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Antiandrogenic and Estrogenic Compounds: Effect on Development and Function of Male Reproductive System

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1. Introduction

In the last 50 years the increase in the frequency of male reproductive abnormalities has been observed in human (Auger et al., 1995; Bergström et al., 1996; Carlsen et al., 1992; Skakkebaek et al., 2001; Thonneau et al., 2003). Epidemiological studies have shown increasing trends in the incidence of cryptorchidism (undescended testis) and hypospadias (abnormal location of the urethral opening) in several regions of Australia, Europe, and the United States (Acerini et al., 2009; Boisen et al., 2004; Källén et al., 1986; Nassar et al., 2007; Paulozzi, 1999; Toppari et al., 2001). Moreover, several reports indicated that semen quality have declined during last century (Auger et al., 1995; Carlsen et al., 1992; Swan et al., 2000; Sharpe & Irvine, 2004). Decreasing sperm concentration and percentage of motile spermatozoa, and increasing number of spermatozoa with morphological alterations were observed in European population between 1940 and 1990. For instance, it has been found that the prevalence of an abnormally low sperm count in young men reaches even 15–20% (Andersson et al., 2008; Jørgensen et al., 2006, 2011). In earlier study by Jørgensen et al. (2001) significant geographical variations in semen quality have been also described. Although, the reason for these regional differences is not fully elucidated, some data indicate that a correlation exists between impaired semen quality and exposure to pesticides used in agricultural areas (Swan et al., 2003). Interestingly, it has been noticed that in the industrial areas, where peoples are exposed to high levels of industrial chemicals, the birth sex ratio can be altered; in some region of Canada male birth sex ratio (i.e. number of male births per total number of births) have reached only 0.3 during the period 1990 – 2003 (Mackenzie et al., 2005).

In 2001 Skakkebaeck and co-workers have suggested that cryptorchidism, hypospadias, testicular cancer and oligozoospermia are interrelated disorders comprising a single syndrome, called the testicular dysgenesis syndrome (TDS) (Skakkebaeck et al., 2001; Skakkebaeck & Jørgensen, 2005). This idea arose from the observation that cryptorchidism and hypospadias are closely linked to testicular cancer, because in men with a history of one of these anomalies significantly increased risk of testicular cancer was described (Davenport et al., 1997; Dieckmann & Pichlmeier, 2004; Sharpe & Irvine, 2004). Moreover, oligozoospermia is frequently found in men, who develop testicular cancer (Møller & Skakkebaeck, 1999). The disorders included in TDS are believed to result from disruption of

hormone synthesis or action during fetal development of reproductive system. Indeed, numerous experimental studies have demonstrated that prenatal exposure to some environmental chemicals may disrupt the endocrine system in males and thus interfere with hormone-dependent development (Delbès et al., 2006; Fisher, 2004a; Gray et al., 2006).

Male reproductive system anomalies have been also reported in wild living animals (Vos et al., 2000). In fish, sexual reversal, decreased sperm count and motility, and spermatogenesis impairment were noticed (Barnhoorn et al., 2004; Jobling et al., 2002; Vajda et al., 2008). Feminization and abnormal gonadal development were observed in reptiles and birds (De Solla et al., 1998, 2006; Fry, 1995; Guillette et al., 1994), whereas in mammals, such as panthers or polar bears cryptorchidism and reduced size of reproductive organs were found (Mansfield & Land, 2002; Sonne et al., 2006). An interesting example of the species in which environmental pollutants may be the cause of reproductive system abnormalities is Sitka Black-Tailed Deer. It was reported that in the population living in the Aliulik Peninsula of Kodiak Island extraordinary high percentage (75%) of the males exhibited cryptorchidism when compared with males living elsewhere on the Kodiak Archipelago, among which only 12% were cryptorchid (Bubenik et al., 2001; Veeramachaneni et al., 2006a). Additionally, abnormal antlers and testicular neoplasia were frequently observed in cryptorchid deer from Aliulik Peninsula. The authors hypothesized that it was likely that testis and antler dysgenesis resulted from exposure of pregnant female (or alternatively, historic exposure of founders) to some estrogenic endocrine disrupting agent(s) present in the environment (Veeramachaneni et al., 2006a).

Although the substances affecting endocrine system were studied from 1950', the term "endocrine disruptor" was introduced in 1991 at Wingspread Conference, organized to evaluate the adverse effects observed in wildlife in the Great Lakes region in North America (Colborn & Clement, 1992; Colborn et al., 1993). According the World Health Organization (2006) endocrine disruptor (ED) is "an exogenous chemical substance or mixture that alters the function(s) of the endocrine system and thereby causes adverse effects to an organism, its progeny, or a (sub)population". In 2009, The Endocrine Society presented the Scientific Statement in which endocrine disruptor was defined as "a compound, either natural or synthetic, which through environmental or inappropriate developmental exposure alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment" (Diamanti-Kandarakis et al., 2009).

