Bisphenol A and Male Reproductive System

Bisfenol A ve Erkek Üreme Sistemi

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ABSTRACT

Bisphenol A (BPA) is an alkylphenol endocrine disruptor chemical (EDC). It is a building block for polycarbonate (PC) plastics and epoxy resins and it is used in food packaging, canned foods, baby bottles, baby food jars and medical devices. Recently, researchers have shown an increased interest in BPA and its effect on reproduction, neurodevelopment and metabolism. The experimental data are rather controversial, and there is no general consensus about BPA's effects. In this review, potential impacts of the BPA on male reproductive system in prenatal and postnatal period are summarized.

Key Words: Bisphenol A, leydig cell, sertoli cell, sperm, sperm quality, testosterone

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ÖZET

Bisfenol A (BPA) bir alkilfenol endokrin bozucu kimyasaldır (EDC). Polikarbonat (PC) plastikler ve epoksi reçineler için bir yapı taşıdır ve gıda ambalajı, konserve gıdalar, biberonlar, bebek maması kavanozları ve tıbbi cihazlarda kullanılır. Son zamanlarda, araştırmacılar BPA ve BPA' nın üreme, nörogelişim ve metabolizma üzerine olan etkilerine artan bir ilgi göstermektedir. Deneysel veriler oldukça tartışmalıdır ve BPA'nın etkileri hakkında genel bir fikir birliği bulunmamaktadır. Bu derlemede, BPA'nın prenatal ve postnatal dönemde üreme sistemi üzerindeki olası etkileri özetlenmiştir.

Anahtar Sözcükler: Bisfenol A, leydig hücresi, sertoli hücresi, sperm, sperm kalitesi, testosteron

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INTRODUCTION

One of the most produced chemical for consumers' products is a synthetic monomer of plastic named bisphenol A (BPA). There is a wide use of this synthetic monomer such as in drinking containers, food packaging and medical devices (1). The concerns about the use of BPA at numerous fields have risen after the researchers studied about the effects of it at many organs. The reason for these worries are because the possible harmful effects to human health due to its mechanism as an endocrine-disrupting chemical (EDC). Almost one hundred human studies have described the link between BPA and its effects on reproductive system, neurodevelopment process, thyroid function ability, and metabolic health areas (2). There is an inhibition leaded by BPA on cell proliferation and an increase at the levels of apoptosis rates (3). BPA can affect the steroidogenic enzyme expression and the production of testosterone in Leydig cells. Finally, this leads the testosterone levels to decrease (4). BPA can disrupt the progression of germ cell development. The probable effect may be the spermatogenic defect in the developing testis (5). We reviewed the effects of BPA on male reproductive system; the potential effects at spermatogenesis-related hormone balancing, spermatogenesis and sperm quality.

Sources of Exposure to BPA and Its Derivatives

Bisphenol A (BPA) (chemical structure of HO-C6H4-C(CH3)2-C6H4-OH) is an alkylphenol endocrine disruptor chemical (6) which was first synthesized by a Russian chemist Aleksandr Dianin in 1891. The ability of BPA to act as an estrogen agonist was not found until 1936 (7). BPA was discovered as a building block about 20 years later to be used in polycarbonate (PC) plastics and epoxy resins. More than 40 years BPA is used in food packaging as canned foods, baby bottles, Sippy cups, baby food jars; at children's products, medical devices, flooring also via inhalation of contaminated indoor air.

In human body the metabolism of BPA is made in the liver by uridine 5'-diphospho-glucuronyl transferase (8) and the half-life of BPA is about 5.4 hours (9). There are numerous scientific studies about BPA's small amounts which are measured in parts per billion to an increase risk of for example, infertility (1), immune-related diseases (10) and disturbing the functions of the nervous system (11). A study published in 2009 at Harvard T.H. Chan School of Public Health demonstrated that participants who drank from polycarbonate bottles for a week showed a two-thirds increase in their urine for chemical BPA. This esteemed study was first to warn people with a title ''emergency announcement'' given about the BPA's possible harmless effect. According to a quantitative competitive enzyme-linked immunosorbent assay the rates of the migration of BPA from polycarbonate water bottles were from 0.20 ng/h to 0.79 ng/h. There was a difference when it comes to boiling; exposure to boiling water had increased the rate up to 55-fold (12).

