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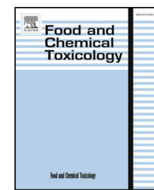

Impact of low-dose chronic exposure to bisphenol A and its analogue bisphenol B, bisphenol F and bisphenol S on hypothalamo-pituitary-testicular activities in adult rats: A focus on the possible hormonal mode of action

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ABSTRACT

Bisphenol A an estrogen-mimic endocrine disrupting chemical, used to manufacture polycarbonate plastics and epoxy resins with toxic effects for male reproduction. Due to its toxicity, industries have started to replace it with other bisphenols. In this study, the toxicity of BPA analogues (BPB, BPF and BPS) was evaluated in a chronic study. We investigated whether the chronic exposure to low bisphenols doses affects spermatogenesis with outcomes on oxidative stress and male reproductive system. Male rats (22 day old) were exposed to water containing 0.1% ethanol for control or different concentrations of BPA and its analogues BPB, BPF and BPS (5, 25 and 50 μg/L) in drinking water for 48 weeks. Results of the present study showed a significant alteration in the gonadosomatic index (GSI) and relative reproductive organs weights. Oxidative stress in the testis was significantly elevated while sperm motility, Daily sperm production (DSP) and number of sperm in epididymis were reduced. Plasma testosterone, LH and FSH concentrations were reduced and estradiol levels were high in 50 μg/L exposed group. These results suggest that exposure to BPA and its analogues for chronic duration can induce structural changes in testicular tissue and endocrine alterations in the male reproductive system.

1. Introduction

Plasticizer such as bisphenol A (BPA) is an environmental pollutant detected in wildlife, humans samples and environment (Corrales et al., 2015). BPA exposure is associated with many human diseases and is suspected to affect many body's physiological functions (Chen et al., 2016a; Chevalier and Fénichel, 2015; Seachrist et al., 2016). Having several concerns for a safer world of BPA there have been several alternatives of BPA introduced into environment known as BPA analogues (Chen et al., 2016a). Bisphenol B (BPB), bisphenol F (BPF) and bisphenol S (BPS) are BPA alternatives which are used for the production of Plastics, epoxy resins, polycarbonates for lining large food containers, water pipes and coatings of Food containers, dyes, paper products and food packaging materials (Chen et al., 2016a; Danzl et al., 2009; Eladak et al., 2015; Goodson et al., 2002; Kinch et al., 2015; Rochester and Bolden, 2015; Yang et al., 2014). BPA analogues have increased concerns regarding emerging environmental pollutants where some of these analogues are detected in concentrations higher than BPA (Caballero-Casero et al., 2016; Chen et al., 2016a). For example, in a study from Italy the concentrations of BPB were higher than BPA in serum samples of healthy women and endometriotic women (Caballero-Casero et al., 2016). Similarly, in another study from Saudi Arabia in the urine of general population the concentrations of both BPS and BPF were higher than BPA (Chen et al., 2016a). In another study food products sold in New York and Albany were analyzed and 75% were detected with bisphenols measurable amounts (Liao and Kannan, 2013). BPS and BPF have been identified up to detectable amounts in food items and paper products (Goldinger et al., 2015; Liao and Kannan, 2014b; Russo et al., 2017). Across the Globe several studies have shown detectable amounts of BPA analogues in the urinary samples, umbilical cord samples and maternal samples (Asimakopoulos et al., 2016; Heffernan et al., 2016; Liu et al., 2017; Lu et al., 2016; Ye

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et al., 2015). BPA and its analogues observed in in vitro studies induced a number of physiological changes in cell lines of red blood cells, pre-adipocytes and testis (Boucher et al., 2016; Desdoits-Lethimonier et al., 2017; Maćczak et al., 2017; Mokra et al., 2017). Studies on rodents show that BPA analogues affects hormone concentrations, testis function, sperm production and sperm DNA damage (Castro et al., 2013; Li et al., 2016; Oliveira et al., 2017; Shi et al., 2017). Many studies of bisphenol A analogues suggest that these chemicals have greater neuroendocrine disruptive effects as BPA where they lead to complex behavioral changes in rodent species (Catanese and Vandenberg, 2016; Kim et al., 2015; Ohtani et al., 2017; Rosenfeld, 2017). Where, these chemicals also affect the gene expression in hypothalamus and other brain areas (Cano-Nicolau et al., 2016; Huang et al., 2016; Qiu et al., 2015, 2018; Zhang et al., 2017, 2018). BPA analogues have also been studied to induce hormonal imbalance in E2 synthesis, thyroid hormone production and testosterone levels (Cano-Nicolau et al., 2016; Kwon et al., 2016; Le Fol et al., 2017; Li et al., 2016).

In vitro and in vivo studies regarding BPA analogues are scare and limited data have shown that these chemicals have reproductive toxicity (Chen et al., 2016a; Naderi et al., 2014). These chemicals also have endocrine disrupting actions in vivo studies and are also estrogenic in nature (Kitamura et al., 2005; Rosenmai et al., 2014; Yamasaki et al., 2004). BPB, BPF and BPS are considered as alternatives to BPA and it is important to understand that whether these compounds are similar or more potent in endocrine disrupting activity than BPA.

