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Endocrine Disruptors: Very Low Doses with Genuinely High Impacts on Male Reproduction

Michal Jeřeta and Jan Nevoral

Abstract

Endocrine disruptors (EDs) are chemical substances that affect physiological processes in the body via hormonal regulation. They are often detected in food, plastic water bottles, cosmetics, and many other daily need items. Thereafter, EDs are detected in many bodily fluids, pointing out the real exposure to even very low doses. Permanent and long-term utilization of EDs has harmful effects on male reproductive health mainly due to interference with sex hormone synthesis and mechanism of action. However, with decreasing dosage of EDs, the possibilities of unpredictable modes of action arise. In addition to various molecular actions of individual EDs, the interference of individual ones represents another dimension of the ED issue. This review provides an overview of the EDs and their possible impact on reproductive health in males, with focus on sperm quality with the mighty potential of epigenetic transmission to further generations. The “posttranslational” effect of EDs in really low doses in real exposure routes is stigmatized in this review, being strongly considered as creeping molecular action of individual EDs as well as amplifications of their copresence in the environment.

Keywords: endocrine disruptor, bisphenol, regrettable substitution, posttranslational modification

1. Introduction

Maturation of sperm cells (spermatogenesis) is a continuous process starting in puberty. The process is stimulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Until the onset of puberty, spermatogonia are quiescent and their quantity does not change significantly. After sexual maturity is reached, an expressive activation of mitochondrial activity and the process of spermatogenesis begin, leading to the formation of spermatids. They are then transformed into spermatozoa by the spermiohistogenesis process, when a round spermatid changes into a sperm cell with a tail, middle section, and head. However, whole spermatogenesis, including gonadal ridge colonization and differentiation of primordial germ cells (PGCs), followed by further development, begins during early embryogenesis. In light of this fact, there are several exposure windows when environmental noxi can hit spermatogenesis along the entire process.

Considering the transmission of extraneous agents, the hemotesticular barrier (HTB) represents the morphological division of the seminiferous tubulus into two

compartments: basal and adluminal. The barrier is crucial for full functionality of germinal epithelium, as well as for the elimination of negative impacts of environmental pollutants. Physiologically, this strict division ensures free paracellular movement of substances among the compartments, such as water, nutrients, electrolytes, hormones, and paracrine factors. HTB provides protection of the emerging sperm cells from autoimmune damage by antibodies to sperm cells produced if the barrier was impaired, and the immune system would be in contact with spermatozoa during puberty when the body has already reached immunocompetence. Therefore, the cross talk of the immune system and HTB is potentially another sensitive target to a pollutant impact.

There is a basal compartment in close proximity to the basal membrane. This segment contains vessels and nerves, and spermatogenesis is initiated here. Spermatogonia and spermatocytes up to the proleptotene stage are present here. This segment is necessary for nutrition. The spermatogonia are subsequently transported through tight intercellular junctions to the adluminal compartment which is a place of spermatogenesis completion and subsequent metamorphosis of spermatids to spermatozoa. Both compartments are demarcated by the blood-testis barrier (BTB). Vessels and nerves are no longer present in this segment, and the nutrition of the germinal epithelium cells is covered by the Sertoli cells. The impact of various doses and concentrations of EDs on the male reproductive system can affect the functions of this barrier. The differentiation and development of the male reproductive system depends on elementary estrogen/androgen ratio, and the antagonistic and agonistic effects of EDs often disrupt their balance. The development of testicular tissue is crucial for further development of the entire reproductive system, as the endocrine activity of testicles determines overall masculinization of the body. Any disruption in the development of the testicles can therefore impair the overall masculinization process and sperm production.

Sperm concentration in men decreases worldwide, and spermiogram parameters deteriorate mainly in the Western world population [1]. Among others, huge amounts of endocrine disruptors (EDs) in our environment can cause this state. This final manifestation of the noxious effect of EDs has an unknown background, such as dose, kinds of EDs, interactions, and crosstalk of individual EDs and/or the timing of the exposure. Therefore, biomonitoring data represents significant input for experimental designing, leading to the description of molecular action in simulated conditions. Based on the newest findings, the record of the biological impact of individual EDs is an ongoing research issue leading to indicating the found compounds as endocrine disruptors.

Many cases of impaired sexual development due to the effects of EDs are also known from the animal kingdom. For example, reduction of penile length was observed in crocodiles living in waters contaminated with EDs [2]. EDs can significantly influence not only the process of spermatogenesis but also the development of testicular tissue. It has been documented that increased exposition of pregnant mice to BPA caused alterations of organelles, that is, mitochondria and lysosomes, in Sertoli and Leydig cells, respectively. These alterations led to maturation disorders in spermatocytes and androgen synthesis inhibition [3].