It seems like people who are exposed to BPA from these products are compromising their health day by day. Hence, there should be a restriction for the usage of BPA. At United States of America some companies have totally transitioned away from the use of BPA and BPA alternatives. None of their cans contained any BPA-based epoxy resins after analysis (13). Argentina (2012), Belgium (2013), Brazil (2012), Canada (2010), and France (2010) prohibited the usage of BPA from baby bottles (14). Ministry of Food, Agriculture and Livestock from the Republic of Turkey published a notification on June 10, 2011 declaring ''to the consumer groups defined as infants, their productions, which is made from polycarbonate materials are forbidden to be used'' (15).

There are some alternative ways for replacement of BPA in cans or for costumers to follow. For safer packaging glass containers or paperboard based packaging can be used. For costumer's attention, they can use glass or ceramic for food storage, avoid canned foods whenever possible, looking for glass packed soup and sauces and finally soak their beans overnight and cook them the next day can also be options.

Potential Teratogen Effects of BPA at Prenatal Development Stages

At prenatal life the unborn child is always in danger from the environment which mother is surrounded. Pollution, food, water and even our clothes are counterproductive these days. One of these threatening factors is an endocrine disrupting chemical (EDC) which is known as bisphenol A (BPA). Even though BPA has a teratogenic effect on embryos during their critical period of organogenesis (16) unfortunately some of the bisphenol derivatives are found in for example at babies nursing bottles and pacifiers (17). According to a BPA research related to fetal health, women who were exposed to the highest BPA had the lowest estimated growth rates for fetal head circumference. The researchers suggest that during pregnancy as the con¬centrations of BPA increase in urine was associated with a decreased fetal growth for both fetal weight and head circumference (18).

The most sensitive time of the prenatal period is the embryonic period during the third to eighth weeks. At the end of the eighth week fetal period begins and extends to term. In the meantime, the risk of whole structural defects being induced decreases, but organ systems may still be affected. During the fetal period, the brain continues to differentiate so that toxic exposures may cause learning disabilities or mental retardation at that time (19). There are plenty of studies focused on the ability of BPA to affect the developing brain even at very low doses. The cerebral cortex, hippocampus and hypothalamus in the rodent brain is affected by prenatal and perinatal EDC exposure. Due to their epigenetic actions on the sex-specific behavioral effects, BPA and EDC's can disrupt normal steroid programming of the brain. As a result, this can lead to differential gene expression such as DNA methylation and histone modifications (20). In fact, the altered genome caused by EDC's effect can be passed from one generation to another which has control on hormone level, neurobiological, physiological functions, and behaviors toward the offspring (21). There is a link between BPA and neurotoxicity. Several animal studies report BPA to affect synaptogenesis and neurogenesis processes which are known as the brains self-regeneration against trauma and disease. It is an important knowledge that both, even at low doses, BPA and bisphenol S (BPS) affect neurodevelopment by altering these processes (22).

Autism spectrum disorders (ASD) have strong associations with environmental factors and genetic components (23). According to epidemiological studies there is a relationship between maternal BPA exposure and ASD. The metabolomics analyses showed a correlation between ASD and essential amino acid metabolism pathways (24). Even micromolar concentrations of BPA are able to decrease synaptic density in cultured rat hypothalamic neurons. BPA can change DNA methylation, gene expression, and behavior, but whether these events are causally linked is unknown (25).

