Bisphenols Disturbing Male Reproductive System

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BPA is identified as an endocrine-disrupting chemical that deteriorates the physiological function of the hormones of the male reproductive system. Bisphenol F (BPF), bisphenol S (BPS), and bisphenol AF (BPAF) are actively explored as substitutes for BPA and are known as BPA analogues in most manufacturing industries. These analogues may demonstrate the same adverse effects as BPA on the male reproductive system; however, toxicological data explaining the male reproductive hormones' physiological functions are still limited.

aromatase | bisphenol F | bisphenol AF | bisphenol S | HPG axis | steroidogenesis | spermatogenesis

1. Introduction

Bisphenol A (BPA) (*4,4'-dihydroxy-2,2-diphenyl propane*) is an organic synthetic monomer, reported to be one of the most produced chemicals in the world. About 7 million tonnes of BPA was produced in 2013, and this figure is estimated to be growing annually [1][2]. BPA was initially synthesized by the scientist Aleksandr Pavlovich Dianin in 1891. BPA's resistance to high temperatures, shatterproof nature, and electrical insulation capability has led to this chemical being predominantly used in most epoxy resin and polycarbonate plastic industries [3][4][5]. Epoxy resin is a precursor chemical of any product that requires resilience and high durability, such as a dental sealant, amalgams, tanks, sports equipment, roads, structural adhesives, and coating materials in cans [6][7][8][9]. Polycarbonate plastic is also used as packaging or as containers for many daily consumable products, such as vegetables, fruits, milk bottles, plastic bags, and food and beverage containers. Furthermore, these polycarbonate plastics can also be involved in the packaging of personal care products such as shampoo, body wash, and cosmetics [7][8][9][10][11][12][13].

The extensive use of BPA in various industries has resulted in environmental pollution: BPA has reportedly been found in rivers, lakes, soils, sediments, home dust, and air [14][15][16][17][18]. The most alarming concern is that BPA has also been detected in human biological samples, such as in the blood, urine, sweat, breast milk, and in the umbilical cord [19][20][21]. BPA in human biological samples is expected, as it can be found in their food and drinking water, indicating that the most common source of BPA exposure in humans is oral [22][23][24][25]. Furthermore, BPA can also be exposed to humans via the dermis, which mostly occurs when someone is in indirect contact with thermal receipt paper. Humans may also be exposed to BPA through inhalation [26][27][28][29]. Recently, the negative impact of BPA has been widely reported by scientists and has been identified as a well-known endocrine-disrupting

chemical (EDC) [30][31][32]. Previous studies have reported that exposure to BPA causes many diseases, such as tumours, cardiovascular diseases, neurodegenerative diseases, metabolic diseases, such as diabetes mellitus, autoimmune diseases, and male and female infertility, and can disturb the development of children, babies, and foetuses [29][33][34][35][36][37][38]. BPA increases the risk of transgenerational toxicity effects in the offspring, proven by an increase in epigenetic markers such as H3K9Ac and H3K27Ac in the spermatozoa due to parental BPA exposure [39][40].

The extensive adverse effects of BPA on human health have raised alarming awareness in society. Therefore, this chemical is being replaced with its analogues. Among the commonly used BPA analogues are bisphenol F (BPF), bisphenol S (BPS), and bisphenol AF (BPAF) [18][41][42][43][44]. These analogues share the same basic structure as BPA, where the two benzene rings are attached either with the short carbon or with other chemical chains [45][46]. However, these BPA analogues did not undergo proper toxicity evaluation testing before being used in the industry [47]. In 2015, the Environmental Protection Agency (EPA) reported a negative impact of BPA analogues on the aquatic system, environment, and human health [48]. Like BPA, its analogues also result in carcinogenicity, genotoxicity, neurotoxicity, reproductive toxicity, and developmental disorders [48]. Moreover, these analogues are also being categorized as EDCs.