2. Role of androgens and estrogens in male reproductive tract development and function

Androgens are steroid hormones that play a central role in the development and function of male reproductive system (Dohle et al., 2003). The principal androgens are testosterone and dihydrotestosterone (DHT). High amounts of testosterone are produced in the testes from early stages of fetal development until birth. During prenatal period testosterone is necessary for the differentiation of Wolffian duct into the epididymis, vas deferens and seminal vesicles. It is also involved in the process of testis descent. DHT, synthesized from testosterone by the action of 5 α -reductase, mediates the masculinization of external genitalia and prostate. Studies by Welsh et al. (2008) revealed the existence of a fetal "masculinization programming window", a period within which androgens action is necessary to ensure correct later development of the male reproductive system. Blockade of androgen action

only during this critical period by using androgen receptor antagonists (e.g., flutamide) suppresses development of the male accessory glands and disrupts testis descent leading to cryptorchidism (Macleod et al., 2010; Welsh et al., 2008). In rat masculinization programming window occurs at 15.5–18.5 gestational days, whereas in human it spans from approximately 8 to 14 weeks of gestation (Welsh et al., 2008). In neonates testosterone level is high for a short time, then its production decreases and is maintained at low level until puberty, when rising androgen level mediate growth and function of accessory sex glands, initiation of spermatogenesis and development of secondary male sex characteristics. In mature males androgen action is essential for the maintenance of male phenotype and fertility (Dohle et al., 2003).

The discovery that aromatase (the enzyme converting androgens to estrogens) and estrogen receptors α and β (ER α and ER β) are expressed in male reproductive tract and studies on transgenic mouse models with inactivated estrogen receptor α (α ERKO) or aromatase genes (ArKO) led to the conclusion that not only androgens, but also estrogens are important for development and physiology of male reproductive system (Bilinska et al., 1997; Carreau et al., 2003; Levallet et al., 1998; Lubahn et al., 1993; Kuiper et al., 1996; Robertson et al., 1999). It was demonstrated that during fetal and neonatal life estrogens are involved in control of gametogenesis, promoting germ cell and seminiferous tubule development, and in the regulation of fetal Leydig cell steroidogenesis (Albrecht et al., 2009; Delbés et al., 2005; Vigueras-Villaseñor et al., 2006). Aromatase and ERs are transiently expressed in the hippocampus of newborn males, suggesting that estrogens are involved in brain masculinization (McEwen & Alves, 1999). In the reproductive system of adult males the role of ERs is associated with the maintenance of fluid reabsorption in the excurrent ducts of the testis (Hess, 2000; Hess et al., 1997). Data from studies on male mice with knockout of ER α suggested that long-term atrophy of the testes, observed in these animals, was caused by backpressure of the accumulating luminal fluids. Moreover, estrogens appear to have direct effects on the Leydig cell, controlling testosterone synthesis, and possibly on the seminiferous epithelium (Akingbemi et al., 2003; Hess, 2003). In male, estrogens play also a physiological role in non-reproductive tissues and organs such as bone and cardiovascular system (Oettel, 2002).

Although endogenous estrogens are necessary for normal male fertility, excessive production of these hormones or exposure to exogenous estrogens during fetal or neonatal life could produce adverse outcomes, affecting reproductive system development and adult reproductive functions. Destructive effects of estrogen overexposure on the development of post-meiotic germ cells and testicular atrophy was observed in rodents and humans (Gancarczyk et al., 2004; Toyama et al., 2001; Williams et al., 2001). Moreover, cryptorchidism, spermatogenic arrest, Leydig cell hyperplasia, and decreased serum follicle-stimulating hormone (FSH) and testosterone levels have been reported in the transgenic mouse model with aromatase overexpression (Fowler et al., 2000; Li et al., 2001).

3. Antiandrogens

Antiandrogens are defined as chemicals that interfere with androgen action or production. The compounds shown to have antiandrogenic properties include pharmaceuticals (e.g., flutamide, ketoconazole) as well as environmental contaminants: pesticides (e.g., vinclozolin, linuron) and industrial chemicals (e.g., di(n-butyl) phthalate).

3.1 Flutamide as a model antiandrogen

Flutamide, a pharmaceutical used in therapy of androgen-dependent prostate cancer, and its active metabolite hydroxyflutamide, are non-steroidal synthetic androgen receptor (AR) antagonists, which display pure antiandrogenic activity, without exerting agonistic or any other hormonal activity (Neri, 1989; Singh et al., 2000). Flutamide is regarded as a model antiandrogen and in experimental studies it is often used as a positive control in screening assays used for the identification of endocrine disruptors (O'Connor et al., 1998).

In utero exposure to flutamide was shown to alter reproductive development and function in male rat offspring (Mikkila et al., 2006). Recently, it was reported that flutamide interferes with desert hedgehog (Dhh) signaling in the fetal testis, resulting in impaired fetal Leydig cell differentiation. Leydig cell dysfunction was reflected by suppressed levels of insulin-like factor 3 (Insl-3) and testosterone and reduced expression of steroidogenic enzymes, cytochrome P450scc and 3 β -hydroxysteroid dehydrogenase (3 β -HSD) (Brokken et al., 2009). Insufficient levels of testosterone and Insl-3 in the fetal testis could, in turn, prevent full masculinization. Decrease in gonad and accessory sex glands weight, cryptorchidism, testicular histological lesions and increased germ cell apoptosis have been reported in adult male rats exposed to flutamide during fetal period, indicating that flutamide exerts long-term antiandrogenic effects (Omezzine et al., 2003).

