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Literature Reviews

A Review on Effects of Bisphenol a on Reproductive, Endocrine Systems and its Influencing Mechanism

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Abstract: Background and purpose: Bisphenol A (BPA) is a pervasive environmental toxicant with known adverse effects on human immune system and nervous system et al. Although, BPA is widely known to affect endocrine function in animals, the linkage between human exposure to BPA and human reproductive function is still not clearly clarified. Results: Systematic review of all articles about BPA and human reproductive function identified in SCOPUS and PubMed. Literature was summarized in narrative form and results are presented per category. Some observational surveys investigating the relationship between BPA exposure and human reproductive and/or endocrine function are inconsistent. Conclusion: Our review integrates the studies of BPA on reproductive and/or endocrine system in recent years, mainly explains the effects of BPA on these systems and provides the basis for subsequent studies on BPA.

Keywords: Bisphenol A, Endocrine Disruptor, Reproductive Hormone, Semen Quality

Introduction

The monomer bisphenol A is a synthetic phenolic compound widely utilized for the manufacturing of polycarbonate and epoxy resins dedicated to food containers, such as cans and water dispensers. Global demand growth for BPA is expected to approximate 6–10%/y (Wright-Walters *et al*., 2011). Today, it is one of the highest-yield chemicals in the world, produced with more than 8 billion pounds yearly and sent roughly 100 tons into the atmosphere per year (Rubin 2011). Everyone is exposed to BPA through skin and inhalation; besides, these polymers can release BPA into water and food (Hernandez *et al*., 2019) and, it can be detectable in urine from the vast majority of Americans (Schug *et al*., 2011).

Endocrine Disrupting Chemicals (EDCs) are widely distributed in the environment, both natural or synthetic compounds can disrupt the endocrine system though imitating or antagonizing the endogenous hormones (Bhandari *et al*., 2015). BPA, as one of the most widespread and plentiful EDCs, can stimulate natural hormones to alter the reproductive endocrine system, which bring a negative effect on reproductive physiological functions (Caserta *et al*., 2011) and eventually influence entire populations (Yuan *et al*., 2015) Fig. 1.

Up to now, the effects of EDCs on reproductive physiology and endocrine system has not been systematically clarified. Thus, given such critical effect on reproductive and endocrine systems, we summarize briefly the regulatory role of BPA in reproductive related factors.

Materials and Methods

Our studies was conducted by systematic literature retrieval in Medline, Web of Science and PubMed databases. We identified the following search terms: “Bisphenol A” AND “reproduction” OR “endocrine” OR “androgen” OR “estrogen” OR “exposure” OR “hormone” OR “estradiol” OR “testosterone” OR “sperm” OR “sperm function” OR “spermatogenesis” OR semen quality OR “sexual function” and searched out the relevant literature. All data involved in related studies of animal as well as human and relevant reviews on the linkage between BPA and reproductive, endocrine systems were included in our study. Data were categorized and summarized according to the various aspects on which BPA may effect,

such as effects on hormones and its influencing mechanisms. The list of the genes, enzymes and hormones involved throughout the whole paper is listed with their acronyms and full title in Table 1. The genes mentioned is presented in lowercase italics.

BPA Effects Endocrine and Reproductive

There is evidence that BPA has similar chemical structure to estrogen and may be involved in the actions towards estrogen and androgen receptor system at fairly low doses by acting as agonists or antagonists for Estrogen Receptor α (ERα) and Estrogen Receptor β (ERβ) (Kinch *et al*., 2015). Accumulating evidence including rodent and *in vitro* studies supports that BPA is able to bind to androgen receptor or estrogen receptor so that it has estrogenic as well as anti-androgenic impacts (Alonso-Magdalena *et al*., 2012; Melzer *et al*., 2011).

BPA interferes with hormone biosynthesis and metabolism through the role of endogenous ligands, leading to unbalance of endocrine system (Diamanti-Kandarakis *et al*., 2009), which proved that BPA may influence reproductive function *via* various hormone-mediated mechanisms. BPA may intervene with human cellular steroidogenesis by means of strong combination to human ER (Takeuchi *et al*., 2006) and influence the production of steroid hormones by intervening the expression of steroid synthetase (Zhou *et al*., 2008), change levels of steroid hormone and induce reproductive and embryo toxic effects (Mlynarčíková *et al*., 2005).

In addition, it has been demonstrated in animal studies that BPA has the unfavorable impacts on male reproductive health, which is evidenced by obstacle of spermatogenesis and steroidogenesis, poor sperm quality, male infertility and sex disorders (Peretz *et al*., 2014). There are also some studies showing that BPA reduces production of testosterone during male development, induces prostate diseases, affects spermatogenesis (Yeung *et al*., 2011) and results in apoptosis of male germ cells and Sertoli cells (Li *et al*., 2009; Qian *et al*., 2014). Therefore, aberrant hormone levels could be one crucial mechanism. Below we will respectively introduce the effects of BPA on related hormones, proteins or genes and their mechanisms of action Fig. 2.

