides, i.e., rs1421811. Heterozygosity in locus rs632793 of NPPB gene may result in higher concentrations of Pb-B, while allele A in locus rs632793 of NPPB gene seems to determine higher concentrations of ZnPP in persons occupationally exposed to lead. Workers exposed to lead and carrying allele C in locus rs198388 of NPPB gene, particularly in the heterozygotic setup, seem to be predisposed to present higher concentrations of ZnPP. Carriership of A allele in locus rs198389 of NPPB gene probably determines higher concentrations of ZnPP in study group. In summary, among persons occupationally exposed to lead, certain relationships were demonstrated between rs632793, rs198388 and rs198389 polymorphisms of NPPB gene and principal toxicological parameters characterizing exposure to lead.

1. Introduction

Relationship between occupational exposure to lead and cardiovascular diseases has recently become the topic of several scientific investigations. Among respective findings, effects of lead and its compounds were documented in development of arterial hypertension, arteriosclerosis, cardiac arrhythmia, morphological and functional disturbances within heart and blood vessels (Glenn et al., 2003; Gonick et al., 1997; Kasperczyk et al., 2005; Navas-Acien et al., 2007; Poręba et al., 2010; Poręba et al., 2011a,,2011b; Poręba et al., 2013).

Circulating hormones synthesized by cardiomyocytes include atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). In addition, natriuretic peptide C and urodilatin, structurally resemble ANP and BNP, but synthesized, respectively, by endothelium and kidneys, are also included (Clerico and Emdin, 2004). Natriuretic peptides perform several functions: induce vasodilatation, exert hypotensive, natriuretic and diuretic effects. Moreover, they also inhibit the activity of sympathetic nervous system and renin-angiotensin-aldosterone system (RAA), as well effects of endothelin, cytokines and vasopressin. In addition, they also block mechanisms responsible for cardiovascular hypertrophy and remodeling (anti-proliferative effect). Additionally, they control processes of coagulation and fibrinolysis, and inhibit platelet activity (Clerico and Emdin, 2004).

Relationships were demonstrated between rs198388, rs198389, rs632793, rs6676300 polymorphisms in the gene coding natriuretic peptide B precursor (NPPB) and rs1421811 polymorphism in the gene coding receptor C of natriuretic peptides (NPR3), on one hand, and cardiovascular system diseases, including arterial hypertension, on the other hand (Chen et al., 2010; Kosuge et al., 2007; Lanfear, 2010; Nakayama et al., 2000; Pfister et al., 2013; Poręba et al., 2009; Rehemudula et al., 1999; Rubattu et al., 2013; Wu et al., 2014).

Poręba et al. (2009) provided evidence for relationship between SNP type polymorphism (single-nucleotide polymor-

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phism) rs198389 in the gene of BNP precursor and grade of arteriosclerotic narrowing of renal artery in patients with arterial hypertension. Homozygotes CC in position 381 of BNP gene promoter seemed to be more prone to develop arteriosclerotic lesions in renal arteries. In turn, Chen et al. (2010) documented the relationship between rs198388 BNP polymorphism and arterial hypertension: genotypes rs198388 GA and AA. The presence of A allele was linked to a decreased chance for developing arterial hypertension. Kosuge et al. (2007) demonstrated that polymorphism involving a variable number of tandem repeat polymorphism site in the flanking region of the NPPB gene 5′-end was linked to primary arterial hypertension in women. Wu et al. (2014) proved that rs632793, rs198388 and rs198389 polymorphisms of NPPA-NPPB were related to augmented concentrations of ANP and BNP in serum and a reduced risk of left ventricular dysfunction in patients with ischemic cardiac disease.

Results of several investigations pointed also to relationships between polymorphisms in genes coding receptors of natriuretic peptides and arterial hypertension as well cardiovascular diseases. Rehemudula et al. (1999) showed a relation between dinucleotide repeat polymorphism in intron 2 of NPR2 receptor and arterial hypertension. In turn, Nakayama et al. (2000) found in patients with arterial hypertension the association between microsatellite polymorphism in 5′-flanking region of gene coding NPR1 and myocardial hypertrophy. Lanfear (2010) proved that the common 'ancestral' C-(55) variant of the NPRC P1 promoter is linked to a reduced concentration of ANP and to higher values of SBP and MBP in obese patients with arterial hypertension. A few studies demonstrated a relationship between SNP type 55C > A polymorphism in NPR3 gene and decreased expression of receptors in adipose tissue, resulting in augmented concentrations of natriuretic peptides and manifestation of arterial hypertension. In turn, Rubattu et al. (2013) proved the relationship between certain genetic variant of NPR3 receptor and manifestation of ischemic cerebral stroke. However, Pfister et al. (2013) found no links between rs198389 polymorphism in NPPB and ischemic heart disease or between rs198389, rs5068 or rs198358 polymorphisms and the risk of heart failure. Also Zeng et al. (2014) failed to confirm the relationship between C-1298GT polymorphism in NPPB and arterial hypertension.

