DOCTORAL THESIS

The risk of exposure and the mechanistic actions of perfluorinated compounds on male infertility and metabolic disorders

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Date of Award:
2013

The Risk of Exposure and the Mechanistic Actions of Perfluorinated Compounds on Male Infertility and Metabolic Disorders.

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A thesis submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

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Hong Kong Baptist University

Aug 2013

Abstract

Endocrine disrupting chemicals (EDCs) are ubiquitous in our environment. The risk of the exposure and their effects on ecological and human health has raised public concerns recently. Over the past 20 years, significant levels of EDC contamination have been detected in both abiotic samples (i.e. air, soil and water) and biotic samples (i.e. wildlife and humans) at different geographical regions. Dietary consumption, inhalation dermal absorption are believed to be the major routes of the exposure to EDCs. Pathways of exposure to EDCs can be diverse; the identification of all possible exogenous exposure is not yet a feasible task. There is a need for a transformational change in the approach to contaminants in which more emphasis be placed on correlating population-based data to reveal human-environment interactions. In chapter 2, we analyzed a dataset of human blood samples in order to provide a framework of accumulated concentrations of EDCs. Evidence for the presence of PFCs, BPA and phthalates in the blood samples of most Hong Kong samples is provided. The observed characterizations of the contamination profile in human blood samples suggest a general exposure route to these contaminants. In the subsequent experimental chapters, one of the detected EDCs, PFOS which belongs to a family of synthetic fluorinated hydrocarbons (C_4-C_{14}) with the charged functional moiety of carboxylate, sulfonate or phosphonate will be studied. Because of its unique hydrophobic and oleophobic properties, they have been extensively used in various industrial and consumer products. The carbon-fluoride bonds render PFOS to be non-biodegradable, leading to their persistence in the environment and lengthy serum elimination half-life in animals. The manufacture of PFOS has been banned in most of the countries; however it is still produced

in many developing countries like China. Being geographically closed to China, we are at great risk of exposure to PFOS.

Previous studies demonstrated that PFOS is hepatotoxicity. However, the underlying mechanism and the clinical significance of PFOS-induced biochemical changes in livers are not known. Herein, in chapter 3 a murine model was used to study the mechanistic effects of PFOS-induced hepatotoxicity. A time- and dose-dependent effect of PFOS exposure on hepatic lipid accumulation, resulting from the inhibition of mitochondrial β-oxidation and the disturbance on hepatic lipid transport were demonstrated. The data reveal the similar hallmark features as compared with the development of NAFLD (non-alcoholic fatty liver disease). Of special interest is the fact that PFOS has been suggested to act on PPARs to modulate energy homeostasis and listed as one of the risk factor in the alternation of development programming for metabolic diseases in life. Maternal transfer of PFOS across the human placenta has been reported, however toxicological information regarding the perinatal PFOS exposure to susceptibility of metabolic disorders in adult offspring is not known. In chapter 4, we investigated the effects of perinatal exposure to PFOS on glucose metabolism in animal offspring and whether these effects would be exacerbated under different diets. The effects of the environmental equivalent dose of PFOS exposure on the disturbance of hepatic lipid metabolism and glucose metabolism in pups and adults were demonstrated in F_1 at PND 21 and 63. The phenotypes of insulin resistance and glucose tolerance were evident (i.e. HOMA-IR index and glucose AUC) in the F_1 adults. The metabolic disturbance effects were exacerbated under high-fat diet during postnatal growth, highlighting the synergistic action of dietary fat content and PFOS on the development of metabolic disorders.

In addition to hepatotoxicity, negative effects of PFOS exposure on male fertility have been reported in both *in vitro* and *in vivo* animal models. A considerable number studies demonstrated the inhibitory effects of PFOS on testosterone synthesis and spermatogenesis. Nevertheless, the underlying molecular mechanism has not been fully elucidated. Here in chapter 5, by using an in vitro primary Sertoli cell model that mimics BTB in vivo, PFOS disturbed the organization of F-actin in Sertoli cells was first demonstrated. The localization of actin regulatory and adhesion proteins at the cell-cell interface which are essential to maintain BTB integrity, were disrupted. In addition, PFOS was found to perturb Sertoli-Sertoli cell gap junction (GJ) communication, by down-regulating the expression of the major GJ integral membrane protein, connexin 43. Intriguingly an overexpression of phosphorylated FAK-Tyr^{407} was found to protect, at least in part, the PFOS-induced destruction in BTB integrity. Collectively the study highlighted the mechanistic actions of PFOS on steatosis, impairment of glucose metabolisms and reproductive system, particularly in male.

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