In our recent studies flutamide (50 mg/kg bw) was injected into pregnant gilts during gestational days 20–28 and 80–88, and into male piglets on postnatal days 2–10. We found no changes in testicular morphology of neonatal pigs *in utero* exposed to flutamide, whereas in prepubertal males some of the seminiferous tubules were altered, exhibiting reduced number of Sertoli cells and dilated lumina (Durlej et al., 2011; Kopera et al., 2010). Testes of adult pigs exposed to flutamide *in utero* exhibited moderate alterations of the spermatogenic process: seminiferous tubules showed degeneration of germ cells and their extensive sloughing into the lumen of the seminiferous tubules, however all generations of germ cells could be recognized in the seminiferous epithelium. Testes of neonatally exposed boars contained severely altered seminiferous tubules, exhibiting drastic increase in the number of apoptotic germ cells, hypospermatogenesis or spermatogenic arrest at the spermatocyte level. Alterations of normal histological structure were accompanied by decreased expression and/or disturbed localization of intercellular junction proteins, connexin 43, N-cadherin, β -catenin and ZO-1 in the seminiferous epithelium (Hejmej et al., 2011a; Kopera et al., 2011). Also interstitial tissue was adversely affected; Leydig cells displayed hyperplasia or hypertrophy, increased expression of aromatase and reduced expression of LH receptor. Dysfunction of Leydig cells led to disruption of androgen-estrogen balance (Kotula-Balak et al., submitted for publication). These data suggest that in pigs flutamide acting during fetal, and especially, neonatal period can reprogram the development of testicular cells, leading to morphological and functional alterations of the testis at adulthood.

Interestingly, flutamide exposure has also long-term effects on sperm morphology. Our data showed that in sperm derived from neonatally-treated boars either flattened head or abnormal sperm with altered shape of the acrosome and abnormal packaging of sperm chromatin were frequently observed. Prepubertal treatment with flutamide resulted in an increased number of sperm displaying abnormal midpiece or tail defects (Lydka et al., submitted for publication)

Several studies demonstrated the effects of short-term androgen blockage induced by the administration of flutamide to immature or mature males. In immature rats structure of interstitial tissue and seminiferous epithelium, and the expressions of steroidogenesis-related genes, *Cyp11a1* and *StAR*, were significantly affected by flutamide treatment (Vo et al., 2009). When administered to pubertal animals, flutamide accelerated testes maturation, causing degeneration and detachment of primary spermatocytes and round spermatids (Maschio et al., 2010). In adult males, germ-cell degeneration, alterations in ectoplasmic specialization between the Sertoli cell and spermatids, and premature detachment of spermatids, as well as increase in the relative volume of Leydig cells were observed (Anahara et al., 2008; Maschio et al., 2008). Moreover, our *in vitro* results showed that pig sperm incubated with hydroxyflutamide (50 and 100 µg/mL) displayed disorders in sperm phospholipid membrane, decreased oxidative capability of sperm mitochondria and decreased sperm membrane integrity (Lydka et al., submitted for publication)

3.2 Environmental antiandrogens

3.2.1 Pesticides: procymidone, vinclozolin, prochloraz, linuron and p,p'DDE

Procymidone is used as a fungicide for the control of plant diseases. High quantities of this compound were found in rice, tomatoes and grapes (Gebara et al., 2011; US Environmental Protection Agency annual report, 1994). When administered to pregnant rats, the male pups displayed a reduced anogenital distance, nipple retention, hypospadias, cleft phallus, and reduced sex accessory gland size (Gray et al., 1999; Ostby et al., 1999). Moreover, in prostate and seminal vesicles fibrosis, cellular infiltration and epithelial hyperplasia were observed (Ostby et al., 1999). Chronic treatment of male rats with procymidone inhibited the negative feedback exerted by androgens on the hypothalamus and/or the pituitary, causing enhanced luteinizing hormone (LH) secretion and Leydig cell steroidogenesis, and in consequence, increased serum testosterone level (Hosokawa et al., 1993; Svehnikov et al., 2005). Such a long-term hyperstimulation of Leydig cells induces Leydig cell tumors (Murakami et al., 1995).

Vinclozolin is a dicarboximide fungicide used in the control of *Botrytis cinerea*, *Sclerotinia sclerotiorum*, and *Monilinia spp* on vegetables, fruits and ornamental plants. Vinclozolin and its two active metabolites, M1 and M2, compete for androgen binding to AR and inhibit AR transactivation and androgen-dependent gene expression (Wong et al., 1995). Administration of vinclozolin to pregnant rats resulted in abnormalities of androgen-regulated sexual differentiation in male offspring, including reduced anogenital distance, nipple retention, hypospadias, cryptorchidism, decreased sex accessory gland growth as well as in induction of prostate inflammation and reduced sperm production at adulthood (Cowin et al., 2010; Gray et al. 1994; 1999). Vinclozolin has also been implicated in epigenetic modifications of male reproductive tract via changes in DNA methyltransferase expression (Anway et al., 2008; Anway & Skinner, 2008). The most sensitive period of rat fetal development to the effects of vinclozolin was found to be gestational days 16-17, whereas less severe malformations were seen in males exposed during gestational days 14-15 and 18-19 (Wolf et al. 2000). Peripubertal exposure resulted in delayed pubertal maturation, decreased sex accessory gland and epididymal growth concomitantly with increased serum levels of LH and testosterone (Monosson et al., 1999).

Prochloraz is an imidazole fungicide widely used in gardening and agriculture which acts as both AR antagonist and inhibitor of fetal testosterone production. In addition to

antiandrogenic action, prochloraz antagonizes the estrogen receptor, agonizes the aryl hydrocarbon (Ah) receptor and suppresses aromatase activity (Andersen et al., 2002; Vinggaard et al., 2006). Gestational exposure significantly reduces testosterone production by inhibiting activity of cytochrome P450c17, decreases reproductive organ weights, increases nipple retention and induces malformations (e.g., hypospadias) in androgen-dependent tissues of male offspring (Blystone et al. 2007; Laier et al., 2006; Noriega et al., 2005; Vinggaard et al., 2005).