2. Bisphenols and Hypothalamus-Pituitary-Gonadal Axis in Male Reproductive System

The hypothalamus-pituitary axis is the main centre regulating endocrine hormone production in the human body, including the male reproductive system [2]. The hypothalamus releases the hormones responsible for stimulating the neuroendocrine activity of the pituitary glands, either in the anterior or posterior gland. One of the neuroendocrine activities regulated by the anterior pituitary gland is the HPG axis [3]. The HPG axis encounters three levels of hormone production: the hypothalamus releases the gonadotropin-releasing hormone (GnRH), the anterior pituitary gland secretes the follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the testis, specifically the LC, synthesises testosterone. GnRH, which is released from the hypothalamus, stimulates the anterior pituitary gland to release FSH and LH. Both hormones act on the testes to release target hormones, such as testosterone, oestrogen, progesterone, and inhibin. The primary purpose of this mechanism is to achieve homeostasis balance and modulate the positive and negative feedback of hormone regulation [4][5]. GnRH, LH, and FSH secretion are controlled by the neuropeptide kisspeptin (KiSS1), which is regulated by gene kiss1 [6][7][8]. Generally, the kiSS1 and G protein-coupled receptor 54 (GPR54) complex are involved in HPG axis feedback regulations [49]. KiSS1 binds to GPR54, also known as the kiss1 receptor, to form a Kiss1/GPR54 complex. This complex regulates the neuroendocrine reproductive axis by targeting the GnRH neuron to stimulate GnRH release [50]. Subsequently, GnRH stimulates neuron transmission at the anterior pituitary gland to induce the secretion of gonadotropic hormones, specifically LH and FSH. Furthermore, ERα also plays a significant role in regulating reproductive and sexual behaviour [51][52]. Once E2 binds to ERα in the hypothalamus, it suppresses GnRH secretion [53].

Several experimental studies revealed that BPA and its analogues, such as BPF, BPS, and BPAF, disturbed the HPG axis via KiSS1 and ERα by targeting mRNA gene expression. However, BPA and its analogues have either direct or indirect effects and are still controversial. Previous studies have reported that laboratory animals, such as rats and zebrafish, exposed to BPA showed an increase in Kiss1 mRNA expression in the brain [54][55][56][57]. Exposure to BPA at a dose of 50 µg/kg/bw via drinking water caused an increase in Kiss 1 mRNA expression [55]. The same findings were also recorded in the offspring and pups of rats and the transgenic embryo of zebrafish [54][56][57]. Exposure of zebrafish embryos to 1000 µg/L of BPA and BPS at 120 h post-fertilization (hpf) revealed an increased expression of the Kiss1 gene. Moreover, the Kiss 1 receptor was highly expressed, leading to an increased number of GnRH3 neurons in the hypothalamus [54]. GnRH3 neuron is a neuromodulator that indirectly controls the pituitary gonadal axis of the reproductive system in zebrafish [58][59]. Furthermore, Yang et al. [60] found that male zebrafish in an aquarium containing 0.1 and 1 mg/L BPF showed an increase in the expression of GnRH receptors (GnRHR1 and GnRHR2), which influences the increase of GnRH neurons. Another BPA analogue, BPAF, has also been reported to disturb the HPG axis in the offspring of male zebrafish by increasing the mRNA expression of gnrh2, fshβ, and lhβ [61]. In zebrafish, gnrh2, fshβ, and lhβ are orthologous to human GNRH2, FSHβ, and LHβ, respectively.

BPA and its analogues also showed the ability to interfere with ERα in in vivo and in vitro studies. The BPA and its analogues, BPF and BPAF, increased the binding affinity towards ERα, while BPS has no effect on this receptor in zebrafish embryos [62]. This observation is supported by in vivo studies where subcutaneous exposure to BPA at a dose of 50 mg/kg/bw for two days increased the expression of ERα in the hypothalamus [57]. The same finding was also shown in the transgenic zebrafish embryo exposed to BPA and BPS at doses of 1000 µg/L and 100 µg/L, respectively. In contrast, perinatal exposure to BPA at a dose of 50 µg/kg/bw via drinking water caused a decrease in the expression of both ERα and β in the hypothalamus of male Wistar rats during adulthood [55]. The increase of Kiss1 expression in the brain increases GnRH secretion, stimulating LH and FSH secretion. A study by Bai et al. [56] found that perinatal exposure to BPA at a dose of 2 µg/kg/bw increased the GnRH neuron in the brain, leading to an increase in LH levels in the blood of male rat offspring.

