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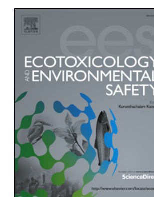

Impairment of bisphenol F on the glucose metabolism of zebrafish larvae

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ABSTRACT

Bisphenol F (BPF) is a substitute of bisphenol A in the production of epoxy resin and polycarbonate. Its extensive use in consumer products leads to a wide human exposure at high levels. Although the adverse effects of BPF on animal health are of increasing public concern, its risks on systematic glucose metabolism and blood glucose concentrations still remain largely unknown. Using zebrafish larvae as the model animal, we investigated the disturbance of BPF exposure on glucose metabolism and the underlying mechanisms. Zebrafish larvae at 96 h post fertilization were exposed to 0.1, 1, 10, and 100 μg/L of BPF for 48 h. Compared with the control group, glucose levels of larvae increased significantly in the 10 and 100 μg/L exposure groups, which are associated with enhancement of gluconeogenesis and suppression of glycolysis induced by high doses of BPF. Additionally, both mRNA expressions and protein levels of insulin increased significantly in the 10 and 100 μg/L exposure groups, while transcription levels of genes encoding insulin receptor substrates decreased significantly in these groups, indicating a possibly decreased insulin sensitivity due to impairment of insulin signaling transduction downstream of insulin receptor. Further, compared with BPF alone, co-exposure of larvae to BPF and rosiglitazone, an insulin sensitizer, significantly attenuates increases in both glucose levels and mRNA expressions of a key gluconeogenesis enzyme. Our data therefore indicate impairing insulin signaling transduction may be the main mechanism through which BPF disrupts glucose metabolism and induces hyperglycemia. Results of the present study inform the health risk assessment of BPF and also suggest the use of zebrafish larvae in large-scale screening of chemicals with possible glucose metabolism disturbing effect.

1. Introduction

Bisphenol F (BPF) is a substitute of bisphenol A (BPA) in the production of epoxy resin and polycarbonate, and is now widely used in the manufacture of consumer products including potable water pipes, industrial floors, electrical varnishes, lacquers, dental sealants, and food packaging (Rochester and Bolden, 2015). Due to the restriction on BPA, the production and consumption of BPF are increasing (Danzl et al., 2009), leading to its detection as a ubiquitous contaminant in various abiotic environments. BPF was measured as the dominating bisphenols in sludge from domestic wastewater treatment plants in Korea, with concentrations ranging from 86.7 to 1780 μg/kg dry weight (Lee et al., 2015). In indoor dusts, BPF concentration was reported to reach 54 μg/kg (Liao et al., 2012). In surface water, sewage water, and sediment samples, BPF concentrations were up to 0.18 μg/L, 0.123 μg/L, and 7.3 μg/kg dry weight, respectively (Fromme et al., 2002). In addition, high levels of BPF were also measured in commercial milk packed in plastic bottles, with concentrations ranging from 1.6 to 26.2 μg/L (Grumetto et al., 2013). These data indicate a widespread human exposure to BPF. Indeed, BPF was detected in 55% of the investigated urine samples collected in 2009–2012 from a group of adults in the United States, with a median concentration of 0.08 μg/L and a highest concentration of 212 μg/L (Zhou et al., 2014). Recent studies have reported that BPF in vitro exhibits similar estrogenic, androgenic, anti-androgenic, genotoxic, and cytotoxic potencies to BPA (Rochester and Bolden, 2015), and is able to produce neurotoxicity in juvenile female rats (Castro et al., 2015), disturb thyroid endocrine system of zebrafish larvae (Huang et al., 2016), cause developmental deformities of zebrafish larvae at high concentrations (> 1 mg/L) (Moreman et al., 2017), and induce oxidative stress in the immune system of juvenile common carp (Qiu et al., 2018). It is worthy to note that both BPA and bisphenol S (BPS), another widely used BPA substitute, were reported to be able to