Linuron is a herbicide employed to control of weeds in crops and potatoes (Gray et al., 2006). It binds AR and inhibits dihydrotestosterone induced gene expression *in vitro* (Lambright et al., 2000). Fetal exposure to linuron resulted in epididymal and testicular abnormalities, reduced anogenital distance and nipple retention; however, in contrast to other AR antagonists, it does not induce hypospadias and cryptorchidism. Moreover, linuron was shown to decrease testosterone production by fetal Leydig cells (McIntyre et al., 2000, 2002a, 2002b; Wilson et al., 2009). Thus its mechanism of action resembles those of phthalates (Gray et al., 2006). Interestingly, when administered to sexually immature and mature rats, linuron decreased weights of accessory sex organs, increased serum estradiol and LH levels, and produced Leydig cell tumors (Cook et al., 1993).

p,p'-DDE (dichlorodiphenyldichloroethylene) is a metabolite of the persistent pesticide, DDT (dichlorodiphenyltrichloroethane). DDT is now banned in most countries, since in 1960' it was discovered that it has endocrine disrupting properties and causes birth defects in human and animals. However, it is still used in some regions to prevent malaria and other tropical diseases spread by insects (van den Berg et al., 2009). p,p'-DDE acts as AR antagonist both *in vivo* and *in vitro* (Kelce et al., 1995). Fetal treatment with this compound was shown to affect male development, leading to reduced anogenital distance, nipple retention and hypospadias (You et al., 1998). Recently, it was reported that p,p'-DDE induces testicular apoptosis in pubertal rats through the involvement of Fas/FasL, mitochondria and endoplasmic reticulum-mediated pathways (Shi et al., 2011).

3.2.2 Phthalates

The diesters of 1,2-benzenedicarboxylic acid, called phthalates, are widely used as plasticizers in the production of toys, medical devices, rainwear, food packaging, and certain cosmetics (Schettler, 2006). Di-n-butyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) and their metabolites have been shown to cause antiandrogenic effects, however, without binding to AR (Frederiksen et al., 2007). Although, the exact mechanism of action is not yet fully elucidated, it was demonstrated that phthalates interfere with Leydig cell function, reducing the expression of most of genes involved in testosterone biosynthesis (Barlow et al., 2003). Fetal exposure to phthalates results in reduced anogenital distance, hypospadias, cryptorchidism, malformed epididymis, and nipple retention (Mylchreest et al., 1999, 2002; Mylchreest & Foster, 2000). At the histological level, multinucleated gonocytes, detachment of gonocytes from the seminiferous epithelium, Sertoli cell-only tubules and Leydig cell hyperplasia were found in the testes of males exposed to DEHP and DBP (Fisher et al., 2003; Mylchreest et al., 2002; Parks et al., 2000). Some of these alterations were permanent and affected testicular function in adulthood, resulting in low testosterone level and reduced sperm count. It is worth noting that histological changes induced in rat by *in utero* exposure to phthalates resemble those observed in patients with TDS (Fisher, 2004a).

4. Xenoestrogens

Compounds with estrogenic activity, called xenoestrogens, comprise a broad range of synthetic chemicals (e.g., diethylstilbestrol, bisphenol-A, octylphenol, nonylphenol), naturally occurring phytoestrogens (e.g., genistein, resveratrol) and heavy metals (e.g., cadmium, lead, and boron).

4.1 Diethylstilbestrol (DES)

DES is synthetic potent non-steroidal estrogen used as a supplement in cattle and poultry feed and as a pharmaceutical (Rubin, 2007). DES was given to pregnant women to prevent miscarriages or premature deliveries from about 1940 to 1970. It was restricted in 1971 because of increased risk of a rare reproductive tract cancer, vaginal clear cell adenocarcinoma, in daughters of women who had taken DES (Gill et al., 1979; Melnick et al., 1987). Further studies have reported multiple adverse effects in males and females as a result of prenatal DES exposure. In males decreased fertility and anatomical malformations of reproductive organs such as cryptorchidism, epididymal cysts and prostatic squamous metaplasia were observed (Driscoll & Taylor, 1980; Marselos & Tomatis, 1992; Mittendorf, 1995).

Nowadays, experimental animals exposed to DES during fetal and neonatal development are useful models for studying mechanisms of endocrine disruption caused by exogenous estrogenic compounds (Diamanti-Kandarakis et al., 2009). In male mice exposed to DES during gestation, cryptorchidism, hypospadias, as well as underdeveloped epididymis, vas deferens and seminal vesicles were observed (McLachlan et al., 2001). Similarly, neonatal treatment of male rats with DES induced a wide range of reproductive abnormalities, including delay of testicular descent, retardation of pubertal spermatogenesis, reduction in testis weight, infertility, and gross morphological alterations in the rete testis, efferent ducts, epididymis and accessory sex glands (Atanassova et al., 1999, 2000; Fisher et al., 1999; McKinnell et al., 2001; Williams et al., 2001). Testes of adult rats neonatally exposed to DES displayed suppression of Leydig cell development and steroidogenesis, reduced Sertoli cell proliferation and spermatogenic impairment. It was shown that DES has both direct and pituitary-mediated effects on the developing testis, leading to decreased expression of AR and reduced FSH level (Sharpe et al., 1998, 2003). Studies on transgenic mouse models with inactivated ERs suggest that DES elicits its toxic effects in the male reproductive tract through an ER α -mediated mechanism (Prins et al., 2001).