In summary the current study provides information about the so called safer alternatives to BPA which have shown similar endocrine disturbances as BPA in animal studies. Most of these disturbances are either steroid or non-steroid pathways. In current study we reported that low concentration of these compounds for a long period of time can impair spermatogenic output and cause changes in the normal spermatogenesis in male rats. The hormonal levels were also altered which suggest that PBA analogues like BPB, BPF and BPS have endocrine disrupting properties by affecting the male reproductive functions in Sprague Dawley rats.

2. Material and methods

2.1. Animals

Male healthy rats (n = 91), weighing (30–40 g) were separated from their mothers on postnatal day 22 (PND 22) and were randomly divided into thirteen groups. Animals were kept in steel cages (7animals/cage) at temperature 22–25 °C and controlled light and dark cycle of 14–10 h light/dark. Animals were fed with laboratory feed (soy and alfalfa free) and water in poly sulfone bottles. All the experimental protocols were approved by the ethical committee of the department of Animal Sciences, Quaid-i-Azam University, Islamabad, Pakistan.

2.2. Experimental design

From PND 23, animals (n = 91) were allocated into thirteen different groups. First served as control and was provided with water containing (0.1% ethanol), while 2nd, 3rd and 4th groups were served with water containing 5, 25 and 50 μg/L BPA respectively. While 5th, 6th and 7th groups were served with water containing 5, 25 and 50 μg/L of BPB. Similarly, 8th, 9th and 10th groups were served with water containing 5, 25 and 50 μg/L of BPF and BPS was also given in water to 11th, 12th and 13th groups at a concentration of 5, 25 and 50 μg/L. All the bisphenols were dissolved in ethanol and the stock solution was diluted with water (final concentration of ethanol in the water was kept below 0.1%). Animals were provided with water alone or water with different concentrations of BPA, BPB, BPF and BPS for the period of 48 weeks. The duration of the exposure was selected according to the OECD test guideline 452 and the doses were selected on the basis of previous studies by (Ji et al., 2013) and (Chen et al., 2017). The BPA, BPB, BPF and BPS solutions in the water bottles was daily replaced with fresh solutions.

After the completion of the experimental period, animals were weighed, and seven animals per group were euthanized by cervical dislocation. Blood was collected from heart through cardiac puncture in heparinized syringes and was subjected to centrifugation at 3000 rpm for 15 min. Plasma was isolated and kept at −20 °C for hormonal assay. Reproductive organs (testis, epididymis, seminal vesicle and prostate) were dissected out and weighed for calculation of gonadosomatic index (GSI) and relative organs weight. Right epididymis and right testis were used for histology while left testis was used for DSP and biochemical analysis. Left epididymis was used for determination of sperm viability, motility and sperm count in the epididymis.

2.3. GSI and relative weight of organs

GSI is an important parameter used for estimation of gonadal maturity in the animals. GSI was obtained for each animal according to the formula used by Barber and Blake (2006).

$$\text{GSI} = \frac{\text{Gonadal weight (g)}}{\text{Body organs weight (g)}} \times 100$$

Relative weight of the organs was determined according to the following formula

$$\text{Relative organ weight}\frac{\text{Organ weight (mg)}}{\text{Body weight (g)}}$$

Relative weights of the organs were expressed as mg/g body weight.

2.4. Biochemical assays

2.4.1. Antioxidant enzymes

Tissues were collected and were processed for the antioxidant enzymes. Tissues were homogenized with automatic homogenizer in phosphate buffer saline and centrifuged at 30,000 g for 30 min. After the centrifugation the supernatant was removed and used for the hormonal analysis, protein estimation and antioxidant enzymes.

2.4.2. Catalase (CAT)

The catalase activity was determined by the method used by (Aebi, 1984) and the change in the absorbance due to H2O2 was measured in the testicular tissues. In this assay 50 ml homogenate was diluted in 2 ml of phosphate buffer with pH of 7.0. After mixing it thoroughly the absorbance was read at 240 nm with an interval of 15 s and 30 s. Change in the absorbance of 0.01 as unit/min was defined as one unit of CAT.

2.4.3. Super-oxidase (SOD)

Superoxide dismutase activity was estimated by the method developed by (Kakkar et al., 1984). In this assay the amount of chromogen formed was measured at 560 nm. The results were expressed in units/mg of protein.

2.4.4. Peroxidase (POD)

POD activity in homogenate was determined by spectrophotometric method of (Carlberg and Mannervik, 1975). In this assay 0.1 ml homogenate was mixed with 0.1 ml of guaiacol, 0.3 ml of H2O2 and 2.5 ml of phosphate buffer and the absorbance was read at 470 nm. Change in the absorbance of 0.01 as unit/min was defined as one unit of POD.

2.4.5. Lipid per oxidation by (TBARS)

Activity of T-BARS was determined in the homogenate by the method used by (Iqbal et al., 1996) and the results were expressed as TBARS/min/ml of plasma. In this assay 0.1 ml of homogenate was

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