In contrast, several previous studies have reported a decrease in the FSH and LH levels in the blood of adult male rats when exposed to various dosages of BPA ranging from 25 mg/kg/bw to 200 mg/kg/bw either via oral gavage or intraperitoneal injection [63][64][65][66][67][68][69][70]. A similar finding was also shown in rats who were exposed to BPA analogues. A study by Ullah et al. [71] showed that BPF at a dose of 1 mg/kg/bw via oral gavage significantly reduced the LH and FSH levels in the plasma of male rats. Therefore, from the previous findings, we may assume that BPA and its analogues at a lower dosage may increase LH and FSH levels via Kiss1 expression. However, a contrasting finding was noted when BPA was exposed at a higher dosage. LH in the blood binds to the LH receptor on the LC membrane to stimulate testosterone synthesis [72]. A previous study reported a decrease in the testosterone levels in the blood of adult male rats when exposed to BPA either during adulthood or exposure of offspring via oral gavage, subcutaneously, or intraperitoneal injection [63][64][65][67][68][69][70].

3. Bisphenols and Steroidogenesis

Testicular steroidogenesis is another important process in regulating the normal physiology of the male reproductive system. Steroidogenesis products such as testosterone, oestrogen, inhibin B, and progesterone play an essential role in maintaining the homeostasis of hormones in blood circulation. LC is a well-known site for steroidogenesis, particularly in the male reproductive system [73]. Steroidogenesis occurs in two different locations in the LC: the mitochondria and endoplasmic reticulum [72][73]. LH in the circulation binds to the LH receptor (LHR) at the LC membrane, thus activating the G protein groups to form the LHR/G protein complex. This complex activates two pathways by increasing cyclic adenosine monophosphate (cAMP) production and allowing the entry of arachidonic acid (AA) into the LC [74]. Next, cAMP activates protein kinase A (PKA) and mitogen-activated protein kinase (MAPK) for the stimulation of the steroidogenic acute regulatory (StAR) protein. This StAR protein is responsible for the transportation and movement of cholesterol from the outer membrane to the inner membrane of mitochondria [75][76].

Meanwhile, the presence of AA in the LC helps control testosterone production by inhibiting cholesterol movement to the mitochondria [77][78]. AA produces prostaglandin-E2 (PGE-2) via the activation of cyclooxygenase-2 (COX-2) and inhibits StAR functions [79][80][81]. Cholesterol is the primary substrate acting as a precursor in testicular steroidogenesis [73][75]. In mitochondria, cholesterol is converted to pregnenolone through the action of CYP11A1 [82]. The pregnenolone then moves into the endoplasmic reticulum, and the steroidogenic cascade of enzyme reaction that takes place involves the CYP450 enzyme (CYP17) and hydroxy steroid dehydrogenase (HSD) enzymes (3β-HSD and 17β-HSD). The conversion of pregnenolone into testosterone can be divided into two pathways (Δ4 and Δ5). These pathways can be alternated depending on the binding affinity of the CYP17 towards the substrates, 17α-hydroxy pregnenolone and 17α-hydroxyprogesterone, which activate the Δ5 and Δ4 pathways, respectively [82]. Humans mainly undertake this activity through the Δ5 pathway, while rats and mice mostly take the Δ4 pathway. In normal physiology, in testicular steroidogenesis, the Δ5 pathway is less prone to be converted to the alternative pathway synthesizing the E2 than the Δ4 pathway.

Nowadays, growing evidence has demonstrated the ability of bisphenols to disturb the steroidogenesis pathway. StAR, a protein responsible for transporting and moving cholesterol into the mitochondria, is among the proteins affected by exposure to BPA and its analogues. The gene and protein expression of StAR was decreased in adult male rats exposed to BPA for 28 days and 42 days, respectively, at a dose of 200 mg/kg by oral gavage [64][66]. Furthermore, BPA analogues such as BPF, BPAF, and BPS also caused a decrease in the expression of StAR mRNA. The expression of StAR mRNA was decreased in BPF and BPAF in the adults and offspring of male zebrafish, respectively [60][61]. Meanwhile, Eladak et al. [83] found that BPF and BPS also significantly decreased the expression of StAR mRNA in mouse foetal testicular cells (mFeTA) at a concentration of 10,000 nmol/L. The disturbance of the StAR mRNA expression may lead to the deterioration of testicular steroidogenesis due to the disturbance in cholesterol transportation and movement into the mitochondria in the LC.