4.2 Environmental xenoestrogens

4.2.1 Industrial xenoestrogens: bisphenol A and alkylphenols

Bisphenol A (BPA) is one of the most important industrial chemicals, which worldwide production is over 500 000 tons per year. It is found mainly in plastic food containers, baby bottles, the resins lining food cans, dental sealants, cardboards, and as an additive in other plastics (Richter et al., 2007). BPA is structurally similar to DES and can act by binding to ER α and ER β , and through other mechanisms, since some effects differ from those observed in response to activation of estrogen receptors. *In vivo* and *in vitro* experiments revealed that BPA mimics estrogen action, however it is also able to antagonize the activity of estradiol, acting as a selective estrogen receptor modulator (SERM) (Welshons et al., 2006). In high concentrations BPA can bind to AR and inhibit the androgen action (Lee et al., 2003). Although BPA is approximately 1000- to 2000-fold less potent than estradiol, exposure to

environmentally relevant doses impacts the reproductive system development and function in male rodents (Richter et al., 2007). It was demonstrated that rodents exposed to BPA during fetal and/or neonatal life had decreased weights of the epididymis and seminal vesicles, but increased weights of the prostate and preputial glands, decreased epithelial height in the efferent ducts and decreased levels of testicular testosterone (Akingbemi et al., 2004; Fisher et al., 1999; vom Saal et al., 1998). Alterations in ectoplasmic specialization between the Sertoli cell and spermatids, abnormalities in the acrosomal granule and nucleus of spermatids, reduced percentage of motile sperm, and increased incidence of sperm malformations were also observed (Aikawa et al., 2004; Toyama et al., 2004). Similar changes in the seminiferous epithelium and reduced fertility were found in adult males treated with BPA (Toyama et al., 2004). BPA was found to act directly on Leydig cell steroidogenesis, affecting the expression of cytochrome P450 17 α -hydroxylase/C₁₇₋₂₀ lyase (P450c17) and aromatase enzymes and interfering with LH receptor-ligand binding (Akingbemi et al., 2004; Svechnikov et al., 2010).

Alkylphenols, such as 4-nonylphenol and 4-*tert*-octylphenol, are used to manufacture the alkylphenol polyethoxylates, non-ionic surfactants used as detergents, plasticizers, emulsifiers and modifiers in paints, pesticides, textiles, and personal care products. Alkylphenols present in the environment, mainly in wastewater and rivers, derive from the release of unreacted alkylphenols during manufacturing as well as from degradation of the alkylphenol polyethoxylates in the environment (Blake et al., 2004; Staples et al., 2001). Currently, alkylphenols have been found in human urine and breast milk (Ademollo et al., 2008; Calafat et al., 2008). Octylphenol and nonylphenol has been reported to exhibit weak estrogenic activity as demonstrated by its ability to bind and activate the estrogen receptors (Kuiper et al., 1998; Lee, 1998; Safe et al., 2000). Although these chemicals are between 100 and 10000-fold less estrogenic than 17 β -estradiol, the widespread use of these compounds causes that they largely contribute to the environmental estrogen pool (Blake & Bookfor, 1997).

Maternal exposure to octylphenol was shown to affect the expression of genes essential for reproductive system development, such as steroidogenic factor-1 (SF-1) and steroidogenic enzymes in rat testes (Majdic et al., 1996, 1997). In the lamb, it was demonstrated to inhibit the secretion of FSH in the fetus with a concomitant decrease in testis size and Sertoli cell number at birth (Sweeney et al., 2000). In adult males exposed *in utero* or neonatally to alkylphenols abnormalities in reproductive organs histology, reduced weight of the testis, epididymis and prostate, reduced testosterone level as well as increased number of abnormal sperm and decreased sperm production were observed (Aydoğan & Barlas, 2006; Jie et al., 2010; Lee, 1998; Yoshida et al., 2001). These alterations may result from both modulation of the hypothalamus-pituitary axis and direct estrogenic action in reproductive tissues (Yoshida et al., 2001). Importantly, all these effects were observed only when relatively high doses (400 mg/kg bw) of alkylphenols were used (Atanassova et al., 2000; Sharpe et al., 2003).

Administration of high doses of alkylphenols to adult males resulted in reduced size and function of the testis, epididymis and male accessory glands, decreased serum LH, FSH and testosterone concentrations, increased apoptosis of germ cells and reduced sperm count (Blake & Boockfor, 1997; Boockfor & Blake, 1997; Han et al., 2004; Gong & Han, 2006; Kim et al., 2007). However, reports on the effects of lower doses (<200 mg/kg bw) of octylphenol on male reproductive system are contradictory (Bian et al., 2006; Kim et al., 2007).

Recently, bank vole, a seasonally breeding rodent, was used to investigate the effects of 4-tert-octylphenol on testes and seminal vesicles, depending on the length of exposure and reproductive status of animals. Adult bank vole males kept under long or short photoperiod were orally administered octylphenol (200 mg/kg bw) for 30 or 60 days. We found that treatment for 30 days had no effect on the reproductive organs, whereas treatment for 60 days adversely influenced sperm morphology as well as weights and histological structure of the testes and seminal vesicles. In these tissues, expression of 3β -HSD and AR, and testosterone levels were decreased, concomitantly with increased expression of aromatase and ER α , and elevated estradiol levels, resulting in androgen-estrogen imbalance. These data indicate that long-term exposure to octylphenol is necessary to affect male reproductive organs histology and hormonal milieu. Furthermore, a subtle difference in the sensitivity to octylphenol between voles kept in different light conditions was noted (Hejmej et al., 2011b). In a further study negative effects of this compound on MA-10 Leydig cells *in vitro* have been reported. In cell cultures treated with different octylphenol concentrations, dose-related changes in the cytoarchitecture of MA-10 cells, including cytoplasm vacuolization and altered size and distribution of lipid droplets, were visible. Moreover, it was shown that high doses attenuate 3β -HSD and AR expression, concomitantly with the reduction of progesterone synthesis. Based on this results it was hypothesized that octylphenol besides binding to ERs may use other potential routes of action such as effects on the AR (Kotula-Balak et al., 2011).