At the critical stages of fetal development EDC exposure can disturb the reproductive organ differentiation by a final of an intersex variation. By the seventh week of gestation, differentiation of male and female external genitalia occurs. Toxics can adversely affect the development of morphological characters via molecular functions while in utero and causes the baby with different types of abnormal morphological variations such as ambiguous genitalia, cryptorchidism, perineal hypospadias, epispadias and clitoromegaly (26). Sometimes these effects can be more specific on reproductive systems. For example, BPA is reported to disrupt spermatogenesis by decreasing the capacity of spermatogenesis and sperm production in male offspring, damaging the Sertoli cell interaction and the blood-testis-barrier (BTB) in rats (27).

Conclusions may vary from some researches based on BPA's exposure on gender. There is a study which estimated the impact of BPA exposure on behavior and cognitive abilities at 3 years old children to determine if there is a difference between type of gender. It is found that gestational BPA exposure affected, especially the girls (28). BPA's possible negative effects upon girls are precocious puberty, breast cancer and polycystic ovary syndrome (29). From another study it is claimed that BPA exposure leads to increased behavior problems in school age boys, but not girls (30). Consequently, we can see that there is no agreed situation about whether BPA's exposure is more effective on boys or girls, but this fact is not going to hide the truth about this chemicals negative effect on the child.

BPA, Spermatogenesis and Sperm Quality

Spermatogenesis is the process of mature sperm cell maturation and differentiation. The aim of spermatogenesis is to produce a unique male gamete that can fertilize an ovum (31, 32). Recently, several studies have focused on the effects of BPA, but the experimental data are rather controversial, and there is no general agreement about the effects of BPA on spermatogenesis and sperm parameters (e.g., sperm count, motility, viability, density and morphology).

The negative effects of BPA on spermatogenesis process can occur during prepubertal, pubertal and adult period. BPA's effect on spermatogenesis and sperm quality has been reported in several experimental animal model studies.

Many studies have indicated that, in rodents, exposure to BPA decreasing free plasma testosterone and 17β-oestradiol level and BPA had negative effect on fertility, histomorphology of testis and sperm parameters (33-35). However, Ashby found no consistent alteration in daily sperm production in 5 replicate studies with 3 various diets with BPA (CE2, RM3,Purina 5002) and no difference in testes, epididymis, prostate, seminal vesicle weights in rats (36).

Different researchers have investigated that apoptosis- inducing activity of BPA on spermatogenesis. BPA was administrated orally (2 µg/kg) for consecutive 14 days in adult rats and spermatogenesis was impaired by suppressing testosterone and follicle-stimulating hormone (FSH) production, promoting germ cell apoptosis and reducing the sperm count (37).

In other study, Xie and coworkers (2016) demonstrated that BPA (0.01, 0.1 and 5 mg/kg body weight) daily exposure in neonatal period induces meiotic arrest during the first stage of spermatogenesis in newborn mice (38). Moreover, BPA increased number of apoptotic cells in the seminiferous tubules. Wang et al. (2017) evaluated that BPA induced apoptosis in mice spermatocyte via G protein-coupled receptor-30 (GPR-30) which is the estrogen receptor (39).

Toyama et al. administered 20 or 200 microg/kg body weight/injection of (BPA) to adult rats and mice for 6 days and determined abnormalities of spermatid such as deforme nuclei, acrosomal vesicles and acrosomal caps in experimental groups (40).

One study found that treatment of Wistar albino rat with BPA (50, 200, and 600 mg/kg/day, orally) caused a decrease in the sperm count, motility and an increase necrotic change of spermatogonial cells in the seminiferous tubules, dead count and head and tail abnormality percentage (41).

Li et al. (2009) pointed out that BPA at different doses (160, 480, and 960 mg/kg/day) on testes of pubertal male mice from postnatal days (PND) 31–44. They showed that no effect of BPA at 160 mg/kg/day, but at 480 and 960 mg/kg/day there was disruption of spermatogenesis through the Fas, FasL, and active caspase-3 expression (42). In another study about postnatal exposure to BPA, it was shown that administering different doses of BPA (0, 20 and 40 µg kg-1 day -1) from postnatal Day (PND) 3 to PND21, PND 35 or PND49 effected the meiotic process of germ cells and spermatogenesis (43).