BPA Effects Testosterone

Effect of BPA on Testosterone in Human body

Adequate studies have found a long-term decline in human testosterone levels (Andersson *et al*., 2007; Travison *et al*., 2007). From the perspective of working exposure, evidenced the negative relationship between serum Free Testosterone (FT) levels and urinary BPA levels on occupational BPA exposure (Zhou *et al*., 2013). From the angle of infertility, Den Hond *et al*. (2015) discovered the inverse relationship between testosterone levels in infertile male and urinary and blood plasma BPA concentrations (Den Hond *et al*., 2015). Likewise, the adverse association between free androgen index (an indicator for FT) and urinary BPA concentrations was detected in men diagnosed as infertile (Meeker *et al*., 2010).

Many experiments in humans have shown that BPA reduces the production of AD that a upstream molecular of T. There is a cross-sectional study on 592 men from China, which revealed the correlation between a high BPA exposure and a reduced AD level in blood (Liu *et al*., 2015). A study recruited 281 male workers exposed to epoxy resin from 4 factories and also discovered that BPA concentrations measured in serum were adversely correlated with AD level (Zhuang *et al*., 2015).

Instead, in a Lassen's study, it was indicated that BPA was positively linked with serum TT (total testosterone) and FT in urinary of young men (Lassen *et al*., 2014) and Galloway's findings also agree with another experiments of adult Italian, which suggested that BPA had a positive correlation with testosterone (Galloway *et al*., 2010).

At the same time, some experiments have shown that BPA exposure has no relationship with testosterone. In a human study, no adverse correlation with testosterone was discovered (Liang *et al*., 2017), although as assessed by serum Gonadotropins (Gn), including LH and FSH, BPA concentrations in urinary is linked to testicular dysfunction. Based on an epidemiology study, Mendiola and his colleagues found that BPA may affect the levels of Sex Hormone Binding Globulin (SHBG) and FAI instead of TT levels (Mendiola *et al*., 2010) and conjectured that the signal of increased LH and FSH may not suffice to induce the alteration of serum TT level. In a research of exposure to BPA diglycidyl ether and mixed organic solvents, it was indicated that urinary BPA was barely related with FT (Hanaoka *et al*., 2002).

Effect of BPA on Testosterone in Animal (Non-Human)

Besides, similar results were existed in animals experiments as well, there are studies indicating that pre- and postnatal BPA exposure can reduce testosterone levels in male offspring (Cardoso *et al*., 2011; Ma *et al*., 2017; Tanaka *et al*., 2006). Regarding pre-pubertal or pubertal exposures, the obvious drop in testosterone (Wisniewski *et al*., 2015) and epididymal sperm counts have been observed in rodent studies after BPA exposure (Herath *et al*., 2004). Rats are one of the best models for medical research. In adult male rats, Tohei *et al*. (2001) confirmed the decline of plasma testosterone levels in male adult rats after treatment by BPA in contrast with control group. Gurmeet *et al*. (2014) had proved that extremely low doses of BPA at which the adverse effects are not observed can negatively influence spermatogenesis, deprive seminiferous tubules of sperm and decrease levels to plasma testosterone significantly. At the same time, there is a study expressing that prenatal BPA exposure

didn't alter testosterone levels of prepuberal male rats (Gámez *et al*. 2014).

Mechanism of BPA Influencing Testosterone

The main source of testosterone is Leydig cells, followed by adrenal cortex reticular bands. Leydig cells secrete testosterone Hypothalamus-Pituitary-Gonad Axis (HPGA). As for the later form, testosterone is synthesized from cholesterol and the specific process of testosterone synthesis is shown in Fig. 3. BPA can affect testosterone secretion in Leydig cells by acting on several key enzymes, such as steroidogenic acute Regulatory protein (StAR), cytochrome P450 11A1 (CYP11A1), aromatase cytochrome P450 (CYP19/P450arom), cytochrome P450 17A1 (CYP17A1) and 3β-hydroxysteroid dehydrogenase (3-β-HSD).in two forms: Basal secretion and gonadotropin-induced secretion regulated by the