4.2.2 Phytoestrogens

Phytoestrogens are plant compounds, structurally similar to 17β -estradiol and thus exhibiting estrogenic or antiestrogenic activity. There are four main classes of phytoestrogens: isoflavones (genistein, daidzein, biochanin A, naringenin), coumestans (coumestrol), lignans (matairesinol) and stilbene (resveratrol). Phytoestrogens are present in fruits, vegetables and leguminous plants, but the main source of these compounds in human diet are soy-based products, i. a. soy-based infant formula, that contain high concentration of genistein and daidzein (Reinli & Block, 1996; Setchell et al., 1997). It is believed that isoflavones exert beneficial effects in prevention of cancer, cardiovascular diseases and osteoporosis, however it was reported that they can adversely affect development and function of male and female reproductive function (Lee et al., 2004; Suthar et al., 2001). This may be of special concern in case of infants fed with soy formula milk. Although, phytoestrogens binding affinity to the estrogen receptors is 1000-10000-fold lower compared with the 17β -estradiol, in infants, which consume even 9 mg/kg/day of isoflavones, mainly genistein, blood concentrations of the isoflavones exceed 1000 times those of endogenous estradiol and are higher than the amount reported to produce hormonal effects in adult women (Henley & Korach et al., 2010; Schmitt et al., 2001; Setchell et al., 1997). Therefore in recent years multiple studies on animal models were undertaken to elucidate the mechanism of action and the consequences of exposure to genistein. In rodents dietary administration of genistein induced Leydig cell hyperplasia and decrease of testosterone level by down-regulation of the expression of steroidogenic enzymes (e.g., cytochrome P450 $_{\text{scc}}$) (Svechnikov et al., 2005). *In vivo* and *in vitro* data indicate that genistein is able to signal through both ER α and ER β , depending on the specific tissue (Mueller et al., 2004). In recent years resveratrol, a stilbene found in grapes and wine, has been widely used to prevent cardiovascular diseases, since it was shown to inhibit oxidation of LDL cholesterol,

platelets aggregation and synthesis of eikozanoids (Kris-Etherton et al., 2002). However, resveratrol appeared to have adverse effect on Leydig cell steroidogenesis through suppression of the expression of StAR and cytochrome P450c17 (Svechnikov et al., 2009).

Estrogenic activity is also attributed to several other compounds derived from plants, for example lavender oil and tea tree oil, frequently used in cosmetics, such as lotions, gels, and creams. It is supposed that exposure to these chemicals may induce prepubertal gynecomastia in humans. *In vitro* experiments revealed that apart from estrogenic activity both lavender and tea tree oil possess antiandrogenic properties (Henley et al., 2007; Henley & Korach et al., 2010).

Interestingly, based on the analysis of published data concerning correlations between exposure to different endocrine disruptors and decrease in sperm counts and increase in testicular cancer rate, Safe (2004) suggested that dietary phytoestrogens, rather than synthetic environmental endocrine disruptors may be involved in induction of reproductive tract disorders in human.

4.2.3 Methoxychlor

Methoxychlor was introduced in 1944 to substitute more persistent and more toxic insecticide, DDT. It is used on agricultural crops, livestock, animal feed, grain storage, home gardens, and on pets. Methoxychlor exhibits mixed estrogenic and antiandrogenic activity: the most active estrogenic metabolite is HPTE [2,2-bis-(*p*-hydroxyphenyl)-1, 1, 1-trichloroethane], whereas other metabolites have antiandrogenic activity (Cummings, 1997; Dehal & Kupfer, 1994; Kelce & Wilson, 1997). HPTE has differential effects on ERs, being an ER α agonist and ER β antagonist (Gaido et al., 1999, 2000). In cultured Leydig cells from immature and adult rats, HPTE was shown to inhibit both basal and hCG-stimulated testosterone production, and these effects were reported to be mediated through the ER (Muroño & Derk, 2005). Recently, a direct inhibitory activity of methoxychlor and HPTE on 3 β -HSD and 17 β -hydroxysteroid dehydrogenase (17 β -HSD) was reported (Hu et al., 2011). Exposure to methoxychlor during gestation or neonatal period affected embryonic testis cellular composition, Sertoli and germ cell numbers, germ cell survival and epididymal sperm count, reducing spermatogenic potential of males (Chapin et al., 1997; Johnson et al., 2002; Suzuki et al., 2004). In adult rat testis methoxychlor induced apoptosis via mitochondria- and FasL-mediated pathways (Vaithinathan et al., 2010).