2. Spermatogenesis, epigenetics, biochemical status of spermatozoa, and implications for male reproduction

The creation of the spermatozoon leads to the terminally differentiated cell with an extremely high level of chromatin methylation and silencing. The final shape of the spermatozoon, often species-specific, requires many morphological and biochemical changes, in particular, dynamic remodeling of the chromatin [4].

Protamination, histone-protamine exchange in elongating spermatids, represents a drastic, expressible change of sperm chromatin [5]. A tight protamine-derived DNA package protects sperm chromatin against damage and, interestingly, even the ratio of protamines PRM1 (sperm protamine P1) and PRM2 (sperm protamine P2) is decisive about sperm quality [6]. In accordance with the tight chromatin package, DNA is strongly methylated, and, therefore, general chromatin silencing is required for sperm stability [7, 8]. Protamination represents a tool for the protection of paternal gene imprinting [9]. Temporal protamine-packaged sperm DNA undergoes a second exchange of chromatin proteins after fertilization, and then maternal histones are incorporated into the paternal pronucleus. Both protamine-histone transition events, first and second in testicular seminiferous tubuli and fertilized oocyte, respectively, are obviously sensitive to environmental influences and represent susceptible exposure windows [10, 11].

Although most core histone is substituted by protamines, a residual species-specific amount of histones resists in the sperm head. In addition to DNA methylome, epigenetic hallmarks of mature spermatozoa include the epigenetic code of residual histones, based on many posttranslational modifications (PTMs) of individual amino acids [12, 13]. These chromatin-repressive histone marks positively correlate with DNA methylome and accompany imprinted genes. Moreover, the sperm histone code shows an exact physiological role in fertilization and early embryonic development [14]. The histone code establishment is highly orchestrated [15] and, therefore, enforces spermatid sensitivity to exposure to environmental pollutants.

Following comprehensive demethylation of parental chromatin after fertilization, the total erasure of the methylation pattern, including gene imprinting on paternal and maternal alleles, is needed for the re-establishment of gene imprinting adequate to the paternal pattern in the sperm cell. This erasure comes early after gonadal ridge colonization, and primordial germ cells (PGCs) occur, at human embryonic days E32 and E10.5 in mice [16]. The recurrent “writing” of the epigenetic pattern into imprinted loci occurs in the late prenatal period when the spermatogonia are formed. This period between erased PGCs and remethylated spermatozoa represents a highly sensitive and quite extensive exposure window, when the epigenetic status can be changed by environmental factors during embryonic development in utero. There is another dynamic chromatin demethylation, many years later, when sperm chromatin remodeling occurs when paternal and maternal pronuclei are developed in the early zygote. This methylation erasure is not complete and excludes parent-of-origin methylation, that is, erasure-resistant loci, such as IAPs, LINEs, and transposon-related loci. Taken together, the transgenerational and intergenerational inheritances of epigenetic shifts (i.e., non-genomic or non-Mendelian inheritance) are based on these two exposure windows, when epigenetic erasure, including gene imprinting in PGCs and imprinted gene-excluding erasure, occur, respectively [17]. The renewal of gene imprinting between PGCs and mature gamete is another power of transgenerational epigenetic inheritance [18]. The dynamics of the epigenetic code is subjected to a well-tuned orchestra of “erasures” (TET oxygenases, histone deacetylases, and demethylases) and “writers” (DNA methyltransferases, histone methyl transferases, and acetyl transferases) (reviewed in [19]). It is assumed that, via EDs, they change the epigenetic code through these upstream factors (the possible methods of exposure are summarized in **Figure 1**).

Doubtless, a properly established epigenetic code plays an extremely important role, in particular in imprinted genes in epimutation-prone gametes. The epigenetic code of the spermatozoon is highly protected by the protamination, determining the stability of the genome and gene imprinting. Otherwise, epigenetic disorders arise: Prader-Willi syndrome, Angelman syndrome, or Silver-Russell syndrome. Moreover, residual histones bring the epigenetic information via histone PTMs.