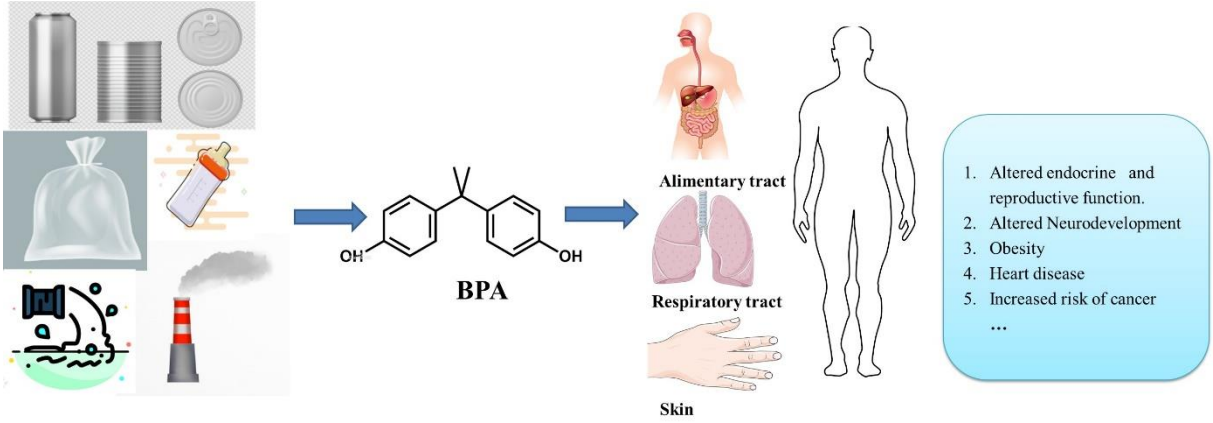

Fig. 1: The ways of BPA exposure through alimentary tract, respiratory tract and skin and its adverse effects on the human body

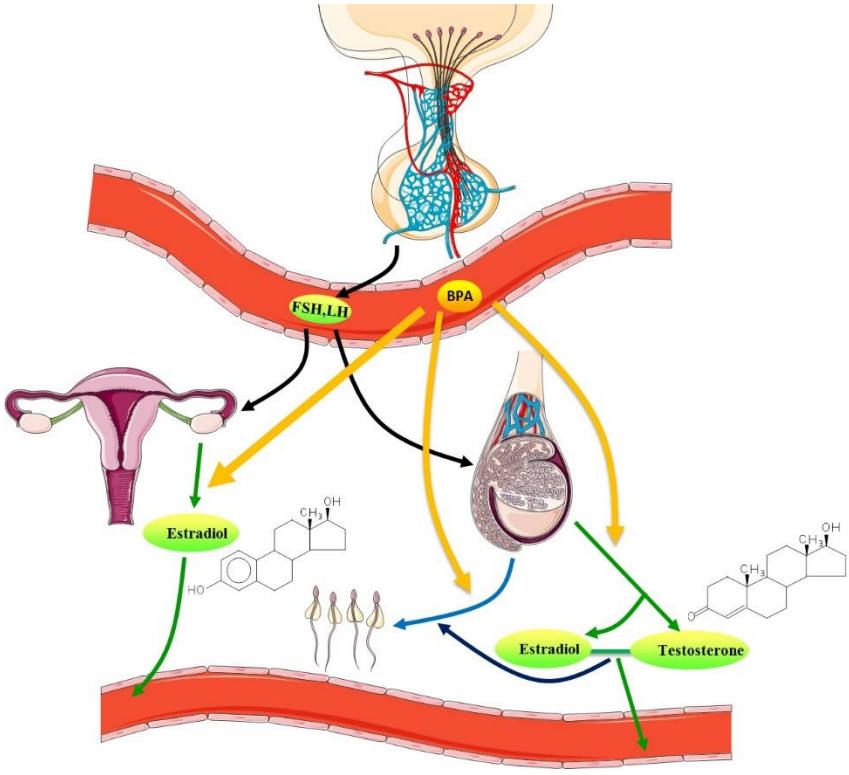

Fig. 2: Effect of BPA on reproductive endocrine system. BPA could make influences in the testis and ovary, then affect the hormone levels, have negative effects on reproductive endocrine system. Acronyms: Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)