In additional, a significant increase in DNA damage to spermatocytes and decrease sperm count and motility was observed, following 12 weeks of BPA (10mg/kg bwt) administration in mice (44). Smilarly, Rahman et al. (2017) reported that, toxic effect of gestational BPA exposure (5 mg/kg, and 50 mg/kg bw/day) on motility, capacitation, and motion kinematics of spermatozoa in mice. However, no or minimal effects were observed in the low-dose (50 µg/kg) BPA group (45). Detrimental effects of BPA on sperm quality showed in experimental animal models has been confirmed by some studies conducted among groups of BPA-exposed human males (46). Data from two studies, which exposed male workers to high levels of BPA, shows that BPA has effects erectile and ejaculatory problems, reduction of sexual desire and sperm morphology and density (47, 48). Meeker et al. (2010) investigated that association between exposure to BPA and sperm parameters in men from an infertility clinic. There were no significant positive correlation between urinary BPA concentration and sperm quality. However, they found that increased DNA damage in sperm and decreased semen quality in BPA groups (49).

In a cross-sectional study with 215 healthy young (18-23 years old), it was investigated that urinary BPA concentrations are associated with a reduction in Leydig cell function, increased serum LH levels and decreased sperm count (50). In another study, researchers investigated that the negative relationship between urinary BPA concentrations and progressive sperm motility in 308 young men. However, they found that no associations of BPA with other sperm parameters (51).

According to another prospective cohort study, Goldstone et al. (2015) investigated the relationship of urinary BPA concentrations and sperm parameters in 418 male partners of couples trying to become pregnant in Michigan and Texas. They found that urinary BPA concentrations were associated with lower percentile of sperm DNA fragmentation and no association with semen parameters (52).

Leydig and Sertoli Cells

The synthesis of steroid hormones (steroidogenesis) and the making of mature sperm (spermatogenesis) are the two major functions of the testes. These functions are carried out with coordination amongst the many cell types such as Sertoli, Leydig, peritubular myoid and spermatogenic cells inside the testis (53). There is strong testimony on the possible influence capacity of BPA to these cellular functions (54).

Numerous investigations using rodent animal models have reported that BPA leads to numerous adverse impact such as a reduction in sperm properties (55), impairment of spermatogenesis (56), interruption of the hypothalamic-pituitary-testicular axis (55), and a decline in the making of testosterone by the Leydig cells (57, 58).

Steroidogenesis is a continuous process within the Leydig cells. These cells produce testosterone, the primary male steroid hormone, as a consequence of the steroidogenic tract under the control of the luteinizing hormone (LH). Releasing of LH is also controlled by hypothalamic GnRH (54, 59).

Testosterone trigger virilization of the male urogenital system in fetal life and helps spermatogenesis and fertility in adulthood. Therefore, as Leydig cell function is altered by EDs such as BPA, male fertility potentially is affected (54, 59). Akingbemi et al applied 2.5 µg/kg/day BPA to male rats at from 12th day of gestational day to 21st day of postnatal day. End of the research administration of BPA did not change serum testosterone levels, but declined making of testosterone by Leydig cell and intratesticular testosterone concentrations in adult animals (59).