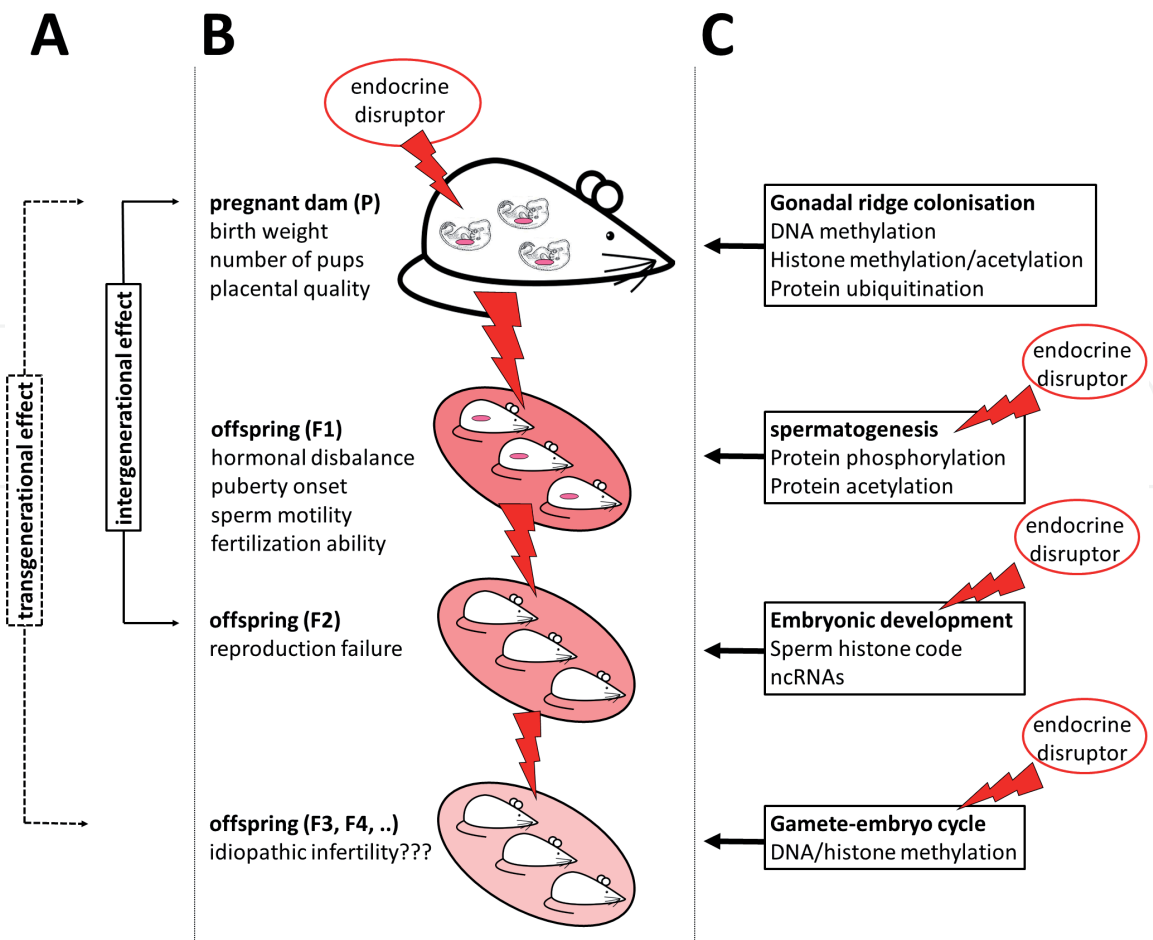


Figure 1. Endocrine disruptors induce non-genomic inheritance through posttranslational modifications (PTMs) of various epigenetic factors. (A) Environmentally impacted posttranslational modifications of proteins incoming into intergenerational and transgenerational effects. (B) Endocrine disruptors are able to affect developing gonads through transplacental transmission in utero. Gonad activity is changed and hormonal levels, puberty onset, and sperm quality are affected. Sperm quality contributes to embryonic development and can influence the health of an offspring, and, therefore, the intergenerational transmission of the ED effect to F2 generation is obvious. Gene imprinting and epigenetic erasure are assumed to be the tools of this effect. The epigenetic code of erasure-resistant loci is possibly affected by ED, and the transgenerational effect appears. Nonspecific symptoms accompany these epigenetic faults, and many disorders are classified as idiopathic. (C) From the molecular point of view, inadequate changes in DNA and chromatin proteins, including PTMs of core histones and/or RNA polymerases, are responsible for the epigenetic record and gene manifestation, and ED becomes potentially dangerous for these protein modifications through “posttranslational” effect. Obviously, male reproduction is endangered through several exposure windows during gamete formation, including epigenetic code erasure and re-establishment. Therefore, in addition to direct modification of chromatin, responsible “erasures” and “writers” (responsible for de-differentiation and gene imprinting, respectively) undergo regulation via PTMs when the EDs’ effect is considered.

Obviously, in addition to the genetic information, the sperm head carries a package of epigenetic notice, very sensitive to the disruption through its establishment throughout the spermatogenesis.