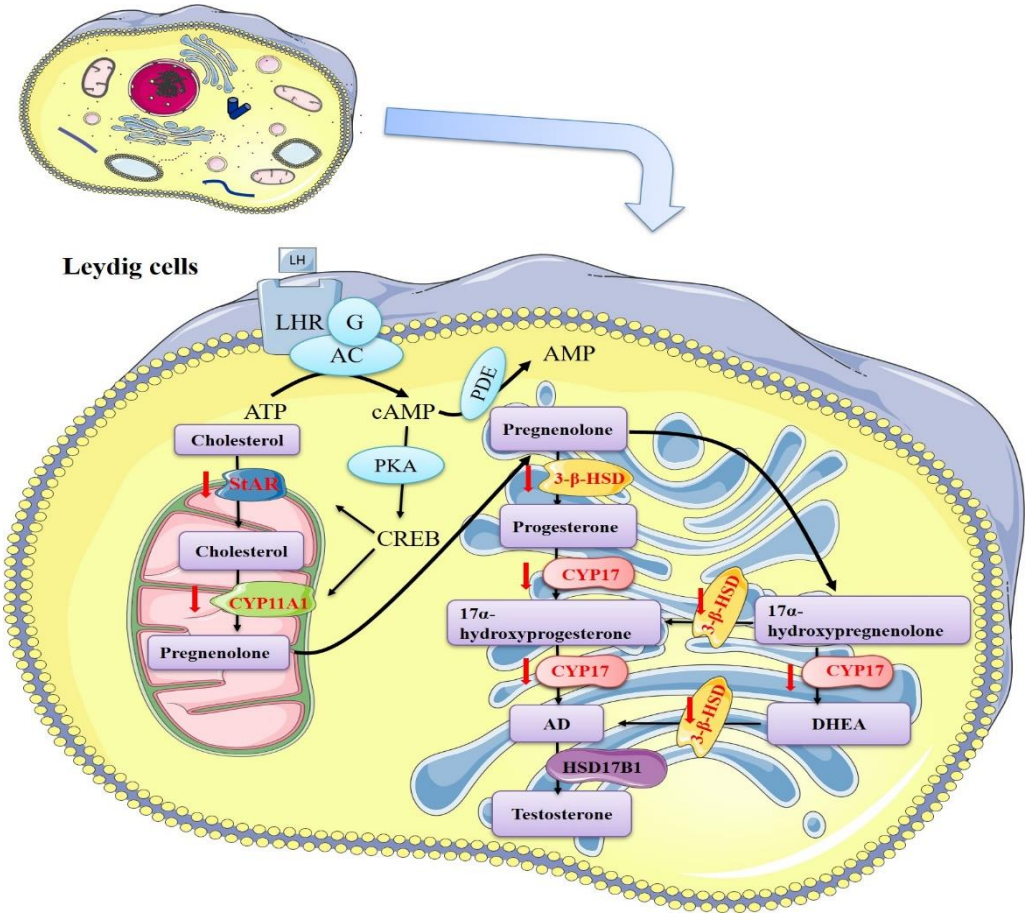

Fig. 3: The action sites of BPA exposure on pathway of testosterone production. BPA could influence the production of testosterone through changing the expression of related genes and steroidogenic enzymes. The BPA action sites were marked in red font a and the red arrows were used to define the impacts (The same as in the following figures). Acronyms: Luteinizing Hormone (LH), Luteinizing Hormone Receptor (LHR), GTP binding protein (G), Adenylate Cyclase (AC), Protein Kinase A (PKA), Phosphodiesterase (PDE), cAMP-Response Element Binding protein (CREB), Steroidogenic Acute Regulatory Protein (StAR), Cytochrome P450 11A1 (CYP11A1), 3β-Hydroxysteroid dehydrogenase (3-β-HSD), Estradiol 17-β-dehydrogenase 1 (HSD17B1), Cytochrome P450 17 (CYP17), Androstenedione (AD), Dehydroepiandrosterone (DHEA)

Table 1: Abbreviations Table

Acronym	Full title	Acronym	Full title
3-β-HSD	3β-Hydroxysteroid dehydrogenase	G	GTP binding protein
ABCA1	ATP binding cassette subfamily A member 1	HPGA	Hypothalamus-pituitary-gonad axis
AC	Adenylate cyclase	HSD17B1	Estradiol 17-β-dehydrogenase 1
AD	Androstenedione	INB	Inhibin B
AHR	Aryl hydrocarbon receptor	IVF	In-vitro fertilization
CREB	cAMP-response element binding protein	LH	Luteinizing hormone
CYP11A1	Cytochrome P450 11A1	LHR	Luteinizing hormone receptor
CYP17A1	Cytochrome P450 17A1	PDE	Phosphodiesterase
CYP19	Aromatase cytochrome P450	PKA	Protein Kinase A
DHEA	Dehydroepiandrosterone	ROS	Reactive oxygen species
E2	Estradiol	SHBG	Sex hormone binding globulin
Erα	Estrogen receptor α	StAR	Steroidogenic acute regulatory protein
Erβ	Estrogen receptor β	SOD	Superoxide dismutase
FSH	Follicle stimulating hormone	T	Testosterone
FSHR	Follicle stimulating hormone receptor	TT	Total testosterone
FT	Free testosterone		

StAR

StAR, a transporter protein localized on the outer mitochondrial membrane, is a necessary regulator of steroid hormone biosynthesis, mainly to mediate transport of cholesterol into the mitochondrial inner membrane and present it to P450scc (CYP11A1), which is also a rate-limiting enzyme regulating synthesis of the related hormones (Ho *et al*., 2018; Selvaraj *et al*., 2015). Transportation of cholesterol in Leydig cells is mediated by StAR, which carriages it from the outer membrane of the mitochondria to the inner membrane.

The results of (Ma *et al*., 2017) and Yang *et al*. (2019) respectively found that, in male offspring of mice and pup, the mRNA expression level of *star* in BPA-treated was considerably declined in comparison with the result in the control group. Another study involving the model organism *C. elegans*, also demonstrated BPA exposure negatively impacted the expression of StAR (Chen *et al*., 2019). A reasonable explanation is that BPA can regulate phosphorylation of StAR, inhibiting its activation. Therefore, it can be concluded that BPA inhibits the transport of cholesterol by decreasing the expression of StAR, thereby inhibiting testosterone production.