The search for a relationship between genetic variability in the system of natriuretic B peptide and principal toxicological parameters in workers exposed to lead seems to be particularly significant in the context of the earlier quoted data. Such studies may manifest new mechanistic aspects of lead, in parallel allowing identification of individuals potentially most sensitive to cardiotoxicity of lead compounds. Moreover, the study may represent a significant step in clarification of differences in propensity for lead toxicity between populations differing in frequency of manifestation involving specific genotypes.

1.1. Objectives

The present study aims to evaluate the effects of selected polymorphisms of NPPB and NPR3 genes on blood lead concentration (Pb-B) and blood zinc protoporphyrin concentration (ZnPP) in persons occupationally exposed to lead compounds.

2. Materials and methods

2.1. Study population

Investigations were conducted on 360 persons (337 men, 23 women, mean age: 44.49 ± 9.62 years) occupationally exposed to lead compounds, foundry employees of the metallurgical and metallic charge preparation sections, smelter workers, refiners or converter workers and female administrative workers (coordination of the supervision of work safety and hygiene). Criteria for inclusion in the study were: employment at the workplaces with exposure to lead (concentration of lead >0.2 maximum admissible concentration (MAC), according to foundry services responsible for work safety and hygiene) and work in the exposure to lead during at least 0.5 years. The size and quality of the environmental exposure for all of the persons included in the study was similar. All persons inhabited the same region at similar distances to the car traffic. For the study group, only subjects who inhabited the region for a longer time (at least for 10 years) were included. Exclusion criteria were: exposure to compounds other than lead in concentration >0.5 MAC, arterial hypertension, diabetes mellitus, ischemic heart disease, obliterative atherosclerosis, renal failure, hypercholesterolemia, hypertriglyceridemia. Moreover, individuals on vegetarian diet were excluded. Clinical characteristics of the studied group are presented in Table 1.

Table 1
Clinical characteristics of studied group.

	X	Me	SD	Min	Max
Age [years]	44.49	47.00	9.62	22.00	62.00
BMI [kg/m^2]	27.60	26.76	3.87	18.83	39.46
Weist circumference [cm]	97.40	97.00	10.71	68.00	129.00
	n		%		
Number	360		100.00		
Gender					
Male	337		93.61		
Female	23		6.39		
Smokers	145		40.28		
Overweight/Obesity	259		71.94		
Overweight	161		44.72		
Obesity	98		27.22		

Max-maximal value; Me-median value; Min-minimal value; SD-standard deviation; X-means.

2.2. Basic measurements

In all persons who qualified for inclusion in the study, a questionnaire examination was conducted, containing anamnesis related to the past diseases, lifestyle and basic anthropometric measurements. Body mass index (BMI) was calculated using the formula: body mass/height^2. Overweight was defined as values of BMI ranging between 25.00 and 29.99 kg/m^2, and obesity as values of BMI ≥ 30 kg/m^2. Blood was sampled for estimation of principal laboratory and toxicological parameters and to analyse the selected SNP type polymorphisms. From every studied individual a sample of approximately 30 ml blood was drawn from brachial vein. Blood was sampled 12 h after the last meal, allowed to clot or mixed with EDTA.

2.3. Toxicological measurements

The examined toxicological parameters included concentration of lead, zinc protoporphyrin and cadmium in blood (Pb-B, ZnPP and Cd-B), concentration of copper and zinc in serum (Cu-S and Zn-S), and concentration of cadmium and arsenic in urine (Cd-U and As-U). Pb-B and Cd-B were measured by graphite furnace atomic absorption spectrometry (Solaar M6, Thermoelemental, UK). ZnPP was measured using rapid, fluorometric screening method by means of Hematofluorymeter ProtoFluor Helena (USA). Cu-S and Zn-S were determined by flame atomic absorption spectrometry (Solaar M6, Thermoelemental, UK). As-U and Cd-U were measured by Hydride Generation Atomic Absorption Spectrometry (HGAAS) using the VP100 Continuous Flow Vapour System. Cd-U and As-U were normalised to the creatinine contents of urine. The princi-