Abbreviations: BPF, bisphenol F; BPA, bisphenol A; BPS, bisphenol S; IR, insulin receptor; IRS, insulin receptor substrate; PEPCK, phosphoenolpyruvate carboxykinase; DMSO, dimethyl sulfoxide; hpf, hour past fertilization; PCR, polymerase chain reaction; PEPCK-M, mitochondrial PEPCK; G6Pase, glucose-6-phosphatase; PEPCK-C, cytosolic PEPCK; HK, hexokinase; PK, pyruvate kinase; PI3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma

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disturb glucose metabolism and induce hyperglycemia of animals (Alonso-Magdalena et al., 2010; Zhao et al., 2018), and therefore are potential risk factors for diabetes mellitus. Epidemiological investigations even showed a positive association between increased levels of urinary BPA and diabetes mellitus (Shankar and Teppala, 2011). However, the risks of BPF exposure on systematic glucose metabolism and blood glucose concentrations of organisms still remain largely unknown.

As the only hormone that can decrease blood glucose concentrations, insulin therefore plays a key role in blood glucose homeostasis of vertebrates (Fritsche et al., 2008). When hyperglycemia occurs, insulin actions by inhibiting hepatic glucose output (glycogenolysis and gluconeogenesis) but promoting tissue glucose uptake and utilization or storage. Deficiencies in insulin production and its signal transduction are involved in both the pathogenesis of type 2 diabetes mellitus (Lin and Sun, 2010) and the pathways through which exogenous chemicals disrupt systemic glucose metabolism. For example, some chemicals like BPS impair glucose metabolism and induce hyperglycemia via lowering plasma insulin levels in organisms (Zhao et al., 2018), while others like di-2-ethylhexyl phthalate and BPA, cause similar adverse effects by damaging the expression of insulin signaling molecules and their phosphorylation pathways (Rajesh et al., 2013; Jayashree et al., 2013; Indumathi et al., 2013). Nevertheless, which pathway is responsible for the interference of BPF with glucose homeostasis of animals needs to be further elucidated.

In researches of diabetes mellitus, most of the available models are rodent-based and were developed using spontaneous or planned genetic derivation, dietary/nutritional induction, chemical induction, surgical manipulation, transgenic/knock-out manipulation, or a combination of the above (King, 2012; Zang et al., 2017). These diabetic, unhealthy animal models are mainly used for investigations of understanding the pathogenesis and prevention of diabetes and diabetic complications, and treatment of these diseases (King and Bowe, 2016). Recently, zebrafish has been increasingly used as an alternative model to study diabetes mellitus and its related diseases, given the advantages of low breeding costs, high fecundity, rapid embryonic/larval development, and similarities in both organ physiology and metabolic regulation to those of mammals (Kimmel and Meyer, 2016; Zang et al., 2017). However, up to now, similar to the rodent models, the use of zebrafish in diabetes mellitus has been mainly limited in pathological researches, while its use in toxicological screening of chemicals with glucose metabolism disrupting effects is relatively rare. Compared with adults, zebrafish larvae possess a much simple but integrated glucose metabolism pathway. The primary energy for cellular division of fertilized fish eggs is provided by oxidation of glucose derived from maternal glycogen reserves, which are extremely low and rapidly depleted (Rocha et al., 2015). In the non-feeding zebrafish larvae at 96 h post fertilization (hpf), as no food is provided and the yolk sac is diminishing, blood glucose is mainly produced by gluconeogenesis (Gut et al., 2013), and is absorbed and oxidized by tissues for energy supply. Notably, increased gluconeogenesis was reported as a major contributor to fasting hyperglycemia in newly diagnosed untreated adolescents and was an early pathological feature of type 2 diabetes (Chung et al., 2015); and liver-specific over-expression of phosphoenolpyruvate carboxykinase (PEPCK), a key enzyme of gluconeogenesis, resulted in hyperglycemia in mouse (Valera et al., 1994). Recent studies have also indicated abnormal gluconeogenesis as an important contributor to systematic glucose imbalance induced by exogenous chemicals including malathion (Abdollahi et al., 2004), arsenic (Huang et al., 2015), and BPS (Zhao et al., 2018). Therefore, compared with wild-type rodents, we believe that zebrafish larvae can be an ideal platform to screen this type of chemicals, as effects of both food and glycogenolysis on blood glucose concentration can be eliminated without genetic manipulation.