CYP11A1

Several significant enzymes participate in steroidogenesis and convert cholesterol to testosterone in the form of catalysis. P450scc, the enzyme encoded by *cyp11a1*, regulates the first step of steroidogenesis. The over-expression of *cyp11a1* partly exists in endocrine cells, including adrenal cortical cells, Leydig cells and ovarian follicular membrane cells (Hu *et al*., 2004).

It is widely known that P450 enzyme is one of the important targets of BPA (Sanderson 2006) and it has been shown that BPA has the ability to activate steroidogenic genes *via* the JNK/c-Jun signaling pathway, thus disrupting the testicular hormone environment (Lan *et al*., 2017). On maternal BPA exposure, it is demonstrated that CYP11A1 expression of male pup germ cell was obviously lower than the control group (Yang *et al*., 2019). Similarly, several studies validated that BPA exposure throughout the entire pregnancy in mice has effects on down-regulating the expression of CYP11A in male offspring (Lv *et al*., 2019; Ma *et al*., 2017).

CYP19

Aromatase (P450 arom) encoded by *cyp19* is another vital enzyme in steroidogenesis. P450 arom has abilities of aromatizing androgen into estrogen. Thus, it acts as the main enzyme involved in biosynthesis of estrogen and androgen (Li and Rahman, 2008).

In male zebrafish adults, mRNA levels of *cyp19* were found reduced in comparison with the blank group (Wang *et al*., 2019). In rat Leydig cells, Akingbemi *et al*., (2004) similarly validated that *cyp17* and *cyp19* are also down expression by 0.01 nM BPA.

CYP17A1

CYP17A1 has both 17α-hydroxylase and 17,20-talyzes this conversion reaction, which can catalyze the conversion of progesterone to 17α-hydroxyprogesterone or the conversion of pregnenolone to 17α-hydroxyprogesterone. The reaction involves 17α-hydroxylation and C17-20 testosterone can be produced by a few steps of the reaction.

Earlier research showed that BPA causes the inhibition of CYP17 expression in testis, thereby decreasing testosterone production (Ye *et al*., 2011; Zhang *et al*., 2011). Gonçalves *et al*. (2018) have shown that in TM3 murine Leydig cells exposed to low BPA concentrations, the related gene *cyp17a1* and *cyp19a1* were downregulated when the testosterone biosynthesis was inhibited.

3-β-HSD

In the process of the production of androgens, Dehydroepiandrosterone (DHEA) is converted into AD by 3-β-HSD. BPA exposure can inhibit the AD level by decreasing the expression of 3-β-HSD (Qiu *et al*., 2013), thereby further affecting the production of testosterone adversely. Another study also showed that CYP11A1 and 3-β-HSD were down-expressed in male mice treated by BPA (Liu *et al*., 2021). Pregnancy exposure of BPA could reduce the expression of 3-β-levels and germ cell apoptosis.

Generally, it has been observed that BPA may suppress testicular functions of rodents in different growth periods *via* changing the expression of steroidogenic related enzymes (Nanjappa *et al*., 2012), which then influences synthesis of steroid hormones and circulating steroid levels. A majority of studies support that BPA exposure may reduce production of testosterone by means of downregulating the related genes, *star*, *cyp11a* and *cyp19*. In addition, the testicular histology changes influenced by BPA may similarly be linked to the down-regulation of such important enzymes' expression (Goncalves *et al*., 2018).

Effect of BPA on Estradiol (E2)

Effect of BPA on Estradiol in Human Body

In a survey about infertile women, Mok-Lin have

revealed that the BPA levels of urinary were adversely associated with the level of serum E2 (Mok-Lin *et al*., 2010). And after BPA exposure, several studies also supported a significant decrease in peak serum estradiol levels prior to oocyte extraction in women undergoing *in vitro* fertilization (IVF) (Bloom *et al*., 2011; Ehrlich *et al*., 2012) Unlike mentioned above, Miao *et al*. (2015) suggested that women exposed to BPA had higher levels of E2 in their urine by contrast with unexposed. The study of Minatoya recruited 514 participants and showed that the BPA level in cord blood was weakly positive associated with E2 (Minatoya *et al*., 2017). Meanwhile, in an experiment on the correlation between maternal urinary phenol concentration and umbilical cord steroid hormone levels, no obvious correlation was revealed between BPA and estradiol level (Liu *et al*., 2016), which was in accordance with two small-scale surveys (n = 41 and n = 74) (Takeuchi and Tsutsumi, 2002; Takeuchi *et al*., 2004), showing serum BPA concentrations had no association with estradiol among women.

Effect of BPA on Estradiol in Animal (Non-Human)

Lee *et al*. (2014) discovered a significant decrease of female rats serum concentration of E2 after BPA exposure and proved its disturbance on the maintenance of normal ovarian functions. Moreover, in female zebrafish, the concentrations of E2 considerably descended following the BPA exposure concentration (Fang *et al*., 2016; Villeneuve *et al*., 2012). In addition, Peretz's study, concerning exposure of BPA in rat *vitro* antral follicle, had also proved this pollutant had the ability to inhibit the production of E2 (Peretz *et al*., 2011), which can bear a resemblance to the study from *Qi et al*. (2020) Samardzija *et al.* (2018) found that 100 μM BPA exposure concentration on granulosa cells of immature rat resulted in an obvious reduction in progesterone biosynthesis. In the female offspring of mice exposed to BPA, Ma's study also showed an increase of serum E2 concentration in offspring of mice (Ma *et al*., 2017).