In addition to the establishment of epigenetic code of sperm histones, achievement of other PTMs of regulating proteins is required. Frequently, the loss of a PTM leads to protein activity lacking, sometimes leading to fatal clinical manifestations, for example, the inability of PARKIN1 S-sulfhydration of cysteine followed by sporadic Parkinson’s disease [20]. During post-ejaculation the sperm changes, such as capacitation and acrosomal reaction; there are many PTMs of key proteins necessary for the achievement of fertilization ability. Therefore, protein kinase A (PKA)-driven phosphorylation of Arg-X-X-(Ser/Thr) motifs is required, as the result of upstream regulation by soluble adenylyl cyclase and cAMP production [21]. However, acetylation of ϵ -amino group of lysine residues arises as regulatory tool for

PKA, and, accordingly, the hyperacetylation of sperm proteins is needed for sperm capacitation [22], essential for sperm hyperactivation in female reproductive tract. Versatile role of protein acetylation is obvious, including aforementioned residual histones as well as protein kinases. Taken together, the impact of endocrine disruptors on histone PTMs [23, 24] as well as sperm phosphorylation [25–27] has been described, and, therefore, the modifications of proteins (protein PTMs) become the likely manner in which disruptors (EDs) work in their real doses.

3. Endocrine disruptors: mode of action and nonlinear effect

There are many shared features of EDs, such as spatiotemporal omnipresence, exposure to very low doses, and, therefore, often a nontoxic effect [28]. Nevertheless, the affection of hormonal balance represents a major sign of them, giving the name to endocrine disruptors [29]. Indeed, there is an increasing number of observations of exposure to EDs, across all age, race, profession, lifestyle, and health status categories [30]. These findings are in accordance with the ubiquity of EDs through the presence in daily need items.

Compound	Phenotype of filial generation	Species	Reference
Antibiotics (Geneticin)	Up-/downregulation of genes responsible for basic metabolism, cell cycle, stress response, and development	<i>Drosophila melanogaster</i>	[108]
Atrazine	Reproduction, altered transcriptome responsible for steroidogenesis, and DNA methylation	Medaka (<i>Oryzias latipes</i>)	[109]
Benzylisoquinoline alkaloids	Reduction of lipid accumulation	<i>Caenorhabditis elegans</i>	[110]
BPA	Affected neurogenesis and damaged social interactions	Mouse (C57BL/6 J)	[111]
DDT	Pathology of gonads, obesity	Rat (Sprague Dawley)	[112]
Dioxin	Testicular tissue abnormalities	Zebrafish (<i>Danio rerio</i>)	[113]
Di(2-ethylhexyl)phthalate (DEHP)	Reproduction failure	Mouse (CD-1)	[114]
Glyphosate	Obesity, prostate, and ovary diseases; kidney failure; birth abnormalities	Rat (Sprague Dawley)	[115]
Methoxychlor	Obesity, ovary, and kidney diseases	Rat (Sprague Dawley)	[116]
Vinclozolin	Alterations transcriptome with disease susceptibility of gonads, ancestry glands, <i>mamma</i> , and kidney	Rat (Sprague Dawley)	[117]

Representative studies are included, testing different compounds (in toxic and sub-toxic doses) on various biomodels, mostly exposed during the establishment of germ cells and gonad maturation. These exposures lead to changed phenotype of filial generation through the epimutation of germ cells. In addition to pregnant exposure, PTMs of epigenetic factors and/or histone code represent a molecular tool of endocrine disruptor-inherited impact along generations, even though the exposure is during adulthood. Although direct human evidence is lacking, there are several indications of the effect of transmission of endocrine disruptors in very low doses, on further generations due to PTM-driven epimutations [106, 107].

Table 1.
Overview of recent knowledge of environmental inheritance of endocrine disruptor effects.

The “family” of EDs is wide and still growing, as is our awareness of their biological impact. Therefore, EDs include polybrominated diphenyl ethers, phthalates, polyethylene terephthalate (PET), bisphenols, and others (**Table 1**). Hence, flame retardants in electronic devices, perfumes, plastic bottles, and polycarbonates, respectively, are the most usual source of EDs. Surprisingly, some daily need items, such as paper bags, cans, receipts, and dental sealants, include bisphenols, although they seem to be free of any endocrine disruptors. Even strict elimination and usage control of pesticides are not able to exclude the endocrine-disrupting effect through contamination of food with residua of some of them, for example, glyphosate [31], atrazine [32], and imidacloprid [33]. Because EDs are so widespread, humans are exposed to them via different routes: oral intake with food and beverages and transdermal exposure and/or inhalation. Some specific routes of exposure are derived from the uniqueness of the stage of ontogenesis, such as transplacental in utero exposure during pregnancy, followed by translactational exposure when a baby is nursed.