Previous findings have also shown disturbance in the gene and protein expression of cytochrome P450 and HSD enzymes either in the mitochondrial or reticulum endoplasmic of LC, such as CYP11A1, CYP 17A1, 3β-HSD, and 17β-HSD. Exposure to BPA at a dose of 200 mg/kg for 28 days reduced the gene expression of CYP11A1 in the testicular mitochondria of male Sprague-Dawley rats [66]. Furthermore, exposure to BPA at the same dose for 42

days also decreased the protein expression of CYP11A1 [64]. In contrast, the expression of CYP11A1 was found to increase in adults and embryos of male zebrafish exposed to BPF and BPAF, respectively [60][61]. The disruption of CYP11A1 either involving the gene or protein expression decreases the conversion of cholesterol to pregnenolone in the mitochondria of LC. The CYP17A1 and 3β-HSD gene expression involved in the steroidogenic enzyme cascade in the endoplasmic reticulum also decreased in BPA-intoxicated rats [64]. The 17β-HSD, 3β-HSD, and CYP17A1 protein expression also decreased in the testis of male Sprague-Dawley rats exposed to BPA [70]. The same findings were also noted with exposure to BPA analogues in either in vivo or in vitro studies. BPF and BPAF exposure decreased CYP17 expression in the testis of zebrafish, while 17βHSD was found to be decreased in the testis of adult male zebrafish after 21 days of exposure to BPF [60][61]. An in vitro study conducted by Eladak et al. [83] found that BPF and BPS at the highest dose (10,000 nmol/L) caused a decrease in the expression of HSD3β1 and CYP17A1 in mFeTA after three days of exposure.

4. Bisphenols and Spermatogenesis

Spermatogenesis occurs within the seminiferous tubules in the testis. The germ cells, such as spermatogonia, spermatocyte, and spermatid, undergo various stages of spermatogenesis to form sperm. Spermatogenesis occurs via specific processes, such as proliferation, differentiation, mitosis, meiosis, and spermiogenesis, to develop mature spermatozoa. Among these specific processes, proliferation, differentiation, and mitosis occur in the basement membrane, while the remaining processes occur in the adluminal compartment [84]. The blood–testis barrier (BTB) is formed after the basal membrane to protect the microenvironment of the adluminal compartment for the processes relevant to that area. Therefore, the germ cells found in the basement membrane are more vulnerable to any toxicants than the germ cells found in the adluminal compartment [72]. The integrity of the BTB is also crucial because changes in its structure may affect the production and morphological structure of the sperm [74]. Spermatogenesis involves not only different stages of germ cells but also SCs. These cells secrete pyruvate and lactate to nourish germ cells during their development and are responsible for the organization of the germ cells [82]. Therefore, any disturbance in the SC causes degeneration and disorganization of the germ cells. Testosterone plays a critical role in spermatogenesis owing to its ability for BTB maintenance, meiosis, Sertoli-spermatid adhesion, and the release of mature spermatozoa [84]. Testosterone maintains the remodelling of the BTB by binding with AR to form the protein involved in the integrity of tight junctions. Testosterone is needed in the completion of meiosis during the development of spermatocytes. Moreover, testosterone also plays an essential role in preventing the elongated spermatid from being released earlier. However, the testosterone hormone helps release the mature spermatozoa into the lumen of the seminiferous tubule, thus preventing spermatozoa from being engulfed by the SC [84].