Mechanism of BPA Influencing E2

Estrogen is synthesized by granulosa cells and intimal cells (the placenta also secretes estrogen) in female and by Leydig cell in male and the specific mechanism in female is shown in Fig. 4. The decrease in estrogen secretion level indicates that the hormonal synthesis function of granulosa cells and intimal cells is impaired.

It has been found that high concentrations of BPA in the urine samples from infertile women are closely correlated with the reduced number of primordial follicles (Silvestris *et al*., 2017). BPA can interfere with follicular development (Chen *et al*., 2017; Zhu *et al*., 2018) and can significantly suppress the proliferation of mouse granulosa cells and the effect was in a dose dependent manner (Xu *et al*., 2002). Yu *et al.* (2018) too found that BPA interfered with the formation of primordial follicles through the estrogen receptor pathway in chick

Adult female rats of long-term BPA exposure can lead to a decrease in expression of StAR and P450 aromatase (Lee *et al*., 2013). Studies on production of steroid hormone in the ovarian granulosa cells from pigs showed that the key genes of steroidogenesis (*star*, *cyp11a1*, *3-β-hsd*) were significantly down-regulated after BPA exposure (Mlynarcikova and Scsukova 2018). Similar to the above study, Peretz *et al.* (2011b) proved that the mRNA levels of *star*, *3-β-hsd* and *cyp11a1* were reduced in isolated follicles after BPA exposure. In a study about parental rare minnow, parental BPA exposure can inhibit offspring ovarian development *via* decreasing the number of mature oocytes and significantly affect the steroid genes *cyp11a1*, *cyp17a1*, *cyp19a1* and *star* at the transcriptional level (Zhu *et al*., 2021). And several studies about rat ovary also concluded that BPA trends to disturb the steroidogenesis process *via* its suppression effect on StAR and P450 aromatase, thereby blocking E2 production (Lee *et al*., 2013; Peretz *et al*., 2011; Ziv-Gal *et al*., 2013). And it was proved that down-regulation of *cyp19* transcription also exists in the placental cell line JEG-3 (Xu *et al*., 2019). Altered expression levels in these enzymes and genes are fundamentally crucial for steroidogenesis. On the contrary, in human granulosa cells, Qi *et al*. (2020) found that low dose BPA treatment dramatically reduced the expression of StAR and have a negative effect on progesterone biosynthesis *via* the upregulation of ATP binding cassette subfamily A member 1 (ABCA1) which is a reverse cholesterol transport that mediates its export. And though experiments concerning granulosa cells from immature mice showed that BPA can elevate the expression of StAR, CYP11A1 and 3-β-HSD, Samardzija *et al*. (2018) observed that exposure to BPA can break up cholesterol homeostasis so that decrease the basal and the FSH-stimulated progesterone production, which further affects estrogen production.

Aromatic Hydrocarbon Receptor (AHR) is a ligand-dependent transcription factor (Ichihara *et al*., 2019). It had been shown that various environmental poisons can activate AHR which is largely distributed among the cytoplasm (Barouki *et al*., 2012). And it has been demonstrated that AHR is essential, both physiologically and pathologically (Zhao *et al*., 2020). AHR was proved to regulate *cyp19* expression when decrease level of ovarian estrogen (Baba *et al*., 2005).

(2020) discovered that 10 μM BPA treatments on human ovarian granulosa cell line led to an obvious reduction in progesterone biosynthesis.

Ziv-Gal *et al*. (2013) designed the experiments to explore the influences of BPA on follicle function, observing BPA could act on AHR and influence the expression of Bcl2, an anti-apoptotic factor closely related to follicular atresia. They thought BPA can influence AHR signaling pathway and development of follicles to affect the endocrine system including reducing E2 levels. Further, Lee *et al*. (2013) observed a decline in E2 levels of ovarian follicular cells after BPA treatment, discovered an elevated count in apoptotic caspase-3 positive cells at the same time, which were able to cause follicular atresia and luteal degeneration.

Contrasting with the above mechanism, there are still a large amount of surveys showing that exposure to BPA is positively correlated with E2 concentration. As mentioned above, the Déchaud *et al*. (1999) 's study is different from the result mentioned here. Furthermore, since it own the structure similar to E2, BPA has estrogenic activity and could competitively bind to SHBG to increase the E2 concentration in the serum. These arguments supported experiments in which BPA is positively correlated with E2, perhaps these are why some experiments back positive correlations. Similarly, the studies in which BPA has nothing to do with E2 can also be understood.