4.2.4 Heavy metals

Numerous heavy metals (e.g., cadmium, lead, arsenic, boron, mercury, antimony, aluminum, cobalt, chromium, lithium) have been demonstrated to adversely affect the reproductive function of human and experimental animals. For example, cadmium, used in battery electrode production, galvanizing, plastics, alloys and paint pigments, has potent estrogen- and androgen-like activities *in vivo* and *in vitro* (Sikka et al., 2008; Takiguchi & Yoshihara, 2006). In mice exposed to cadmium during late gestation and puberty markedly reduced weights of testes, epididymides, prostate and seminal vesicles, and decreased testosterone levels were observed. Moreover, testicular expression of StAR and steroidogenic enzymes, such as cytochrome P450_{scc}, 17 α -HSD and 17 β -HSD, was down-regulated (Ji et al., 2010, 2011). In the seminiferous tubules, cadmium caused disruption of the blood-testis barrier and oxidative stress, leading to germ cell degeneration, seminiferous tubules vacuolization, and aberrant morphology and apoptosis of Sertoli cells (de Souza

Predes et al., 2010; Zhang et al., 2010). Epidemiological and animal studies have additionally demonstrated a carcinogenic effect of cadmium on the prostate (Nakamura et al., 2002).

Lead, another metal widespread in the environment, has adverse reproductive effect on the testes and the hypothalamic-pituitary axis. In animal studies, lead has been shown to reduce serum testosterone and FSH levels, disrupt spermatogenesis and induce oxidative cellular damage in epididymis (Foster et al., 1998; Marchlewicz et al., 2004; Sokol et al., 1985). Clinical studies have associated exposure to lead with reduced libido, reduced sperm motility and sperm count, chromosomal damage, infertility, and changes in serum testosterone (Braunstein et al., 1978; Winder, 1989).

5. Mechanisms of action

Endocrine disruptors affect cellular processes by different modes of action. They can act by mimicking the action of naturally produced hormones, blocking their receptors in target cells or altering the synthesis or metabolism of hormones and hormone receptors. It is important to note, that many endocrine disruptors have more than one mechanism of action (e.g., methoxychlor) (Gaido et al., 2000). Some can be metabolized to hormonally active compounds, exhibiting different properties (e.g., DDT and its metabolite DDE) (Kelce et al., 1995). Moreover, even compounds with the same supposed mechanism of action can induce different effects after exposure. It was also demonstrated that action of some xenoestrogens may be different in various tissues; thus they can act as SERMs (e.g., BPA, resveratrol, naringenin) (Gehm et al., 1997; Gould et al., 1998; Yoon et al., 2001).

5.1 Interaction with hormone receptors

Endocrine disruptors can bind to specific hormone receptors and act via agonistic or antagonistic mechanism. Numerous xenoestrogens (e.g., BPA, alkylphenols, genistein) activate estrogen receptors, interacting with their binding pockets (Lehraiki et al., 2011; Mueller, 2004; Singleton & Khan, 2003). It is possible due to structural similarities of these compounds to estradiol. The affinity of xenoestrogens to the estrogen receptor and/or their ability to initiate nuclear retention and transcriptional effects is usually lower than those of estradiol. It is worth noting, however, that weak activity via receptor-dependent pathway does not necessarily predict the potency of the chemical acting via another signaling pathway. Moreover, many xenoestrogenic compounds bioaccumulate in fat tissues, resulting in prolonged exposure (Watson et al., 2011). Several estrogenic chemicals, among others flavonoids and resveratrol, have been shown to interact not only with ERs, but also with aryl hydrocarbon receptor (AhR) (Revel et al., 2003; Van der Heiden, et al., 2009).

Antiandrogens, such as flutamide, vinclozolin, prochloraz and linuron, repress AR-mediated transcriptional activation, by competitive inhibition of endogenous androgens binding to their receptor (Gray et al., 1999; Lambright et al., 2000; Mohler et al., 2009; Noriega et al., 2005; Vinggaard et al., 2002). Binding of antiandrogen may result in a conformational change of ligand binding domain of AR appropriate for the interaction with co-repressors, instead of coactivators (Berrevoets et al., 2002; Hodgson et al., 2008).

Besides classical intracellular steroid hormone receptors, several membrane steroid receptors, capable to mediating non-genomic steroid actions, have been described (Thomas & Dong, 2006; Watson et al., 2007). BPA has been shown to bind to membrane-bound form of ER α (mER) and a transmembrane G protein-coupled receptor 30 (GPR30) (Watson et al., 2005). This GPCR-mediated non-genomic action included activation of cAMP-dependent

protein kinase and cGMP-dependent protein kinase pathways and a rapid phosphorylation of the transcription factor cAMP response-element-binding protein (CREB) (Bouskine et al., 2009). Recent results revealed the possibility that BPA may have adverse effects on spermatogenesis via activation of extracellular signal-related kinases 1 and 2 (ERK1/2) (Izumi et al., 2011). Also alkylphenols and phytoestrogens appear to activate non-genomic pathways, signaling via calcium influx and activation of mitogen-activated protein kinases (MAP kinases) (Bulayeva & Watson, 2004; Wozniak et al., 2005).

5.2 Alterations in synthesis, metabolism and transport of hormones or their receptors

It was reported that some endocrine disruptors can interfere with steroid synthesis or metabolism, acting via non-receptor mediated mechanisms (Fisher, 2004b). Phthalates induce antiandrogenic effects, however they do not interact with the AR (Lehraiki et al., 2009; Stroheker et al., 2005). It was demonstrated that DBP and DEHP decrease fetal testosterone synthesis by reducing the expression of steroidogenic genes, such as *Cyp17*, *Cyp11a* and *StAR* (Barlow & Foster, 2003; Borch et al., 2006; Howdeshell et al., 2007; Parks et al., 2000). Phthalates were also shown to decrease the expression of *Insl-3*, a factor produced by fetal Leydig cells. *Insl-3* is an important regulator of testicular descent and phthalate-induced reduction of *Insl-3* is consistent with the high incidence of cryptorchidism (Gray et al., 2006; Laguë & Tremblay, 2008; Wilson et al., 2004). In contrast to phthalates, *in utero* exposure to prochloraz decreases testosterone production by direct inhibition of the activity of steroidogenic enzymes without affecting the mRNA expression of these enzymes (Blystone et al., 2007; Wilson et al., 2008).

