Available online at www.sciencedirect.com

ScienceDirect

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

Sub-chronically exposing mice to a polycyclic aromatic hydrocarbon increases lipid accumulation in their livers

Yuanxiang Jin[1], *Wenyu Miao*[1], *Xiaojian Lin, Tao Wu, Hangjie Shen, Shan Chen, Yanhong Li, Qiaoqiao Pan, Zhengwei Fu*[*]

College of Biological and Environmental Engineering, Zhejiang University of Technology, Hangzhou 310032, China

ARTICLE INFO

Article history:
Received 7 May 2014
Received in revised form
11 July 2014
Accepted 19 July 2014
Available online 28 July 2014

Keywords:
Polycyclic aromatic hydrocarbon
Sub-chronic exposure
Lipid metabolism
Gene transcription
Mice

ABSTRACT

The potential for exposing humans and wildlife to environmental polycyclic aromatic hydrocarbons (PAHs) has increased. Risk assessments describing how PAHs disturb lipid metabolism and induce hepatotoxicity have only received limited attention. In the present study, seven-week-old male ICR mice received intraperitoneal injections of 0, 0.01, 0.1 or 1 mg/kg body weight 3-methylcholanthrene (3MC) per week for 10 weeks. A high-fat diet was provided during the exposure. Histopathological lipid accumulation and lipid metabolism-related genes were measured. We observed that sub-chronic 3MC exposure significantly increased lipid droplet and triacylglycerol (TG) levels in the livers. A low dose of 3MC activated the aryl hydrocarbon receptor, which negatively regulated lipid synthesis in the livers. The primary genes including *acetyl-CoA carboxylase (Acc)*, *fatty acid synthase (Fas)* and *stearoyl-CoA desaturase 1 (Scd1)* decreased significantly when compared with those in the control group, indicating that *de novo* fatty acid synthesis in the hepatocytes was significantly inhibited by the sub-chronic 3MC exposure. However, the free fatty acid (FFA) synthesis in the adipose tissue was greatly enhanced by up-regulating the expression of peroxisome proliferator-activated receptor γ (PPARγ) and sterol regulatory element binding protein-1c (SREBP1C) and target genes including *Acc*, *Fas* and *Scd1*. The synthesized FFA was released into the blood and then transported into the liver by the up-regulation of *Fat* and *Fatp2*, which resulted in the gradual accumulation of lipids in the liver. In conclusion, histological examinations and molecular level analyses highlighted the development of lipid accumulation and confirmed that 3MC significantly impaired lipid metabolism in mice.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a family of persistent and hydrophobic environmental toxins that originate from the incomplete combustion of carbon-based fuels and some carbon-containing fuels, such as wood, coal, diesel, fat and tobacco, among others (Van-Metre and Mahler, 2005; Weisman et al., 2010). Measurable and relatively high levels of different PAHs have been observed around the world

[*] *Corresponding author at*: College of Biological and Environmental Engineering, Zhejiang University of Technology, 18, Chaowang Road, Hangzhou, China. Tel.: +86 571 8832 0599; fax: +86 571 8832 0599.
E-mail address: azwfu@zjut.edu.cn (Z. Fu).
[1] These authors contributed equally to this work.
http://dx.doi.org/10.1016/j.etap.2014.07.014
1382-6689/© 2014 Elsevier B.V. All rights reserved.

in urban atmospheres, surface water, sediment, soil, plants and even in different organisms, such as fish, in recent years (Klumpp et al., 2002; Wang et al., 2006; Li et al., 2009, 2012; Korosi et al., 2013). More importantly, PAHs can enter the body from various sources including coal, coke and diesel fuel burning, cooking activities, grilled meats, cigarettes and also from the suspended particulate matter in the air (Bonner et al., 2005; Wang et al., 2013). As a result, wildlife and humans will suffer from either observable or imperceptible consequences by PAHs exposure. A number of previous studies have indicated that PAHs could be activated as ligands to bind with aryl hydrocarbon receptors (AHR) (Mimura and Fujii-Kuriyama, 2003; Ovesen et al., 2011). AHRs belong to the basic helix-loop-helix/Per-Arnt-Sim (bHLH/PAS) family. In the absence of a ligand, the AHR is sequestered in the cytosol by two heat-shock protein 90 molecules. As ligands, PAHs can competitively bind to AHR and are then translocated into the nucleus. In the nucleus, they heterodimerize with the AHR nuclear translocator (ARNT) and recognize their cognate DNA-binding site, the xenobiotic response element (XRE), which is located in the regulatory regions of AHR-responsive genes, leading to the activation of target gene transcription (the most well-characterized genes are *cyp1a1* and *cyp1b1*) (Abel and Haarmann-Stemmann, 2010; Wang et al., 2004; Beedanagari et al., 2010). PAHs have been of great concern in recent years because of their carcinogenic properties, which are very harmful to humans and wildlife.