Effect of BPA on Semen Quality and Male Sexual Function

It is acknowledged that inhibin can be synthesized in Sertoli cells and its concentration functions as an indicator which can rate the Sertoli function of Sertoli cell. Compared with fertile men, it is observed that the expression of Inhibin B (INB) are greatly decreased in men with fertility disorders (Kumanov *et al*., 2006), which was in accordance with earlier studies that revealed BPA exposure was associated with abnormal sperm morphology and reduced sperm density (Li *et al*., 2011).

BPA could reduce testosterone production and affect the function of prostate and testis as well as spermatogenesis (Yeung *et al*., 2011). From the perspective of BPA work exposure, in several studies of men occupationally exposed to BPA, outcome was found that the exposure is related with declining sperm quality, concentration, motility and male sexual dysfunction, including reduced libido or erectile dysfunction, etc. (Adoamnei *et al*., 2018; Cariati *et al*., 2019; Li *et al*., 2010a; 2010b; 2011).

In addition, animal experiments have also found the negative influences of BPA on male reproductive health (Liu *et al*., 2021; Peretz *et al*., 2014). Several toxicological surveys have suggested prenatal or perinatal exposure to BPA in rodents results in varieties of disadvantageous reproductive consequences, including epididymal weight loss, reduced daily sperm production (Salian *et al*., 2009a, b) and increased prostate weight (Nagel *et al*., 1997). Experiments about prepubertal rat testis also showed the outcome that exposure to BPA is confirmed to reduce sperm counts and quality and alter the testicular histology (Balci *et al*., 2020). Therefore, abnormal hormone levels may be one significant mechanism.

However, there are still some studies that do not match the above. One cohort studies (Goldstone *et al*., 2015) assessed the correlation between BPA and semen quality among reproductive aged men and found little evidence showing that BPA reduced the semen quality of the population tested. One cross-sectional study (Mendiola *et al*., 2010) showed no significant correlation between any semen parameters and BPA concentrations in urine. A study of maternal exposure to BPA showed that testicular function does not adversely affect testicular function in adulthood even if there is a potentially weak positive correlation with certain testicular function parameters detected (Hart *et al*., 2018).

It is widely known that Sertoli cells are crucial to maintain male reproductive functions. Previous experiments have demonstrated that BPA can induce apoptosis in Sertoli cells and male germ cells, thereby inhibiting sperm production (Li *et al*., 2009; Qian *et al*., 2014). Studies examined on rat Sertoli cells have shown that BPA can inhibit their vitality and induce apoptosis (Qiu *et al*., 2013; Wang *et al*., 2015). Wang *et al*. (2015) observed that BPA exposure could induce apoptosis of Sertoli cells mediated by the Pten/Akt signaling pathway Fig. 5. In turn, Qi *et al*. (2014) confirmed that BPA also induces Sertoli cell apoptosis *via* activating the JNKs/ P38 pathway. In early puberty, BPA disrupts sperm production and changes the spermatogenic tubule epithelial morphology, it can increase Reactive Oxygen Species (ROS) production while decreasing the antioxidant activity of catalase and Superoxide Dismutase (SOD) enzymes (Abubakar *et al*., 2020; Ullah *et al*., 2019). There are also studies supporting BPA to induce apoptosis in Sertoli cells by causing excessive ROS production and mitochondrial dysfunction (Wang *et al*., 2017). which was also in accordance with the study of Barbonetti *et al*. (2016) that pro-oxidative/apoptotic mitochondrial dysfunction can influence sperm integrity, as well. The toxicity of BPA on male reproductive showed that DNA/histone methylation change make contribution to the decreased of sperm quality (Zhu *et al*., 2020).