Most EDs are released into the environment in a very low amount, and, therefore, the human intake is appropriately much smaller. This is the result of the legacy action of responsible authorities (European Food Safety Authority, EFSA; Food and Drug Administration, FDA), which has established the limits of intakes (tolerable daily intake, TDI) for many ED compounds. However, extremely low doses have been recognized as having a biological effect. In the light of this fact, the earlier

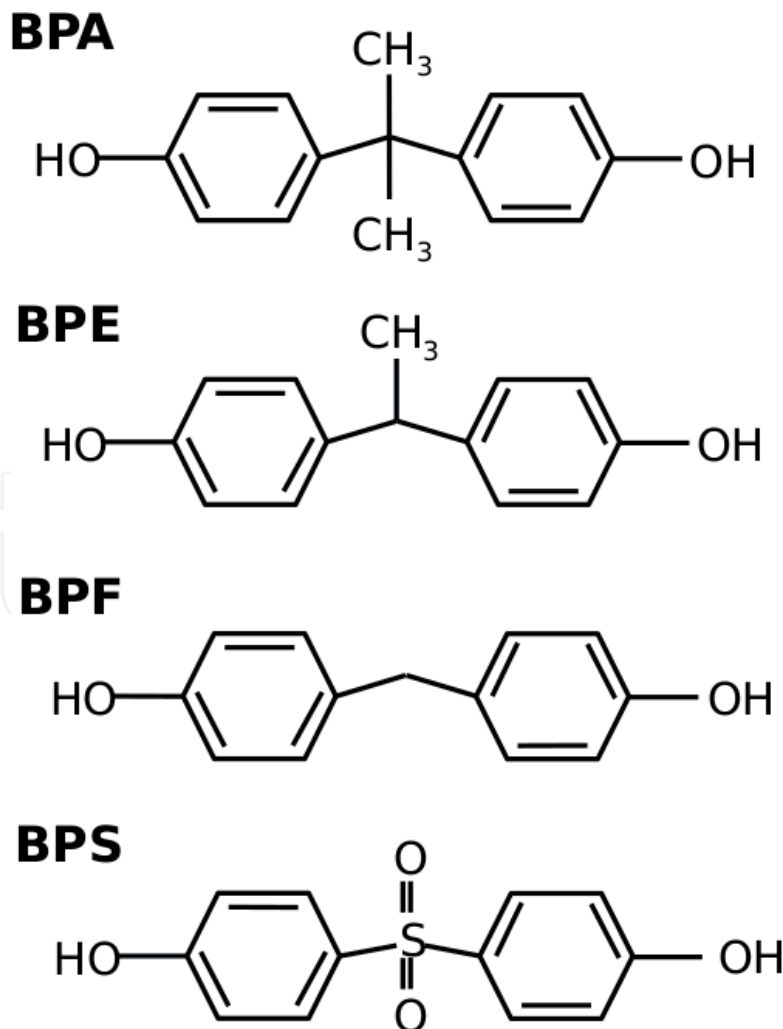


Figure 2. Molecular structure of BPA and its alternatives. BPA, bisphenol A (2,2-Bis(4-hydroxyphenyl)propane); BPE, bisphenol E (4-(1-(4-hydroxyphenyl)ethyl)phenol); BPF, bisphenol S (4,4'-dihydroxydiphenylmethane); BPS, bisphenol S (4,4'-sulfonylbisphenol).

accepted quantities of no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) lose importance. Interestingly, lower doses show often more deleterious effect than the higher ones, pointing out the nonlinear effect [29]. The response of the cell, tissue, or an organism on the dose is in a non-monotonic (i.e., U-shape) curve [34]. It was difficult to accept this phenomenon, but recently we consider it to be one of the features of EDs [35–37].

After many substances were described to be an ED, elimination or total restriction followed. Therefore, several compounds have been introduced as a substitution. *n*-Hexane and alternative bisphenols (BPS, BPF, and BPAF) have become widespread, such as alternatives to dichloromethane and bisphenol A (BPA), respectively, although the unambiguous safety of these substitutions has not been proved (chemical structure of selected bisphenols is presented in **Figure 2**). For instance, BPA usage has been banned in children's toys and baby bottles, and, in addition to these, BPA-free products were introduced based on the consumer preferences [30]. However, BPS to BPA exchange has taken place, although "endocrine" safety has not been elucidated. In this point of view, we can denote it to be a regrettable substitution, and comprehensive testing of these alternative compounds is required.

4. The impact of EDs on male reproductive health

According to a range of studies, the effect of EDs is significant mainly during the development of the male reproductive system. The cocktail effect of multiple substances in low concentrations with similar action target has been described many times. Particularly trans-uterine exposition during embryonic development is critical, when testicular dysgenesis syndrome can develop [38]. There is a presumption that it is caused by impaired function of Leydig cells and testosterone production [39]. For initiation of prostate development and masculinization of the sex ducts, the presence and correct ratio of steroid hormones is necessary. Nevertheless, EDs often act as inhibitors of 5- α reductase enzyme that is necessary for the conversion of androgens to testosterone and inhibitors of aromatase necessary for androgens aromatization to estrogens [40].

4.1 Effect on gonads and accessory glands

Cryptorchidism: This is a serious developmental disorder which may be also caused by exposition of the fetus to EDs in utero and subsequent feeding with breast milk with a high concentration of EDs [41].