In addition to their carcinogenic properties, the roles of PAHs in hepatotoxicity and hepatic steatosis have also caused great concern in recent years (Kawano et al., 2010; Angrish et al., 2011). Hepatic lipid metabolism is known to be regulated by a variety of pathways. Previous studies have indicated that the AHR-mediated pathway was also involved in the hepatic lipid metabolism process. Sato et al. (2008) used a microarray assay to reveal that low-dose 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) treatment altered the transcription of genes related to cholesterol biosynthesis, lipogenesis and glucose metabolism in the mouse liver, suggesting that the AHR is involved in regulating cholesterol and lipid metabolism. Tanos et al. (2012) reported that AHR activation repressed the expression of hepatic fatty acid synthesis genes including *acetyl-CoA carboxylase (Acc)*, *fatty acid synthase (Fas)* and *stearoyl-CoA desaturase 1 (Scd1)* in the livers of C57BL/6J mice. As agonists of AHRs, PAHs and dioxins may therefore play very important roles in hepatic lipid metabolism.

The liver is the major lipogenesis tissue. The triacylglycerol (TG) content of hepatocytes is generally regulated by the activity of cellular molecules that facilitate hepatic free fatty acid (FFA) uptake, fatty acid synthesis, esterification and hepatic fatty acid oxidation and TG export (Nguyen et al., 2008). Thus, both the enhanced synthesis and uptake of fatty acids would lead to the accumulation of lipids in the liver. At the molecular level, hepatic fat metabolism is regulated by an abundance of key transcription factors such as peroxisome proliferator-activated receptors α and γ (PPARα and γ) and sterol regulatory element binding protein-1c (SREBP1C), which mediate the expression of target genes related to fatty acid synthesis including *Acc*, *Fas*, *Scd1*, *glyceraldehyde 3-phosphate acyltransferase* (*Gpat*) and the expression of genes related to fatty acid oxidation including *carnitine palmitoyltransferase-1α* (*Cpt1α*) and *hormone-sensitive lipase* (*Hsl*) (Jump et al., 2005; Nguyen et al., 2008; Hagiwara et al., 2012). Previous studies indicated that PAH exposure disturbed lipid metabolism by influencing different endpoints. For example, Kawano et al. (2010) reported that a single intraperitoneal injection of 100 mg/kg BW 3-methylcholanthrene (3MC) enhanced the expression level of PPARα and fatty acid translocase (FAT). The authors indicated that 3MC induced hepatic microvesicular steatosis by increasing the expression level of FAT. However, the mechanism through which PAH exposure disturbs lipid metabolism has not been fully elucidated in a mammalian system.

In the present study, we focused on lipid metabolism in mouse livers followed by exposure to low-dose 3MC for a long period of time. Adult male ICR mice were injected with 0.01, 0.1 and 1 mg/kg BW/week 3MC, which is a common isomer of methylcholanthrene, for 10 weeks. We then analyzed the hepatic and serum parameters related to fat and cholesterol metabolism including the TG, TC, FFA and VLDL levels. Additionally, the quantity of lipid droplets in the hepatocytes was determined by cryosection to illustrate the lipid accumulation induced by sub-chronic 3MC exposure. The mRNA levels of genes related to fatty acid synthesis, oxidation and transport were then further determined to elucidate the potential mechanism underlying the lipid metabolism disruption induced by this PAH at a low dose over a long period of exposure. All the information acquired in this study is intended to provide new insights into how PAHs induce the sub-chronic mammalian toxicity.

2. Materials and methods

2.1. Chemicals

The original 3MC (CAS No.: 56-49-5, purity: 99.9%) was purchased from Supelco (Bellefonte, USA) and dissolved in corn oil (Wako, Japan) before injection.

2.2. Animals and experimental design

A total of 30 6-week-old male ICR mice were purchased from the China National Laboratory Animal Resource Center (Shanghai, China). The mice were kept in our animal facilities (illuminated with strip lights to shine 200 lx at cage level with a photoperiod of 12 h light and 12 h dark; 22 ± 1 °C) for 1 week prior to the experiments. Water and food were available *ad libitum*. The mice were then randomly divided into 5 groups. One group was given a basal diet (BD) and defined as the BD group. The remaining 4 groups were fed a high-energy diet (HD). For standardizing the intake volume according to their bodyweights, intraperitoneal injection was adopted in the experiment. The 4 groups of mice received intraperitoneal injections of 0, 0.01, 0.1 or 1 mg/kg body weight (BW) 3MC per week for 10 weeks, and the groups were named HD, HD-0.01, HD-0.1 and HD-1, respectively. During the exposure, the BD and HD groups were injected with the same volume of corn oil without 3MC. The composition of the BD was previously described, and the mineral and vitamin mix was prepared according to AIN-76 (Bieri, 1979). The HD treatment was prepared by adding 10% sucrose (wt/wt), 25% lard (wt/wt) and 1%

Download English Version:

https://daneshyari.com/en/article/2583593

Download Persian Version:

https://daneshyari.com/article/2583593

Daneshyari.com