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Persistent organic pollutants distribution in lipoprotein fractions in relation to cardiovascular disease and cancer

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ABSTRACT

Persistent organic pollutants (POPs) are lipophilic environmental toxins that have been associated with cardiovascular disease (CVD) and cancer. The aim of this study was to investigate the concentrations of POPs in human high and low/very low-density lipoproteins (HDL and LDL/VLDL) and the possible association with CVD and cancer occurrence in individuals living in a contaminated area. Lipoproteins from 28 individuals (7 healthy controls, 8 subjects with cancer, 13 subjects with CVD) were isolated and the fraction-specific concentration of 20 different POPs was analyzed by high resolution gas chromatography/high resolution mass spectrometry. The activity of Paraoxonase 1 (PON1), an anti-oxidant in HDL, was determined in plasma of these 28 subjects and additional 50 subjects from the same area excluding diseases other than cancer or CVD. Fourteen polychlorinated biphenyls (PCBs) and three organochlorine pesticides were detected, and especially highly chlorinated PCBs were enriched in lipoproteins. Significantly higher concentrations of POPs were found among individuals with CVD or cancer compared to controls. Principal component analyses showed that POP concentrations in HDL were more associated with CVD, while POP concentrations in LDL/VLDL were more associated with cancer. PON1 activity was negatively correlated to sumPCB and a co-variation between decreased arylesterase-activity, increased PCB concentrations and CVD was found. This study shows that POPs are present in lipoproteins and were more abundant in individuals with CVD or cancer compared to healthy controls. The results also indicate that PCB exposure is accompanied by reduced PON1 activity that could impair the HDL function to protect against oxidation.

1. Introduction

Persistent organic pollutants (POPs) are a heterogeneous group of man-made chemicals, with a long half-life, that accumulate in fat tissues due to their lipophilic nature. POPs, as defined by the Stockholm Convention, hosted by the United Nations Environment Programme (www.unep.org), include polychlorinated biphenyls (PCBs), dioxins, organochlorine pesticides (OCPs) as well as polybrominated diphenyl ethers (PBDEs) (Wikoff et al., 2012). Several studies have found associations between increased serum or plasma concentrations of POPs and an increased risk for negative health effects in the general population, including cardiovascular disease (CVD) (Lind et al., 2012; Sergeev and Carpenter, 2010), diabetes (Faerch et al., 2012; Lee et al., 2011) and cancer (Engel et al., 2007; Hardell et al., 2006). The causal association between POPs and cancer has however been questioned (Golden and Kimbrough, 2009). In addition, some studies show that people living in industrial contaminated areas have higher concentrations of POPs in plasma compared to control populations (Hovander et al., 2006) and that people consuming locally produced food in contaminated areas have higher concentrations of POPs compared to people consuming locally produced food in non-contaminated areas (Donato et al., 2006; Langer et al., 2007).

Although banned for more than thirty years, PCBs still persist in the environment and in food sources such as fish, meat and dairy products (Diamond et al., 2010). The 209 different PCB congeners can either be

Abbreviations: AhR, aryl hydrocarbon receptor; CVD, cardiovascular disease; HCB, hexachlorobenzene; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HRGC–HRMS, high resolution gas chromatography/high resolution mass spectrometry; LOD, limit of detection; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDL/VLDL, low-density lipoprotein/very low-density lipoprotein; OCDD, octachlorodibenzo-p-dioxin; OCP, organochlorine pesticide; p,p′-DDE, 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene; p,p′-DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; PBDE, polybrominated diphenyl ether; PC, principal component; PCA, principal component analysis; PCB, polychlorinated biphenyl; PON1, paraoxonase 1; POP, persistent organic pollutant; sumPCB, sum of PCB Congeners; VLDL, very low-density lipoprotein.

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coplanar or non-coplanar, depending on the positions of the chlorine atoms. The coplanar congeners resemble dioxins and these dioxin-like PCBs have been shown to activate the aryl hydrocarbon receptor (AhR) (Henry and DeVito, 2003). The AhR affects different signaling pathways including the retinoic acid receptor, the estrogen receptor and nuclear factor κB and may also have a role in the regulation of T-cell differentiation (Quintana, 2013). The toxicity of the non-dioxin like PCBs is poorly understood but believed to be mediated through non-AhR mechanisms. In vitro, these PCBs have been shown to antagonize androgen receptor activation, affect estrogen receptor activation, inhibit gap junction communication and bind to transthyretin (Hamers et al., 2011). Also, neuronal toxicity through the Ryanodine receptors has been described (Wayman et al., 2012). OCPs including 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene (p,p′-DDE), hexachlorobenzene (HCB) as well as the PBDEs, which are structurally similar to PCBs, are believed to be endocrine disruptors by their interference with different hormone systems (Karami-Mohajeri and Abdollahi, 2011; Li et al., 2008; Vonderheide et al., 2008). Furthermore, negative effects of POPs may be related to induction of proinflammatory pathways (Gauthier and Girard, 2001; Karami-Mohajeri and Abdollahi, 2011).