BPA carry out biological actions in the body mostly through its estrogenic properties. Estrogen receptors (ERs) are highly expressed as well as androgen receptors at male reproductive tract including Leydig cells (60, 61). It is reported that estrogens are as important as androgens in male reproductive tract biology (62). Though ER-α (ESR1) and ER-β (ESR-2) which are subtypes of ER are present in males, ER-β appears more abundant and in a greater number of cell types in the male reproductive system (60, 63). LH hormone binds to these receptors and starts biological pathway leading to synthesis of estrogens. A number of researchers have reported that BPA has the ability to bind the estrogen receptor and bring about defects in the reproductive tract at studies in vitro rodent models (64-66). It is assumed that BPA has a higher affinity for ER-β but BPA can active ER-α and ER-β-mediated transcription process with comparable effectiveness in some tissues (61, 67, 68). Previous investigations have reported that BPA acts as an AR (Androgen Receptor) antagonist and can interact with ER-α and ER-β (69). BPA performs an inhibitory impact on steroidogenesis of the Leydig cell and ERs help possibly forming of this effect (59, 70).

Recently, in vitro and in vivo experiment about the effects of BPA on Leydig cells have shown that BPA works directly as a mitogen in these cells. Song and Lee et al, have stated that BPA may cause affect in the body through activation of MAPK (mitogen-activated protein kinases) (71). In another study by Sriraman et al was examined BPA-induced proliferative activity in Leydig cells with progenitor, immature and adult Leydig cells isolated from 21, 35 and 90 day aged rats. End of the study it is reported that proliferative action in Leydig cells was associated with cell cycle progress, probably mediated by PCNA (proliferating cell nuclear antigen) and cyclin D3 (72).

Moreover, BPA has the ability to exhibit antiandrogenic activity (73, 74) and rise bioavailability of sex steroid hormones via interrupting metabolic breakdown (61, 75). In addition, due to suppressing expression of LH receptors (LHCGR) and the enzyme HSD17B3, BPA reduces releasing of androgen (61).

Furthermore, many scientists have argued that there is a paracrine relationship exists between Leydig cells and Sertoli cells (76-78).

Sertoli cells, which found in a blood-testis barrier (BTB), are the somatic cells of the testis and have a crucial function in helping proliferation and differentiation of spermatogenic cells throughout mammalian spermatogenesis (79, 80). The BTB separates the seminiferous epithelium into the basal and adluminal (apical) compartment (79). Spermatogenesis is a very complex, dynamic and organized process occurring in the seminiferous tubules epithelium (81).

Function of Sertoli cells is under control of FSH hormone whose secretion is linked to hypothalamic-pituitary-testicular axis so these cells have FSH receptors on their membranes. FSH hormone producing or Sertoli cell function is disturbed by BPA may blight reproductive function in exposed males (82).

Recent evidence has revealed that AMH (Anti-Müllerian hormone) released from Sertoli cells is a goal for endocrine disruptors using estrogenic property (61, 83). In an experiment using male rat, Nanjappa et al demonstrated that a decrease in amount of AMH possible effects interactions between Sertoli cells and Leydig cells. It is also probably that BPA reducing the amount of AMH in Sertoli cells is a piece of a broader effect on Sertoli cell (61).

Several studies investigating adverse impact of BPA on male reproductive system have been carried out on primary Sertoli cell culture and cell lines. Detailed examination of the effect of BPA to Sertoli cells isolated from 18-day-old Wistar rats by Lida and Maehara reported that BPA decreased cell viability. BPA also caused the Sertoli cells to show changes in morphology involving blebs on the membrane, failure of cytoskeletal structures, cell rounding and condensation and fragmentation of DNA that fit the morphological properties of apoptosis (84). These increases in apoptosis may arise from an induction of caspase-3 by BPA (85). Furthermore, another study with Sertoli cells isolated from18-day-old Sprague Dawley rats showed that over 50µM BPA administration could reduce the viability of Sertoli cells and lead to more apoptosis. It is also underlined that Pten/Akt pathway might be associated with the apoptotic impacts of BPA on Sertoli cells (86).

Li and Song examined that the effect of BPA at high doses (160, 480, and 960 mg/kg/day via gavage) on the testes of pubertal male Kunming (China) during postnatal days 45, 60, and 90. They reported that high-dose (480 and 960 mg/kg/day) BPA induces apoptosis of Leydig and germ cells in the mouse testis by using the Fas-signaling pathway (42, 87).

