Endocrine disruptive compounds and male reproduction

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Abstract
Endocrine disruptors (EDs) are chemical substances that affect physiological processes in the organism via hormonal regulation. The EDs are present in the environment and objects of everyday use. They are often detected in food, particularly released from packaging of canned food, but also from plastic water bottles, and they are also found in cosmetics and fertilizers. They are commonly detected in children's toys, banknotes, receipts and many more objects. Permanent and long-term utilization of EDs has harmful effects on human reproductive health mainly by interference with sex hormone synthesis and mechanism of action. The endocrine disruptors show many negative effects on male reproductive system. Any change during synthesis or activity of sex hormones can cause abnormal reproduction, including developmental anomalies of the sexual system, disruption of testicular development or deterioration of sperm quality. Mainly the impact on the development of testicles in prenatal and early postnatal period can be crucial for reproductive health in males. This review provides an overview of the EDs and their possible impact on reproductive health in males with focus on sperm quality and development of testicles.

Running title: bisphenol, reproduction, endocrine disruptor, oocyte, sperm

Keywords: Endocrine disruptors and male
Endocrine-disrupting chemicals are a class of chemicals that mimic, block or interfere with the production, metabolism or action of hormones in the body. Endocrine disruptors (EDs) are ubiquitous in our environment, food and consumer products, they pose a threat not just to public health but to global health. The endocrine system is important for male reproductive development because androgens (such as testosterone) promote the maturation of male secondary characteristics as well as the process of spermatogenesis.

Interaction of endocrine disruptors with male reproductive system

Development of testicles in the prenatal period is crucial for further reproductive potential of man and is intensely hormonally regulated. The differentiation of male reproductive system depends on fetal androgen production. Disruption of androgen production mainly during the period of virilisation (weeks 8-14 of fetal development) can cause testicular dysgenesis [1]. The endocrine disruptors (such as BPA) are known to cause occurrence of developmental anomalies on urogenital tract, reduction of the epididymides size, enlargement of the prostate, decrease of ejaculate volume and sperm concentration in males.

There are several mechanisms of action of endocrine disruptors on male reproductive system and spermatogenesis. Most important is disruption of hepato-testicular barrier described for example for BPA and di(2-ethylhexyl)phthalate metabolites [2]. These substances disrupt synthesis of proteins (occludin, clausin – 11) necessary for formation of solid intercellular junctions (zonula occludens) between the Sertoli cells. This leads to dysfunction of the junctions an overall disruption of hepato-testicular barrier stability, which may cause not only disruption of spermatogonia division, but also development of autoimmune disorder [2]. BPA also influences estrogen and androgen receptors in testicles. Small molecule of BPA affects physiological function of estrogen receptors by the means of competition with E2 and beta estradiol. This leads to disruption of steroidogenesis [3]. BPA shows also affinity for LH receptor and this way affects production of testosterone in the Leydig cells [4].

Testicular dysgenesis syndrome

Testicular dysgenesis syndrome (TDS) is characterized by the symptoms of hypospadias, cryptorchism, decreased sperm quality and malignant testicle tumors. TDS can be caused by a genetic mutation, however recent studies has proven that exposure of fetal testicle to environmental substances has a significant effect [5]. These substances include estrogens and anti-androgens found in food and water resources contaminated with synthetic hormones and pesticides used in agriculture [6]. It is assumed that this exposure causes abnormalities in function of the Sertoli and Leydig cells. This way, the development of germ cells is impaired and differentiation of embryonic tissue is abnormal. Dysfunction of the Leydig cells leads to reduction of testosterone and INSL3 (= insulin-like factor 3) production. Consequences of this disruption are cryptorchism, hypospadias and shortening of anogenital distance. Impairment of the Sertoli cells function can result in dysfunction of germinal epithelium leading to insufficient production of quality spermatozoa and development of malignant testicle tumors in later periods [4].

EDs’ mechanisms of action are very variable. For example exposure of neonatal marmoset to di(n-butyl) phthalate (DBP) caused aggregation of the Leydig cells. This state of testicular tissue is considered to be an accompanying factor for testicular dysgenesis [7]. Some studies have shown that MEHT (a reactive phthalate metabolite) activates PPAR (peroxizome-proliferation activated receptor) signalling pathway and via activation of PPAR:RXR receptor inhibits transcription of aromatase, an enzyme important for reproductive system development [8, 9]. Moreover, by the means of PPAR activation, MEHT impairs transcription of steroiogenically positive genes StAR and p450c17. The StAR is a mediator of cholesterol transfer to mitochondria of the Leydig cells and the p450c17 is a steroid-converting enzyme. Dysfunction of these proteins negatively influences testosterone production [10]. In addition, another phthalate DBP decreases expression of SCF and e-kit receptor, which are crucial for the Sertoli cells and gonocytes interaction. This causes reduction of the Sertoli cells proliferation intensity in prenatal period [11].