As mentioned above, biosynthesis of estrogens is catalyzed by the enzyme aromatase. Various endocrine disruptors were reported to alter the expression or activity of aromatase, leading to testosterone-estradiol imbalance. Enhanced expression of aromatase was found in testes of males exposed to octylphenol and BPA (Hejmej et al., 2011b; Kim et al., 2010), whereas prochloraz reduced aromatase expression (Vinggaard et al., 2006). Estradiol level can also be influenced by inhibition of *SULT 1A1* and *2E1* enzymes, which catalyze inactivation of estrogens by sulphation. It was shown that alkylphenols and phthalates, suppressing these enzymes, cause a rise in the levels of the free active endogenous estrogens (Waring & Harris, 2005).

Some endocrine disruptors may additionally influence the expression levels of hormone receptors, shifting the balance between concentrations of endogenous ligand and its receptor. For instance, it was reported that exposure to DES (McKinnell et al., 2001; Williams et al., 2001) and octylphenol (Hejmej et al., 2011b; Kotula-Balak et al., 2011) results in up-regulation of *ERα* and down-regulation of *AR* in male reproductive tissues.

In case of steroid hormones, the level of bioavailable hormone is determined not only by the level of synthesis and metabolism, but also by concentration of steroid hormone-binding globulin (SHBG), protein involved in transport of steroids in the blood. Studies revealed that endocrine disruptors may influence SHBG level, altering the level of free, bioavailable hormone (Bagchi et al., 2009; Sikka & Wang, 2008).

It should be mentioned, that xenoestrogens and antiandrogens affect reproductive functions not only acting directly on reproductive organs, but also disturbing hypothalamus-pituitary-testicular axis. For example, in adult male rats exposed to BPA during pre- and early postnatal periods, LH serum levels showed no changes, whereas FSH and testosterone levels decreased significantly (Cardoso et al., 2011). Secretion of FSH was also reduced following prenatal octylphenol and vinclozolin exposure (Sweeney et al., 2000; Veeramachaneni et al., 2006b).

5.3 Epigenetic mechanisms

Epigenetic modifications are regulators in numerous biological processes, including spermatogenesis. Key mechanism in establishing epigenetic change is DNA methylation, which usually suppresses expression of the gene. Several studies revealed that endocrine disrupting chemicals are implicated in epigenetic programming and DNA methylation (McLachlan, 2001; Skinner & Anway, 2005). Indeed, hypermethylation found in several genes in the sperm DNA (i. a. *Mest*, *Snrpn*, *Peg1* and *Peg3*) was accompanied by the reduction of semen quality (Stouder & Paoloni-Giacobino, 2010). These changes may be heritable, if they occur during certain stages of development (Crews & McLachlan, 2006). It was demonstrated that methoxychlor and vinclozolin when administered during prenatal period interfere with testis development and lead to increased spermatogenic cell apoptosis and decreased fertility in the adult males. These spermatogenic defects were also evident in subsequent generations (Chang et al., 2006; Skinner & Anway, 2005). Also maternal exposure to BPA resulted in postnatal changes in DNA methylation status and altered expression of specific genes in offspring (Bernal & Jirtle, 2010; Kundakovic & Champagne, 2011).

Taken together, estrogenic and antiandrogenic compounds act by multiple mechanisms of toxicity disrupting the interactions among the interconnected signaling pathways in reproductive tissues. Importantly, in the environment organisms are usually exposed to mixtures of multiple endocrine disruptors, which can produce cumulative effects, regardless of the mode of action of the individual mixture component (Gray et al., 2006).

6. Conclusion

Experimental studies clearly suggest that estrogenic and antiandrogenic compounds could cause alterations of sexual differentiation and impairment of male reproductive functions. Although the process of spermatogenesis is directly vulnerable to exposure to endocrine disrupting agents only in sexually mature males, above-mentioned data imply that exposure during the period of reproductive system development may have subsequent impact on the reproductive functions in adulthood. Fetal and neonatal exposures might result in the reprogramming of the developmental process of testicular cells, leading to their irreversible dysfunction. In contrast, adverse effects on the process of spermatogenesis in adulthood can be reversible (Sharpe, 2010; West et al., 2005). It is likely, therefore, that fetal and neonatal periods are of critical importance, when considering the role of hormonally active chemicals in male reproductive functions.

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8. References

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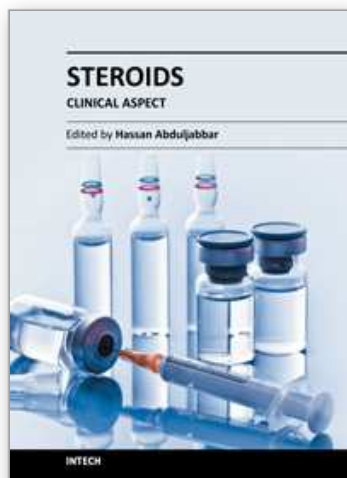
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