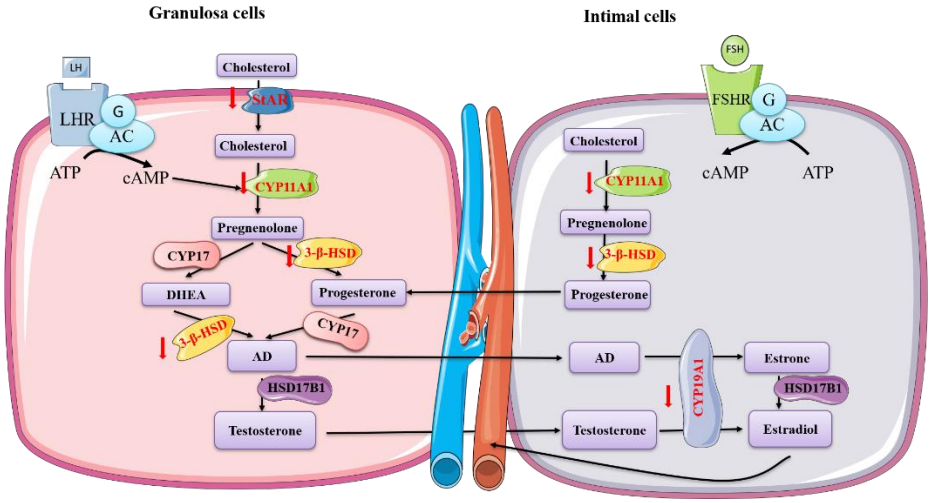

Fig. 4: Effect of BPA exposure on pathway of estrogen synthesis. BPA could influence the synthesis of estrogen through changing the expression of related genes and steroidogenic enzymes. The signaling pathway molecules highlighted in red are BPA sites of action. Acronyms: Luteinizing Hormone (LH), Luteinizing Hormone Receptor (LHR), Follicle Stimulating Hormone (FSH), Follicle Stimulating Hormone Receptor (FSHR), GTP binding protein (G), Adenylate cyclase (AC), Protein Kinase A (PKA), Phosphodiesterase (PDE), cAMP-response element binding protein (CREB), Steroidogenic Acute Regulatory Protein (StAR), Cytochrome P450 11A1 (CYP11A1), 3β-Hydroxysteroid Dehydrogenase (3-β-HSD), Estradiol 17-β-Dehydrogenase 1 (HSD17B1), Cytochrome P450 17 (CYP17), Aromatase cytochrome P450 (CYP19/P450arom), Androstenedione (AD), Dehydroepiandrosterone (DHEA).

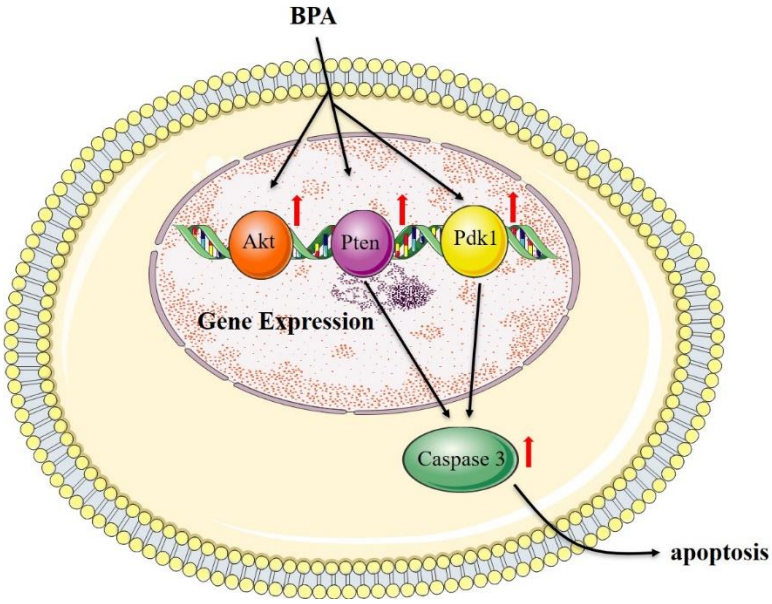

Fig. 5: As described in's findings. BPA could induce the apoptosis of rat Sertoli cells through Pten/Akt signaling pathway (Wang *et al*., 2015)

Conclusion

There is no doubt that BPA as an environmental interferer has an adverse effect on human endocrine and reproduction. This review gathers some researches articles, concludes the impacts of BPA on reproductive hormone, sperm quality, male sexual function and discusses their generation and change mechanisms. There are differences in the results of studies, the reasons for which are various. First, people are differences in

lifestyle, eating habits, education levels, age, gender, etc. of subjects in different studies and experimental animal also have disparity in dose, method of administration and time of exposure to interferers. Second, people may be exposed to a variety of EDCs in their living environment, often in a state of "co-exposed" and some studies suggest that "co-exposure" may amplify the health effects of BPA (Vandenberg *et al*., 2007), therefore, the study of the impact of BPA on human health needs to consider the impact of other EDCs that may exist. Third, some studies have a small sample size and some studies do not consider the effects of confounding factors. In addition, several surveys assessed the impacts of BPA exposure on the reproductive system by testing serum, urine BPA levels even semen parameters of different sorts of samples, which may explain inconsistent results (Vitku *et al*., 2016). All of these factors may be the reasons why the experimental results are inconsistent. In general, BPA inhibits spermatogenesis by the direct effect of disturbing the Sertoli cells function and the indirect influence of reducing testosterone production.

Further summary of the endocrine and reproduction have made in this review according to the recent literature. Meanwhile, Due to the ubiquity of BPA in the environment, we can only provide some theories of BPA toxicity, but still cannot solve the effects of BPA on the body. Next, on the basis of BPA toxicity as a causative factor of the endocrine and reproductive system abnormalities, proposed a new prospective that if we can research a new biomarker to detect the occurrence of abnormalities.

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Author's Contributions

Ganghui Ye: Contributed to conceptualization, design and writing.

Liting Zheng: Contributed to writing and revising.

Chang Meng and Yuefeng Dong: Contributed to drafting.

Hongyan Xu: Contributed to editing.

Qinglu Wang: Contributed to conceptualization and design.

Ethics

Neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal. The authors declare that there are no conflicts of interest in this study.

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