Environment International 119 (2018) 466–477

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Human exposure to polycyclic aromatic hydrocarbons: Metabolomics perspective

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ARTICLE INFO

Handling Editor: Robert Letcher

Keywords:
PAHs
Carcinogenesis mechanisms
Metabolic pathways
Metabolomics techniques
Human exposure biomarkers
Multivariate statistical analysis
Animal models

ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are organic contaminants exhibiting carcinogenic toxicity. They are widespread in the environment, especially in urban areas. Humans are exposed to PAHs via inhalation, ingestion and dermal contact. Though much research has investigated their toxicity, little is known regarding the metabolic responses in humans after exposing to PAHs. However, those studies are important since PAHs become carcinogenic after metabolic activation by humans as indirect-acting carcinogens. As such, it is important to study their metabolism in humans based on metabolomics analysis. The goal of metabolomics study is to obtain a comprehensive view of metabolic reactions in humans after exposing to PAHs to better control the underlying metabolisms and reduce their genotoxicity. This article reviewed the biomarkers, analytical techniques including nuclear magnetic resonance and mass spectrometry, big data multivariate statistical analysis, and animal models that have been utilized to better understand the biological effects of PAHs, PAH-derivatives, and their metabolites and biotransformation products on humans.

1. Introduction

1.1. Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are organic contaminants consisting of at least two fused aromatic rings in different structural arrangements. There are several hundreds of PAHs, but only 16 PAHs are listed as priority contaminants by USEPA (Banger et al., 2010). As organic contaminants, much research has characterized their concentrations, analysis, bioavailability and health effects during the past decade (Kim et al., 2013; Li et al., 2014; Ruby et al., 2016). With fused aromatic rings and being semi-volatile, PAHs are relatively stable and hydrophobic in the environment. Generally speaking, their hydrophilicity and mobility decrease with increasing benzene rings.

Most PAHs in the environment result from incomplete combustion and pyrolysis processes of organic carbon, including biomass, petroleum, and coals (Abdel-Shafy and Mansour, 2015). PAHs come from natural and anthropogenic sources, and based on their formation processes, PAHs can be classified into pyrogenic, petrogenic, and biogenic (Buczyńska et al., 2013). Due to their volatility, PAHs can be transported far from their original sources and accumulate in various environmental matrices. As such, PAHs are ubiquitous in the environment, including soils (Beriro et al., 2016; Ruby and Lowney, 2012), water (Menezes et al., 2015; Nielsen et al., 2015), air (Galarneau, 2008; Ma and Harrad, 2015), sediment (Kim et al., 2008; Xu et al., 2016), dust (Xiang et al., 2016; Xiang et al., 2018) and food (Bansal and Kim, 2015; Plaza-Bolaños et al., 2010).

PAHs are carcinogenic, so they are of major risks to human health. According to USEPA, seven PAH compounds are probable human carcinogens, including benz[*a*]anthracene, benzo[*a*]pyrene (BaP), benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a*,*h*]anthracene, and indeno[1,2,3-*cd*]pyrene (Banger et al., 2010). Humans are exposed to PAHs through three main pathways: ingestion, inhalation, and dermal contact (Ma and Harrad, 2015; Ruby et al., 2016). Occupational exposure may occur to workers by breathing exhaust fumes or smoke (Fernando et al., 2016; Navarro et al., 2017).

Exposure to PAHs is linked with various adverse health effects including oxidative stress (Wang et al., 2015), diabetes (Yang et al., 2017), inflammation (Ferguson et al., 2017), infertility (Xia et al., 2009), cardiovascular disease (Jomova et al., 2012) and poor fetal development (Sexton et al., 2011). Short-term health effects include eye and skin irritation, nausea and vomiting, and inflammation while long-

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https://doi.org/10.1016/j.envint.2018.07.017
Received 17 May 2018; Received in revised form 9 July 2018; Accepted 9 July 2018

term include various cancers, DNA and proteins damage, and gene mutation (Abdel-Shafy and Mansour, 2015; Kim et al., 2013). Although unmetabolized PAHs are also toxic, a major concern is the ability of their reactive metabolites, such as epoxides and dihydrodiols, to bind to cellular proteins and DNA. The resulting biochemical disruption and cell damage lead to mutations, developmental malformations, tumors, and cancer (Ewa and Danuta, 2016; Kim et al., 2013; Moorthy et al., 2015). Since PAHs often exist as a group, understanding their composition differences helps to accurately assess their toxicity (Abdel-Shafy and Mansour, 2015). In addition, uncovering the dynamics of PAH metabolisms and possible toxic effects help to better understand their impacts and control their metabolic pathways in humans.

1.2. Environmental metabolomics

Metabolomics studies the metabolites present in an organism, cell, or tissue by investigating the unique chemical fingerprints of a specific cellular process leave behind, i.e., their small-molecule metabolite profiles (Rochfort, 2005). As such, it focuses on the biochemical processes involving metabolites and biotransformation products of various chemicals. It is a quantitative measure of the multi-parametric metabolic responses of living systems to pathophysiological stimuli or genetic modification (Worley and Powers, 2015). The metabolome collects metabolites in a biological organism, which are the end-products of cellular processes. Gene expression data and proteomic analyses reveal the gene products produced in a cell, representing one aspect of cellular function. In addition, metabolic profiling provides a snapshot of cell physiology. Metabolic profiling of biofluids, cells, and tissues is a routine tool for biomarker discovery. Owing to innovative developments in informatics and analytical technologies, and the integration of orthogonal biological approaches, it is possible to expand metabolomics to study the impacts of PAH exposure on humans. Its inherent sensitivity and subtle alterations in biological pathways can be detected to provide insight into the mechanisms underlying various physiological conditions and aberrant processes (Johnson et al., 2016).