Hypospadias: It has been documented that utilization of EDs in the form of medication for pregnant women led to various disorders of testicular development [42].

Testicular cancer: The half-life of the EDs with lipophilic character is up to 30 years. It has been observed that mothers of adult men with testicular cancer had high levels of polychlorinated biphenyls (PCBs) in the blood, which led to the conclusions that the ability of PCBs to accumulate in the body makes their presence one of the factors contributing to development of this type of cancer [43]. Considering the half-life of many toxins, for example, PCBs, we can assume that these toxins will achieve their endocrine-disrupting effect as their real amount in the environment decreases, while their toxic effects are not taken into account anymore.

Prostate hyperplasia: It has been described in rats that exposition of males to low doses of estrogens and xenoestrogens led to prostate hyperplasia. These results support concerns that, in today's plastic era, this phenomenon will also manifest

in adult men [44]. Moreover, in 2017, it was documented that doses of BPA equivalent to doses potentially present in the environment caused increased growth of prostate cells [45].

4.2 Effect on spermatogenesis

Sperm concentration in ejaculates of men has been decreasing for a long time, mainly in Western world populations (the USA, Europe, Australia, and New Zealand) [1]. This long-term process has been observed since the 1970s. The situation might be caused by environmental changes, primarily by the increased occurrence of various EDs [46]. It is generally acknowledged that the process of sperm production is significantly reduced by FSH and LH, while alterations on this level may cause impairment of spermatogenesis to infertility [47].

4.3 Effect on cells of germinal epithelium

It is known that EDs are capable of influencing the offspring in utero through transplacental transmission and via breast milk and that they cause disorders that can be transferred epigenetically to further generations. In certain periods of fetal development, testicles are estrogen-sensitive, and their excessive exposure to this hormone can result in complete arrest of steroidogenesis. EDs with an estrogenic character can interfere with the correct functioning of the reproductive system.

During spermatogenesis, spermatogonia are transformed to spermatozoa when a round spermatid changes into a sperm cell with tail, middle piece, and sperm head. For this process, Sertoli cells play a key role as they form the functional blood-testis barrier (BTB) with very tight junctions. This barrier is dynamic and demarcates the basal compartment and adluminal compartment of seminiferous tubules. The barrier is necessary to prevent damaging of sperm cells by the immune system, since contact of blood and mature sperm cells leads to the production of antibodies to spermatozoa. These antibodies can then enter the seminal plasma and damage sperm cells. The principle of the hemotesticular barrier are very tight junctions between the Sertoli cells which divide the structure of seminiferous tubules into basal and adluminal compartments.

4.4 Disruption of the blood-testis barrier (BTB)

Effects on the hemotesticular barrier can significantly affect spermatogenesis and can have an impact on embryonic development of testicular tissue. The division contributes to unlimited capillary supply of nutrients, hormones, and other biomolecules which are needed for mitotic renewal of spermatogonia, their proliferation, and differentiation. However, the other developmental stages must not come into contact with blood. If this barrier did not exist or was damaged, antibodies to sperm cells would be produced, which could ultimately result in male infertility [48].

BTB and effect of EDs: Detachment of both compartments is ensured by tight intercellular junctions of adjacent Sertoli cells. These are very tight connections represented mainly by tight junction, adherens junction, desmosome, and gap junction types. The riskiest period is when spermatocyte at the proleptotene stage passes through the barrier, which needs to undergo structural changes. It is this particular period when the effect of substances such as the endocrine disruptors is most significant.

It is known that the level of free BPA in blood plasma decreases the concentrations of occludin, N-cadherin, and connexin 43, which are proteins that

significantly contribute to the production and regeneration of tight junctions. Decreased levels of these proteins affect the function of BTB [49].

Taken together, a very low dose of EDs seems to have the most deleterious impact. There are obviously different modes of action of EDs, and, all the more so, the molecular targets of EDs are the center of interest of the current studies describing disruptors.

5. Molecular mechanism of EDs in extremely low doses

The toxic effects of many compounds are well-known and described, and the amount of published findings is still growing by thousands of papers each year. In general, genotoxicity and carcinogenesis [50], oxidative stress induction [51], and DNA damage and cell senescence [52–54] are known impacts of several toxic compounds. However, sub-toxic effects of toxic compounds (pesticides and drugs) described earlier as well as seemingly safe compounds (alternative bisphenols) represent a serious risk for human public health. For this reason, there are many biomonitoring initiatives, followed by legislation and the development of next-generation plastics.