Furthermore, BPA also had been shown to increase death of the Sertoli cells by blocking endoplasmic reticulum Ca2+ pumps and the action of Ca2+-ATPase of testis at a micro Molar dose of BPA in TM4 Sertoli cell line (88).

Recently, the influence of BPA on cell viability, mitochondrial function and CaM-CaMKII-ERK1/2 signal tract have investigated at TM4 Sertoli cells. TM4 cells were cultured with 0, 0.02, 0.2, 2.0, 20 µM BPA. They suggested that CaM-CaMKII-ERK shaft might convey apoptotic signals to the mitochondria through BPA-induced cell apoptosis (87). Data from several sources have identified that BPA induces apoptosis of Sertoli cells and male germ cells (42, 85-88).

One of the most important tasks of Sertoli cells is also to regulate intratubular and intercellular environment adluminal to the tight junctional complexes (89). Fiorini et al. investigated impact of BPA on intercellular junctions of Sertoli cell using SerW3 Sertoli cell. It is reported that SerW3 Sertoli cell lines produced characteristic constituents of tight (occludin and zonula occludens-1), anchoring (N-cadherin) and gap (connexin 43) junctions. They found that BPA affects intercellular junctions. This effect arises from decreasing the amount or inducing unusual intracellular localization of these membranous proteins (90).

There are also some studies revealing that BPA forms adverse effects on the BTB integrity of immature rats. Loosing of gap junction function or regulation of tight junction and anchor junction functions at site to preserve the immunological barrier integrity might be lead to this bad effect (91, 92). Furthermore, it has been demonstrated BPA also has capacity to trigger down-regulation of a few genes (Msi1h, Ncoa1, Nid1, Hspb2 and Gata6) connected with Sertoli cell function in 6-week-aged-male mice after prenatal administration (93).

In addition to these, it was stated that low doses of BPA increased oxidative stress and declined levels of insulin receptor substrate 2 (IRS-2) and glucose transporter 8 (GLUT-8) in rat testis (87, 94). In another study, the presence of IRS-1 and -2 has been showed in the peritubular and Sertoli cells of rat testis. This also indicates that insulin has a role in the regulation of glucose uptake and energy metabolism in testis (95).

BPA and the Effects on Prostate

As an endocrine disruptor, BPA can affect many organs which are related to reproductive system. Low doses of BPA can induce the proliferation of the prostate in rats via the epithelium structure. The mechanism is by downregulating the expression of androgen receptors besides upregulating the expression of estrogen receptors. This will lead the cells to an apoptosis process (96). Counting on a histopathological definition to declare that BPA has a testicular toxicity affects, there is a loss of elongated spermatids and degeneration on seminiferous tubule at a male F344/DuCrj (Fischer) rat research (97). Environmental BPA provides evidence that it could cause prostate carcinogenesis. The biomarkers of this prostate malignancy are methylation patterns or related genes, for example PDE4D4, which can be used as a sign for developmental exposure from BPA (98). BPA can increase the entry of calcium and this could start the process to lead a cell migration by activating the enzymes such as metalloproteinases. Finally, by remodeling this calcium signaling this can lead the prostate cancer cell migration (99). Neonatal exposure to xenoestrogens can increase the number of the stem cells which are known targets for carcinogen-induced malignant transformation at prostate. BPA exposure can be a reason for prostate cancer trough DNA methylation (100).

CONCLUSION

BPA is one of the most useful chemical but unfortunately the effects are mostly damage to human body system. Both at low or high doses according to articles BPA has negative effects on male reproductive system. Because of the limit of human researches, there is not enough data for us to be sure about the exact effects or the amount of these effects. More studies should be done for this topic.

Conflict of interest

No conflict of interest was declared by the authors.

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