Lipoproteins consist of an outer layer of phospholipids, proteins and free cholesterol filled with triglycerides and esterified cholesterol. Lipoproteins are classified into three main fractions depending on their density; very low-density, low-density and high-density lipoproteins (VLDL, LDL and HDL respectively). VLDL is synthesized in the liver and transports lipids to peripheral tissues. LDL arises from hydrolysis of VLDL and delivers cholesterol to the cells by receptor mediated endocytosis. HDL is responsible for the reversed cholesterol transport in which excess cholesterol is transported back to the liver for excretion into bile (Brewer, 2011; Rosenson et al., 2012). High levels of LDL cholesterol (LDL-C) are considered a strong risk factor for future CVD, thereby being the rationale for cholesterol lowering therapies. HDL, on the other hand, has been shown to possess anti-inflammatory, antioxidative as well as anti-thrombogenic properties, which have led to the viewpoint of HDL being protective against CVD. In line, low levels of HDL cholesterol (HDL-C) is a risk factor for CVD (Barter, 2011; Chapman et al., 2011). Many HDL functions are determined by the proteins in the particles. One such important protein is paraoxonase 1 (PON1), a calcium-dependent esterase associated to HDL in the circulation (Sirivarasai et al., 2007). PON1 has been shown to provide HDL with anti-inflammatory properties, which includes hydrolyzing lipid peroxides in LDL and preventing foam cell formation in the vascular wall (Gupta et al., 2009; Precourt et al., 2011). PON1 has also been shown to hydrolyze several metabolites of organophosphate pesticides such as paraoxon, chlorpyrifon, oxon and diazoxon (Costa et al., 2005). Furthermore, reduced PON1 activity has been linked to CVD (Mackness et al., 2003), diabetes mellitus (Gupta et al., 2011) and cancer (Elkiran et al., 2007).

Early reports have shown that POPs can bind to lipoproteins (Becker and Gamble, 1982; Maliwal and Guthrie, 1982; Vomachka et al., 1983). However, beside a previous study showing that a large fraction of POPs are associated to LDL/VLDL and HDL in healthy individuals (Norén et al., 1999), little is known about the human lipoprotein distribution of POPs in vivo and how this relates to disease progress. The aims of the current study were 1) to assess the distribution of POPs in lipoprotein fractions and 2) to investigate if the distributions differ in healthy controls as compared to subjects with CVD or cancer and 3) to investigate whether the POP levels can influence the activity of HDL-associated PON1.

2. Method and material

2.1. Study participants

Blood samples were available from participants in a previous questionnaire-based epidemiological study. All study subjects were living in an area polluted by POPs and metals from long lasting local industrial activities, as confirmed by environmental measurements by local authorities. For all individuals, information about age, gender, diseases, medication, diet, smoking, occupational exposure and other life-style factors was available (Helmfrid et al., 2012). After exclusion of individuals with diseases other than cancer or CVD, the total number of subjects available for study was 78. Plasma samples from a subgroup ($n = 28$) of non-smokers were used for POP measurement in lipoprotein fractions. Cancer and CVD cases were randomly selected. Cancer included subjects with hormone-related cancer, skin cancer or lymphoma. The healthy controls were selected so to represent the disease groups with respect to age and gender. Plasma samples covered the full range of sumPCB previously measured (2–10 ng/mL). Thirteen individuals had levels in the first and second quartile (2–4 ng/mL, 4 healthy, 4 with cancer and 7 with CVD) while 15 individuals had levels in the third and fourth quartile (5–10 ng/mL, 3 healthy, 4 with cancer and 8 with CVD) of the whole population. For arylesterase measurements, plasma from all 78 individuals was used. The clinical characteristics of selected samples are presented in Table 1. The study was approved by the local ethics committee.

2.2. Lipoprotein isolation

Very low/low density lipoprotein (VLDL/LDL) and high density lipoprotein (HDL) were isolated from plasma with density ultracentrifugation as described before (Karlsson et al., 2005). To avoid POP interaction with the centrifuge tubes, polycarbonate instead of polyallomer tubes

Table 1
Clinical characteristics of study subjects.

	Healthy controls	Cancer	CVD	Cancer & CVD
Population ($n = 78$)				
N	14	18	28	18
Age (range)	24–79	40–89	41–87	55–90
Gender (male/female)	4/10	7/11	12/16	10/8
Smokers (N)	2	3	1	4
BMI (mean ± SD)	27.0 ± 3.9	25.9 ± 4.8	27.4 ± 4.4	27.6 ± 3.9
Triglycerides mmol/L (mean ± SD)	1.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.5	1.9 ± 0.9
Total cholesterol mmol/L (mean ± SD)	5.9 ± 1.1	5.9 ± 1.2	5.2 ± 1.1	4.9 ± 1.1
Subpopulation ($n = 28$)				
N	7	6	13	2
Age (range)	41–79	52–89	54–87	68–86
Gender (male/female)	3/4	2/4	7/6	1/1
Smokers (N)	0	0	0	0
BMI (mean ± SD)	29.0 ± 2.3	25.2 ± 3.9	26.9 ± 4.5	23.9 ± 0.4
Triglycerides mmol/L (mean ± SD)	2.0 ± 0.6	1.3 ± 0.5	1.8 ± 0.5	1.1 ± 0,1
Total cholesterol mmol/L (mean ± SD)	6.1 ± 1.0	6.8 ± 1.3	5.2 ± 1.0	4.9 ± 1.1