In accordance with toxin elimination during the last decades, people in developed countries have been recently exposed to rather sub-toxic doses in trace amounts. This effect is known as endocrine disrupting, affecting the body in other ways than toxins, that is, genomic, non-genomic, and epigenetic modes of action. While the genomic effect is similar to toxin action, the non-genomic effect is the closest to endocrine disruption; the mimicking of the presence of a hormone, targeting of hormonal signaling, and/or misregulation of hormone production and expression of receptors are known mechanisms of endocrine-disrupting effects [55–57]. Hormonal disbalance impacts the hypothalamus-pituitary-gonadal axis [58], with possible clinical manifestations: changed anogenital distance, morphological changes of sex determinations, and earlier puberty onset [59]. However, the tested doses are very high, whereas, on the contrary, very low doses correspond to the real exposure, often leading to small differences on the level of tissue and cell, without any demonstration of clinical aspects. Although changes in hormonal balance are well-known [60, 61], EDs are even capable of affecting hormonal action directly in a cell without a shift in hormonal profile. Therefore, the estrogen-like and estrogenic effects of BPA have been described in germ [62], ovarian [63], and testicular cells [64, 65]. Frequently, the G-protein-coupled estrogen receptor is a target of the estrogen-like effect of BPA [65, 66], as well as alternative bisphenols [67]. Transcription and subcellular distribution of estrogen receptors ER α and ER β and aromatase, an enzyme converting andro- to estrogens, are changed in bisphenol S-exposed oocytes [68]. These non-genomic alterations are accompanied by cytoskeleton abnormalities. In particular, the meiotic spindle is extremely sensitive [69] and, indeed, affected in mammalian oocytes exposed to bisphenols [68, 70, 71], leading to increased incidence of aneuploidy [72].

The comparable effect of EDs is known during spermatogenesis: BPA is capable of affecting meiotic division and chromosome segregation, increasing the incidence of aneuploidy-derived disorders [73]. In addition, the molecular mechanism of BPA consists in impacting several signal pathways and results in the change of protein kinase A activity and protein tyrosine phosphorylation, ATP generation, and oxidative stress-related enzymes (i.e., peroxiredoxin-5, glutathione peroxidase 4, succinate dehydrogenase), crucial for sperm motility and ability of oocyte fertilization [26, 27, 74]. Dose-response association of BPA and motility parameters of human sperm has been observed [75]. Interestingly, some EDs have shown a

stronger negative impact on Y-chromosome-bearing spermatozoa, and the sex ratio of offsprings can be changed [76, 77].

Many non-genomic methods of ED action lead to inappropriate epigenetic changes of DNA and core histones. Although the sequence of nucleotide remains unaffected, the changes of genome-wide methylation status, as well as silencing or enhancing the individual loci, follow the exposure of EDs. These epimutations result in changed transcriptional activity of the genome with many negative impacts, such as failure of scavenging of reactive oxygen species, DNA damage repair, and/or inadequate mitochondrial biogenesis. These cellular changes lead to clinical manifestations, most of which are diagnosed as “idiopathic.” Obviously, exposure to EDs causes obesity [78], type 2 diabetes [79], metabolic disorders, and infertility [80].

While the exposure of somatic cells creates health problems for exposed individuals, influence on gametes leads to an intergenerational effect when the burden is transduced to the next generation of daughters and sons [81]. Indeed, the exposure to bisphenols impairs genome-wide DNA methylation, as well as histone code in oocytes [71, 82], followed by changes in the imprinting of genes in the embryo and placenta [83]. In spermatozoa, DNA methylation [84] is potentially affected by environmental pollutants, leading to aberrant gene imprinting [85, 86]. It can be assumed that the sperm histone code is sensitive to endocrine disruptors, with effect similar to estrogens, as well as to the involvement of estrogen receptors in histone code establishment [15]. Moreover, the negative role of environmental pollutants in the influence on noncoding RNAs in spermatozoa, another tool of epigenetic regulation [87] with ability to drive epigenetic inheritance [88], is well-known [89, 90].

The exposure in utero and transplacental transmission of an ED affect DNA demethylation in developing PGCs and result in transgenerational inheritance of this burden. Accordingly, the exposure of pregnant rat females to fungicide vinclozolin [91] or DDT [92] leads to modified epigenome, that is, DNA methylome, histone retention in sperm, and ncRNAs. Translactational exposure, another way of indirect influence with environmental agents, is a reason of changes of male reproduction after lactating female mice were exposed to BPA [93]. Moreover, this type of exposure to bisphenols creates a risk of changed nursing behavior and also affects the mammary glands of mothers [94].