BPA and its analogues were reported to disturb spermatogenesis by diminishing the BTB integrity, changing testicular histopathology, and causing sperm defects [85][63][64][65][66][71][86][87][67][68][69][70][88]. A study carried out by Li et al. [89] found a disturbance in the BTB of male Wistar rats, which was proven by the reduction of occludin and nectin-3 when exposed to BPA in a dose-dependent manner. The reduction of occludin was also found in the SCs, which were exposed to BPA in in vitro studies [90][91]. Furthermore, both studies also showed a decrease in the ZO-

1 protein level [90][91]. The disturbances of these proteins lowered the integrity of BTB, which was proven by the reduction in cell viability and androgen receptor (AR) after 6 h of BPA exposure [90]. Moreover, Feng et al. [91] also found that the reduction of occludin and ZO-1 in SCs significantly perturb the tight junction barrier, lowering the integrity of the BTB. The disruption of BTB integrity may allow germ cells in the adluminal compartment to be exposed to toxicants, leading to the disturbance of spermatogenesis in the seminiferous tubules.

Spermatogenesis disruption after exposure to BPA and its analogues can be shown by histological observations, such as reduction in the diameter and epithelial height of germ cells, atrophy and separation of germinal epithelium, and irregular seminiferous tubule structure [65][66][70]. Previous studies reported that BPA exposure causes histopathological changes, proven by the vacuolation, degeneration, and disorganization of germ cells [65][66][70]. The vacuolation and degeneration of germ cells were reported after BPA exposure either via oral gavage for 52 days or intraperitoneal injection on alternate days for 30 days in adult male Sprague-Dawley rats [65][70]. The spermatogenesis process was found to be weak, arrested in the seminiferous tubule of adult male Wistar rats exposed to BPA at a dose of 50 mg/kg via oral gavage for 14 days [69]. Furthermore, the same study also found that spermatocytes are among the most affected germ cells in BPA-intoxicated rats [69]. Wang et al. [66] found that BPA at a dose of 200 mg/kg via oral gavage caused disorganization of germ cells [66]. However, these changes were not observed in BPA analogue-intoxicated rats. Moreover, BPA analogues such as BPF and BPS cause spermatids to become longer, and the absence of mature spermatozoa in the lumen of seminiferous tubules disrupts spermatogenesis in adult male Sprague-Dawley rats [64][71][86]. According to Liang et al. [88], BPA and its analogues (BPS and BPAF) decrease cell viability and increase the DNA damage of the spermatogonia cell line (C18-4). Among these bisphenols, BPAF causes significant outcomes at the lowest concentrations within 24 h of exposure [88].

BPA and its analogues disrupt spermatogenesis, leading to the deterioration of its outcome, which is proven by a reduction in sperm quality. Low sperm production induced by toxicants is usually associated with oxidative stress and the reduction of testosterone in the blood circulation [92][93]. Furthermore, the reduction in sperm development may also be due to abnormal SC causing insufficient nutrition, which is necessary for spermatogenesis [89]. According to previous studies, adult male rats' exposure to BPA causes a decrease in sperm quality, proven by a reduction in sperm production, count, motility, viability, and the integrity of sperm acrosome and plasma membrane mitochondrial activity [63][64][65][66][67][68][69]. BPA at a dose of 50 mg/kg/bw for 14 days caused mild oedema in the LC, leading to a reduction in testosterone, thus lowering the sperm quality of adult male Wistar rats [69]. There is also an association reported between mitochondrial activity and motility in sperm because the mitochondria is the only source of ATP that enables the energy production necessary for sperm movement [68]. The sperm-specific ion calcium (Ca^{2+}) channel (CatSper) is also crucial for sperm motility, hyperactivation, and acrosome reaction. This pH-sensitive channel is responsible for providing enough Ca^{2+} for sperm function [94]. Progesterone is a factor that influences the activation of the CatSper channel for sperm hyperactivation and acrosomal reaction to penetrate the oocyte [94]. Previous findings reported that the expression of the CatSper channel and charges were significantly downregulated and decreased after exposure to 10, 50, and 250 µg/kg/kg doses of BPA to the sperm mice orally [95]. These reductions parallel the finding where the motility and acrosome reaction in the presence of progesterone were significantly decreased as well. Exposure of healthy human sperm to 10 µM BPA analogues showed a similar

effect on the CatSper channel's ability. In a study, the scholars found that BPG, BPAF, BPBP, BPC, and BPB are potent chemicals that inhibit progesterone-induced Ca^{2+} [96]. These BPA analogues are shown to affect Ca^{2+} signaling, which can interfere with normal CatSper signaling and result in infertility [96].

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