Effect of the disruptors on testicle development

Impairment of hormonal balance during gestation and perinatal period by an exposure to exogenous estrogens or anti-androgens leads to malformations in development described as TDS [12]. It has been observed that mice males born to mothers exposed to DES (diethylstilbestrol) during gravidity were infertile and 15 of the 24 males born had developmental abnormalities of testicles including intra-abdominal testes [13]. Exposure of pregnant mothers to the effects of DES during early pregnancy increased occurrence of risk factors associated with testicular cancer, such as genital defects, cryptorchism and decreased sperm quality [14]. Some studies have found a positive correlation between presence of p,p’-DDE (partial agonist of estrogen receptors and antagonist of androgen receptors and primary DDT metabolite) in blood plasma and risk of testicular cancer [15].
Exposure to EDs in utero

An experimental study describing an influence of BPA on reproductive system of male rodents has shown its adverse effect on testicle development and spermatogenesis in adult animals after they were exposed to BPA in utero. This exposure is associated with reduced concentrations of testicular testosterone, reduced daily sperm production and reduced size of epididymides and seminal vesicles [16]. Males exposed in prenatal period to BPA consumed by mother in feed ration had lower sperm count and morphological anomalies occurred more frequently in them than in a control group. Another experiment using mouse as a biomodel studied damage of sperm cells in males exposed to BPA (in utero). This study revealed that males exposed to BPA in prenatal period had lower sperm count than males in control group. The group of males exposed to the highest concentrations of BPA was characterised by morphological anomalies of sperm cells. The groups with the highest concentrations also showed decreased motility of sperm cells. In all the groups of males exposed to BPA, fertilizing ability in the in vitro system was significantly decreased [17].

In utero exposure to phthalates disturbs development of seminiferous tubules and increases multinucleation of spermatogonia [18]. This condition is alarming especially in association with relatively high concentrations of phthalates detected in children [19] and it is known that in women the concentration of phthalates is usually 2 – 4x higher than in men [18]. Therefore there is a concern that neonatal exposure to phthalates can harm development of testicles and that the impact can be greater and more fatal than in adult men.

Rats exposed to the effects of DBP (dibutyl phthalate) in utero showed reduction of anogenital distance (testicular function marker) together with hypospadias and aberrant development of reproductive system when compared to a control [20]. Embryonic mouse testicles exposed to effects of DES in utero were characterised by delayed descent and significant alteration in the Sertoli cells. Male rats and hamsters exposed to TCDD perinatally showed developmental defects in dependence to a dose used. Reduced development of testicles, delayed descent of testicles and impaired concentration and quality of sperm cells were observed [21].

Exposure during puberty

Sexual adolescence is greatly important for a healthy development of testes and overall good reproductive health of males. From this point of view, the period of sexual adolescence is much more sensitive to effects of endogenous substances that can influence the overall spermatogenesis in adult life. It was observed, that in male mice exposed to BPA for seven days during puberty, the sperm counts decreased by 20% in comparison with control group. The same study included also morphological analysis of sperm cells, which revealed mainly morphological abnormalities of head, but also malformations of sperm tail, however less frequent. Abnormalities of sperm cells in the BPA group were more frequent than in the control group by approximately 10%. Moreover, the exposure of mice to BPA during puberty affected sperm quality in adulthood [22]. Exposure of BPA is associated with both damage to genetic information of sperm cells and epigenetic changes in offspring [23].

Changes in histology of testicles were described in a study where mouse males were exposed to the effects of BPA for seven days during puberty. Changes occurred in arrangements of seminiferous tubules. While normally they are firmly arranged around basal membrane, many seminiferous tubules where found in the BPA group, where the germinal epithelial cells detached from the membrane. These changes of seminiferous tubules were observed mainly after exposure to the BPA [22]. Another study that also described abnormalities in histology showed reduced layers of spermatogenic cells as well as impaired areas of these cells [23]. A study focused on overall weight of mice and their testes revealed that body weight was significantly lower in group exposed to BPA during puberty. Absolute weight of testicles was significantly decreased in the group exposed to BPA during puberty [24]. In addition, impaired development of testicles and higher rate of apoptosis in the cells of germinal epithelium were observed in the group of males exposed to the effects of BPA [25]. A study using the TUNEL technique analysed effect of BPA on apoptosis in germinal cells. The count of apoptotic cells was significantly higher in the testicles of mice exposed to high concentrations of BPA when compared to control group, the apoptotic cells were observed mainly in the VII-VIII parts of the seminiferous tubules. These results indicate that exposure to BPA during puberty affects apoptosis in germinal cells in testes [26].

Conclusion

The presented studies emphasize negative effects of EDs on male reproductive system. It is necessary to be aware that studies on animals mostly analyse effects of an individual substance on an organism while in the "real world" human and wild animals are exposed to mixture of EDs that act together and in context. People continuously release new chemicals to the environment without a thorough evaluation of their effects on human and animal health. Development in chemical industry allows relatively fast substitution of prohibited substances with new similar analogues suitable for industrial utilization with completely unknown effects on human and animal health. Legislative process is very lengthy and before a negative effect is unambiguously proven,
the harmful compound is spread globally and used commonly in the population including pregnant women and infants.

Contemporary science is not well prepared for this newly created situation. Most chemicals are not traceable, because sensitive tests are lacking and effects of these chemicals cannot be studied using classical methods, since there are no exposed and absolutely unexposed individuals. Moreover, the effects of many EDs potentiate one another and they are often characterized by non-linear effects.

Ethical approval

The conducted research is not related to either human or animal use.

Acknowledgement

This work was supported by the National Agency of Agriculture Sciences, NAXV, Project No. Q151038 and CellFit COST ACTION CA16119, MSMT INTER-COST LTC 18059, Ministry of Health of the Czech Republic No. NV-18-01-00544 and CZ - DRO (FNBr. 65269705).

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Conflict of interest statement

The authors declare they have no conflict of interest.

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