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Metabolic profiling of residents in the vicinity of a petrochemical complex

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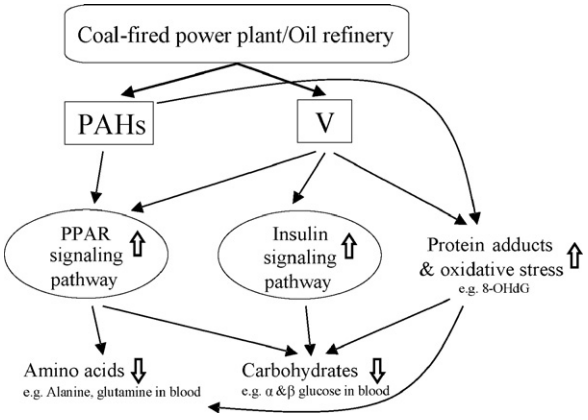
HIGHLIGHTS

- Metabolic effects when exposure to pollutants near a petrochemical complex
- V and PAHs exposure associated with elevated oxidative/nitrosative stress responses
- V and PAHs exposure related to reduced amino acid and carbohydrate levels
- V and PAHs affect metabolic profiling by elevating PPAR and insulin signaling

GRAPHICAL ABSTRACT



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ABSTRACT

No previous studies have simultaneously measured the biomarkers of environmental exposure and metabolome perturbation in residents affected by industrial pollutants. This study aimed to investigate the metabolic effects of environmental pollutants such as vanadium and polycyclic aromatic hydrocarbons (PAHs) on residents in the vicinity of a petrochemical complex. The study subjects were 160 residents, including 80 high-exposure subjects exposed to high levels of vanadium and PAHs and 80 age- and gender-matched low-exposure subjects living within a 40-km radius of a petrochemical complex. The exposure biomarkers vanadium and 1-hydroxypyrene and four oxidative/nitrosative stress biomarkers were measured in these subjects. Plasma samples from the study subjects were also analyzed using ^{1}H NMR spectroscopy for metabolic profiling. The results showed that the urinary levels of vanadium and 1-hydroxypyrene in the high-exposure subjects were 40- and 20-fold higher, respectively, than those in the low-exposure subjects. Higher urinary levels of stress biomarkers, including 8-OHdG, HNE-MA, 8-isoPF2α, and 8-NO_2Gua, were also observed among the high-exposure subjects compared with the low-exposure subjects. Partial least squares discriminant analysis of the plasma metabolome demonstrated a clear separation between the high- and low-exposure subjects; the intensities of amino acids and carbohydrate metabolites were lower in the high-exposure subjects compared with the low-exposure subjects. The exposure to vanadium and PAHs may cause a reduction in the levels of amino acids and carbohydrates by elevating PPAR and insulin signaling, as well as oxidative/nitrosative stress.

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1. Introduction

Previous studies have found that certain acute or chronic diseases are associated with the pollutants emitted by the petrochemical industry, including asthma, respiratory symptoms, and cancers (Pan et al., 1994; Dubnov et al., 2007; Wichmann et al., 2009). However, the detailed pathogenic mechanisms remain unclear due to the complex pollutants emitted by the petrochemical industry, which include particulate matter (PM), sulfur oxides, nitrogen oxides, metals, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs) (Nadal et al., 2004; Chan et al., 2006; Chusai et al., 2012). Studies on the identification of exposure biomarkers, such as the levels of urinary arsenic and 1-hydroxypyrene (1-OHP), which may indicate the association between exposure and internal dose of pollution (Aguilera et al., 2008; Hansen et al., 2008), are limited. Furthermore, only a few early molecular effects, such as oxidative damage, nitrosative stress, and inflammation, have been confirmed as possible mechanisms of the adverse health effects induced by the pollutants emitted from the petrochemical industry (Kuang et al., 2013; Wannhoff et al., 2013; Rosa et al., 2014). Additionally, the comprehensive association between early health effects and exposure to the multiple pollutants in nearby residents has not yet been studied.

It is difficult to identify the numerous hazardous pollutants in the environment and to relate them to specific diseases. Indeed, a new paradigm is needed to evaluate all exposure events and their contribution to the origin or progression of disease. The proposed concept of "exposomes" refers to measures that reflect all exposure events experienced by an individual during his/her lifetime and how those exposures relate to disease (Rappaport and Smith, 2010; Wild, 2012). "Exposomics" is the study of exposomes and relies on the application of many "-omics" technologies, such as genomics/epigenomics, proteomics, and metabolomics, to discover novel biomarkers for exposure assessment (Wild, 2009). Among the -omics technologies, the field of metabolomics has begun to gain interest, along with transcriptomics and proteomics, as one of the most powerful approaches in biological studies (Robertson et al., 2011; Patti et al., 2012). Metabolomics, defined as the comprehensive and quantitative analysis of all metabolites of an organism (Fiehn, 2001), is one of the emerging approaches for understanding the mechanisms of various biological processes and discovering novel biomarkers in clinical and epidemiological studies. This profiling technique has been applied in pharmacology, disease screening, and diagnostic studies (Gowda et al., 2008).