In the present study, zebrafish larvae at 96 hpf were used as the model animal and were exposed to 0.1, 1, 10, and 100 μg/L of BPF for 48 h. The influence of BPF on glucose metabolism was investigated by determining glucose levels and gene expressions of key glucose metabolic enzymes. Then, mechanism underlying these adverse effects was explored by detecting expressions of insulin, glucagon, and insulin signaling molecules. Additionally, to further confirm that whether impaired insulin signaling transduction is the pathway through which BPF induces hyperglycemia, larvae were co-exposed to BPF and rosiglitazone, an insulin sensitizer, and glucose levels and mRNA expressions of PEPCK were measured. Our results raise questions on the safety of substituting BPA by BPF, and also suggest the use of zebrafish larvae in large-scale screening of chemicals with possible glucose metabolism disturbing effect.

2. Materials and methods

2.1. Chemicals

BPF (CAS NO: 620-92-8, purity 99.7%), dimethyl sulfoxide (DMSO) (CAS NO: 67-68-5, purity 99.5%), and rosiglitazone (CAS NO: 122320-73-4, purity 98%) were purchased from Sigma-Aldrich (Shanghai, China). All other chemicals are of analytical grade and were purchased from the Sinopharm Chemical Reagent Beijing Co., Ltd.

2.2. Zebrafish maintenance and exposure

Zebrafish at 5-month age were purchased from a local market in Qingdao, P.R. China. Male fish (with average weight of 0.51 ± 0.06 g and length of 3.5 ± 0.2 cm) and female fish (with average weight of 0.68 ± 0.08 g and length of 4.3 ± 0.3 cm) were acclimated for at least two months under the conditions as following: water temperature at 27 ± 1 °C; pH of 7.6 ± 0.2; dissolved oxygen level of 7.0 ± 0.1 mg/L; and a photoperiod of 14 h light/10 h darkness. Newly hatched *Artemia saline* were fed twice per day, and 2/3 of the water solution was renewed daily. After acclimation, healthy female and male fish (1:2) were paired to spawn. Fertilized eggs were collected in the next morning and allowed to develop in clean water until 96 hpf. At this time, all the embryos had hatched naturally.

Then, 300 larvae at 96 hpf were randomly selected and distributed into a 2 L glass beaker containing 1.5 L of BPF exposure solution (0.1, 1, 10, and 100 μg/L), with 3 replicate beakers set for each group. Both the exposure groups and the control received 0.002% (V/V) DMSO. The selected exposure concentrations are below those that can cause significant differences in survival rate and developmental deformities (Huang et al., 2016; Moreman et al., 2017), and were chosen based on BPF concentrations detected in surface water and human urines. The exposure duration is 48 h and the test solutions were renewed daily. No food was provided during the exposure experiment. With a similar exposure design, Huang et al. (2016) detected the actual concentrations of BPF in test solutions and results showed no significant changes between 0 h and 24 h after water renewal, suggesting stable concentrations of BPF were maintained during the experiment. For BPF and rosiglitazone co-exposure, 96 hpf larvae were exposed to 1 μM rosiglitazone (Elo et al., 2007) and 10 or 100 μg/L of BPF. The exposure experiment was repeated twice.

After exposure for 48 h, approximately 100 larvae in each beaker were randomly selected, anesthetized in cold water, and pooled as one replicate. Then, the collected larvae were dried using filter paper, frozen in liquid nitrogen, and then stored at −80 °C until further analysis. All animal use procedures were approved by the Institutional Animal Care and Use Committee of Ocean University of China.

2.3. Glucose and insulin measurement

One replicate per beaker was subjected to glucose or insulin measurement (n = 6 for each group). Each sample was homogenized using 200 μL of pre-cooling PBS buffer (0.01%) on ice, and centrifuged at

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