Environmental metabolomics is a relatively new technique to assess the biological consequences of chemical exposure (Lankadurai et al., 2013). This approach has advantages to study organism-environment interactions and assess organism functions and health at the molecular level. As such, there are many applications for metabolomics in environmental sciences, ranging from understanding organismal responses to abiotic pressures, to investigate the responses of organisms to environmental stressors. Environmental metabolomics often serves to detect the impact of sub-acute toxicity in organisms prior to overt phenotype changes in addition to revealing the underlying mechanisms of action or synergistic effects of chemical exposures, which often involve a complex mixture of compounds. Therefore, metabolite models can be used to characterize the endpoint of PAH-induced toxic reactions. Metabolomics analysis can be performed, with or without known metabolites being quantified, by using a comprehensive analysis of all metabolites. Non-targeted methods can detect the differences in pictorial description patterns, so it often provides information about the mechanisms, pathways, and biomarkers after chemical exposure (Bundy et al., 2009; Elie et al., 2015).

To avoid distortion and miss-discovery during metabolomics studies, various validations are required. While analytical validation is devoted to measurement examination and chemometric validation to test the reliability of statistical results obtained, biological validation consists of an evaluation of discovered biological knowledge. Biological validation constitutes the most relevant confirmation of the results. Follow-up analytical and biological validation studies to verify both the identification and biological reproducibility of the results are essential to confirm initial findings from metabolomics studies (Godzien et al., 2013).

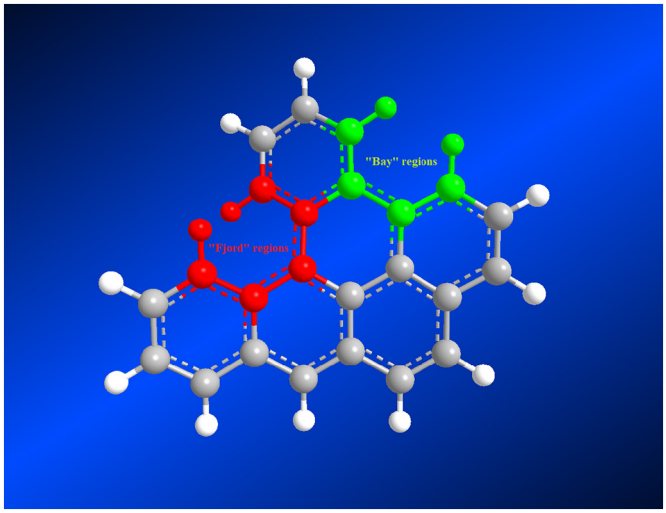

Fig. 1. Biological active “bay” (green) and “fjord” (red) regions in PAH conformation using dibenzo[*a*,*l*]pyrene as an example (Ewa and Danuta, 2016). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Carcinogenesis and transformation of PAHs in humans and animals

PAHs are ubiquitous chemicals in the environment. Some carcinogenic PAHs are genotoxic by inducing mutations to initiate cancer while others are not genotoxic but they enhance cancers (Abdel-Shafy and Mansour, 2015). PAHs that initiate cancer are often modified by enzymes into biotransformation products that react with DNA, leading to mutations. In other words, PAHs acquire carcinogenicity only after they have been activated by xenobiotic-metabolizing enzymes to reactive biotransformation products, which can attack cellular DNA. As such, the alteration of DNA sequence in genes regulating cell replication may increase the possibility of cancer and other diseases (Moorthy et al., 2015). The biological activity of PAHs is related to their structures, which are formed between angular condensed aromatic rings resulting from regional distortions with maximal impact, termed as “fjord” and “bay” regions (Fig. 1) (Ewa and Danuta, 2016). Though their reactivity depends on the density of electron charges, geometric distortions in molecules also influences charge distribution and indirectly its reactivity. While PAHs with “fjord” regions (e.g., dibenzo[*a*,*l*]pyrene) are non-planar, which bind preferentially to adenine nucleotides, PAHs with a “bay” regions (e.g., benzo[a]pyrene-BaP) are planar, which bind to guanine nucleotides (Xue and Warshawsky, 2005). Furthermore, increase in their non-planarity lowers their ability to be biotransformed to reactive forms, which produce DNA-damaging adducts. Mutagenic biotransformation products of PAHs include diol epoxides, quinones, and radical PAH cations, which can bind to DNA to form bulky complexes called DNA adducts. While stable adducts may lead to DNA replication errors, unstable adducts react with DNA strands by removing purine bases (either adenine or guanine). Such mutations, if not repaired, can transform genes encoding normal proteins into cancer-causing oncogenes. In addition, quinones can also repeatedly generate reactive oxygen species (ROS), which may independently damage DNA (Ewa and Danuta, 2016).

Among enzymes, those in the cytochrome P450 (CYP) family including CYP1A, CYP1B, CYP2C, and CYP2E may metabolize PAHs to diol epoxides. Exposure to PAHs can increase the production of cytochrome enzymes, which convert PAHs into mutagenic diol epoxides. In this pathway, PAH molecules bind to the aryl hydrocarbon receptor (AhR) to activate the transcription factor, thereby increasing the production of cytochrome enzymes (Nebert et al., 2004). As a result, PAHs can form several OH-PAHs isomers, which are excreted and can serve as