Whereas endocrine-disrupting hypothesis is assumed for very low doses of EDs, there is a relevant phenomenon of interactions of individual EDs. The comprehensive work of T. Pollock and his colleagues produced valuable results, describing cross talk of common EDs. The combined presence of bisphenols is considered to be deleterious [95] as well as the simultaneous presence of triclosan, a soap compound [96, 97]. Degradation of bisphenol is inhibited under other ED exposure, and, obviously, the co-exposure achieves various modes on how to affect the body [98]. In addition to human and mammalian models, there is evidence of interaction of xenobiotics and pesticide residues [99], as well as synergistic interactions of organophosphates and pyrethroids [100], potentially leading to the collapse of honey bee colonies [101]. In contrast to synergic effects leading to the increase of the deleterious impact, competition of some pollutants is known, and, surprisingly, a reverse effect of the synergic activity of pollutants has been described, where one pollutant protects cells against damage caused by another pollutant [102]. The molecular action of interacting pollutants remains to be unexplained in mammalian models, and there is obvious need for further study. Also the results of these studies will influence public health protection.

6. Perspectives

The aforementioned routes of exposure to EDs, including their interactions, obviously lead to different systemic response as the result of molecular action in tissues and cells. The molecular mode of action seems to be the key for the elimination of EDs' negative effect on the body. Based on already described manifestations of EDs in higher and lower doses, two dose-dependent modes of action are recognized: toxic effect and endocrine disruption. It seems that the current issue of EDs is in extremely low doses without clinical manifestations, leading to "idiopathic" infertility, metabolic syndrome, and other failures with nonspecific symptoms. Moreover, intergenerational and transgenerational inheritances occur because of the change of the epigenetic code of germ cells. The posttranslational modifications of crucial proteins, particularly regulating epigenetic factors, seem to be a common feature of these very low doses. In accordance with this, we can mark this effect to be "posttranslational." The possible contribution of posttranslational modifications of key proteins is indicated in **Figure 1**.

There is an obvious direct impact of EDs on male reproduction due to oral, respiratory, and/or transdermal exposure. Thereafter, both the gonads and accessory glands are affected, leading to the failure of male reproduction, often diagnosed as idiopathic. On the spermatozoon level, direct protein targeting is assumed, including cytosolic proteins as well as sperm histone code. Even protamine PTMs are considered to have a biological role, and, in accordance with the abovementioned importance of acetylated lysines, protamine acetylation seems to be most potent for sperm quality. The impact on DNA and chromatin proteins (i.e., histones and protamines) represent hazardous mode of inter- and transgenerational transmission of ED-driven epigenome.

In addition to the direct impact of EDs, indirect impact is also observed. The exposure of EDs during pregnancy and prenatal life represents the most dangerous exposure method when the germline is affected during gene imprinting erasure and re-imprinting in developing spermatozoa [85] and oocytes [103]. This exposure window allows an ED to affect the health of a generation of grandchildren through transgenerational inheritance [104, 105]. Epigenetic transmission to further generations involves various modifications, such as DNA and histone methylation, histone acetylation, and other PTMs of core histones, as well as epigenetic writers and erasures, translational factors, and others. Obviously, PTMs actually drive the phenomenon of the epigenetic inheritance, and the molecular impact of individual EDs is still unknown, as is their interaction (**Table 1**).

There is a strong need for further study focused on the ED-modulated epigenetic code and its manifestation in the body. In accordance with our "posttranslational" hypothesis of ED action, comprehensive screening of the most crucial PTMs should be taken into account in an assessment of individual EDs. Taken together, biomonitoring has an extremely significant role in the fight against EDs, as does the subsequent testing of EDs in the ascertained doses. Simulation of real exposures to individual EDs and their interactions are appropriate, using both in vitro and in vivo experimental assessments. Finally, advanced screening methods capable of identifying PTMs are needed for qualified recognition of an ED as harmful/harmless.

Acknowledgements

The study of endocrine disruptors is supported by the Czech Health Research Council (NV18-01-00544); H2020 (Human Biomonitoring Initiative HBM4EU);

MH CZ-DRO (FNBr, 65269705), project MSMT LTC18059; COST action CellFit CA16119; the Charles University Research Fund (Progres Q39); and the National Sustainability Program I (NPU I) Nr. LO1503 provided by the Ministry of Education, Youth and Sports of the Czech Republic (MEYS CR); project No. SVV 02690 awarded by MEYS CR; and project No. CZ.02.1.01/0.0/0.0/16_019/0000787 “Fighting Infectious Diseases,” awarded by MEYS CR and financed by the European Regional Development Fund. We would like to thank Ms. Iveta Zimova, Mr. Vaclav Rucka, and all graduate and pregraduate students for their kind help with the experimental work.

Conflict of interest

The authors declare no conflict of interest.

Author details

Michal Jeřeta^{1*} and Jan Nevoral^{2,3}

1 Department of Obstetrics and Gynecology, University Hospital and Masaryk University, Brno, Czech Republic

2 Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Czech Republic

3 Department of Histology and Embryology, Faculty of Medicine in Pilsen, Charles University, Czech Republic

*Address all correspondence to: jeseta@gmail.com

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