Metabolites are the end products of cellular regulatory processes, and metabolic changes can reflect the response of biological systems to genetic or environmental changes (Fiehn, 2002). Metabolomics has traditionally been used to study the effects of various health factors, such as dietary intake (Holmes et al., 2008; O'Sullivan et al., 2011); alcohol consumption (Jaremek et al., 2013); and exposure to pesticides (Bonvallot et al., 2013), aromatic hydrocarbons (Xu et al., 2013), metals (Ellis et al., 2012; Wang et al., 2012), and river water (Zhang et al., 2012). As an unbiased, high-throughput global analysis of metabolites, metabolomics allows the identification and quantification of individual metabolites (Gomez-Casati et al., 2013), and can be applied in environmental risk assessment through the characterization of the overall influence of multiple exposures in humans (Griffin and Shore, 2007).

The aim of this study was to investigate the metabolic responses of people exposed to the potential specific pollutants emitted from a petrochemical complex using metabolomics and oxidative/nitrosative stress biomarkers. We aimed to identify the potential metabolic changes and adverse health effects that may occur in residents in the vicinity of a petrochemical complex.

2. Materials and methods

2.1. Study area and emission sources

Emissions from three oil refineries and one coal-fired power plant within the No. 6 Naphtha Cracking Complex, the largest petrochemical complex in Taiwan, encompassing up to 2603 ha situated on the west coast of central Taiwan in the Mailiao Township, Yunling County, were studied. Our study area included 10 townships with similar socioeconomic development levels that are 0–40 km away from the complex (Fig. 1). The oil refineries, with an oil production capacity of 25 million tons per year, and the coal-fired power plant, with an electricity-generating capacity of 1.8 million kW per year, account for 60% PM_{10} and 40% $PM_{2.5}$ of the emissions of the entire complex. There are two main stacks at a height of 50 m for the oil refinery plants and three main stacks at a height of 250 m for the coal-fired power plant (TEPA, 2007; FPCC, 2015). Two representative stacks were selected to be the emission source of the oil refineries (UTM-E: 167883, UTM-N: 2633516) and of the coal-fired power plant (UTM-E: 167247, UTM-N: 2632285) in the No. 6 Naphtha Cracking Complex. The distances of the addresses of the study subjects to the emission sources in the complex were calculated using a Euclidean distance formula. In previous studies, we found that air emissions are a major route for the elevation of urinary vanadium (V), a specific pollutant from oil refineries, and 1-hydroxypyrene (1-OHP), a major metabolite of PAHs emitted by coal-fired power plants; these pollutants represent burdens for the nearby residents (Yuan et al., 2015a, 2015b).

2.2. Study subjects and exposures

From 2009 to 2012, we established a cohort of 3230 residents who lived for more than five years in the study area, completed the questionnaire survey, and for whom the biomarkers of urinary V and 1-OHP for the exposure to emissions from the oil refineries and coal-fired power plants of the petrochemical complex were determined. To reveal the clear distinction of exposure to V and PAHs for residents in the vicinity of the petrochemical complex, the current study selected 160 study subjects from the cohort and the locations of these study subjects are shown in Fig. 1. Among the study subjects, 80 lived within a 10-km radius of the petrochemical complex and had urinary V and 1-OHP levels higher than the 75th percentile of that of all of the cohort residents; this represented the high-exposure group. The other 80 study subjects lived farther than the 10-km radius and were matched with the 80 high-exposure study subjects with regard to gender and age ± three years; this represented the low-exposure group. We collected one morning spot urine sample from each study subject in a 15-ml BD tube (Vacutainer) stored at −20 °C until analysis, and urinary levels of V, 1-OHP, and oxidative/nitrosative stress biomarkers were determined. Blood samples were drawn by nurses into BD Vacutainer® tubes with ethylenediaminetetraacetic acid (EDTA) anticoagulant, which were centrifuged to collect plasma samples that were stored at −80 °C for metabolomic analysis. HBsAg and Anti-HCV for hepatitis B and C were analyzed in all study subjects at the National Taiwan University Hospital medical diagnosis laboratory. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital, and informed consent was obtained from each participant.

2.3. Analysis of exposure biomarkers

The urinary levels of V in the study subjects were analyzed using an inductively coupled plasma mass spectrometry (ICP-MS) method. A 1.0-ml urine sample was diluted with 2.0 ml 2% nitric acid and filtered through a 0.45-μm filter prior to transfer to an ICP-MS instrument for analysis (Agilent 7500c, Agilent, Santa Clara, United States). The urinary V levels of the standard reference materials (SERO, Billingstad, Norway) analyzed by our method were within the acceptable range provided by the SRM. The relative error of the 10 spiked samples in each batch of samples was below 10%. The method detection limit (MDL) of the urinary V was determined to be 0.026 μg/l.

Urinary 1-OHP levels were determined using a high-performance liquid chromatography (HPLC) method. Each urine sample (10 ml) was adjusted to a pH of 5.0, and 20 μl of β-glucuronidase/arylsulfatase