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Environmental Endocrinology: Endocrine Disruptors and Endocrinopathies

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1. Introduction

An endocrine disruptor (ED) is defined by the US- Environmental Protection Agency as “an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis, reproduction, development, and/or behavior” (U.S. EPA., 1997). This definition encompasses a rather heterogeneous group of molecules from naturally occurring substances (e.g., phytoestrogens) to biochemically manufactured compounds such as plasticizers, pesticides, industrial solvents, pharmaceutical agents (diethylstilbestrol) and heavy metals.

Endocrine disruptors were originally considered to exert their biological action through nuclear steroid receptors by mimicking or antagonizing natural hormone’s action (Waring & Harris, 2005) with the majority of them acting as pseudoestrogens and less possessing anti-androgenic or anti-estrogenic properties (McLachlan et al., 2006). Today, basic scientific research shows that the mechanisms are much broader than originally recognized and include interaction with transcriptional factors, non-nuclear steroid hormone receptors, gene regulation or even transgenerational effects by targeting germ cell lines (Anway & Skinner, 2006, 2008; Tabb & Blumberg, 2006).

In addition, targets for endocrine disruption extend beyond the traditional estrogen/androgen -mediated reproductive system. Within the last few years, scientists also have expressed concern about the potential role of EDs in increasing trends in obesity and diabetes, the major life-threatening diseases of modern world. At present, all hormone-sensitive physiological systems seem to be vulnerable to EDs, including brain and hypothalamic neuroendocrine systems; pituitary; thyroid; cardiovascular system; mammary gland; adipose tissue; pancreas; ovary and uterus in females; and testes and prostate in males (Diamanti-Kandarakis et al., 2009).

Undoubtedly, the issue of endocrine disruption has attracted considerable scientific attention with the weight of data obtained from wildlife populations, animal models and epidemiological studies growing extensively during the last years. After all, the unprecedented increase in the production and use of industrial and agricultural chemicals during last decades makes human exposure inevitable through multiple sources. Adults are exposed mainly through the ingestion of contaminated drinking water, food and breathing polluted air. Infants are exposed to EDs through breast milk, baby products, and polluted

air while fetuses are exposed through the placenta and are more vulnerable to harmful, irreversible, pathological changes in adult life. People occupationally exposed to pesticides, fungicides and industrial chemicals are considered to be at highest risk for developing an endocrine abnormality as well as humans acutely exposed to an accidental release of an endocrine disrupting chemical.

This chapter reviews the evidence linking endocrine disrupting chemicals to a broad spectrum of clinical perturbations from reproduction and thyroid to metabolic regulation. A summarized review of literature focused on the strongest experimental data and human epidemiological studies targets to elucidate the underlying interactions between endocrine disruptors and endocrine abnormalities.

2. Reproductive function and endocrine disruptors

Reproductive health is traditionally considered as one of the well-studied fields in endocrine disruption. The effects of EDs on reproduction are amply documented in both wildlife and laboratory populations while interfering with human reproductive function is highly plausible. Establishing causality between human reproductive health and exposure to a certain environmental contaminant is challenging as several confounders need to be taken into account.

A critical concern is the potential lag between exposure to EDs and the manifestation of a reproductive disorder as in humans this period may be years or decades after initial exposure. The timing of exposure is key to human disease as the developmental periods from periconception and during pregnancy, infancy, childhood, and puberty are considered as critical and sensitive windows of susceptibility to environmental insults. Furthermore, chronic exposure to low amounts of mixtures of EDs than acute exposure to a single compound, as in many animal models, is the most possible scenario when studying human reproduction. In addition, as in other systems in the organism, EDs effects on human reproduction could be varied by individual differences in metabolism, body composition and susceptibility due to genetic polymorphisms (Diamanti-Kandarakis et al., 2009).

In the human female, the first evidence of endocrine disruption was provided almost four decades ago by diethylstilbestrol (DES), a synthetic oestrogen prescribed therapeutically in a large scale in the mid-20th century in order to prevent miscarriage in pregnant women. The observation of an uncommon gynecologic neoplasm, vaginal adenocarcinoma, in daughters born 15–22 yr earlier to women treated with this potent synthetic estrogen during pregnancy was the first clinical evidence of DES disruption on reproductive system (Herbst et al., 1971). Posterior studies have identified additional adverse effects in female off springs including increased risk for structural reproductive tract anomalies with a characteristic T-shaped uterus, infertility, menstrual irregularity and poor pregnancy outcomes manifested as spontaneous abortion, ectopic pregnancy, and preterm delivery (Kaufman et al., 1982, 2000; Palmer et al., 2001). Furthermore, DES grand-daughters born to mothers prenatally exposed to diethylstilbestrol exhibit irregular menstrual cycles and possible infertility (Titus-Ernstoff et al., 2006). These robust clinical observations together with experimental data support the causal role of DES in female reproductive disorders.

Increasing data from wildlife and laboratory studies support a role of EDs in the pathogenesis of several other female reproductive disorders during a broad developmental spectrum from puberty onset to menopause (Diamanti-Kandarakis et al., 2010; McLachlan et al., 2006; Woodruff et al., 2008). The catalogue of reproductive aberrations possible related to

ED exposure is extending to include early/delayed puberty, polycystic ovarian syndrome (PCOS), impaired fertility and fecundity, premature ovarian failure, endometriosis, uterine fibroids, aneuploidy, pregnancy complications as well as breast and endometrial tumors (Caserta et al., 2008; Diamanti-Kandarakis et al., 2009).

To give few examples, earlier menarche onset has been observed in girls exposed to polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), phthalate esters and DDT while there are other data that link phthalates to premature thelarche and increased risk of endometriosis (Woodruff et al., 2008). With regard to human puberty, scientific interest is focused on the potential effect of environmental factors on puberty timing. This is based on the observation that since the 19th century there have been significant modifications in puberty timing with earlier age of thelarche and menarche in girls (Euling et al., 2008a). This puberty timing alteration has been associated, apart from apparent improvements in general health and nutrition, with a potential impact of endocrine-disrupting chemicals, particularly the estrogen mimics and antiandrogens (Euling et al., 2008b, Jacobson-Dickman & Lee, 2009).

Adult female reproductive functions are also disrupted by environmental chemicals with the strongest evidence incriminating heavy metals and especially lead exposure. Most modifiable risk appears to be associated with exposures in unique populations (contaminated fish consumers) or occupational groups (farmworkers) (Mendola et al., 2008). Furthermore, recent evidence imply a potential role of Bisphenol A (BPA) in the PCOS pathophysiology given that in women with PCOS, BPA levels were found to be higher compared to BMI-matched healthy women and also to be positively and strongly associated with androgen levels (Kandaraki et al., 2010). Serum BPA concentrations are significantly higher in men than in women (Takeuchi et al., 2002) and in women with ovulatory dysfunction compared to regularly ovulating women (Takeuchi et al., 2004). As PCOS pathogenesis remains partly unraveled, the role of environmental factors and in particular BPA could also been proposed in PCOS development.

With regard to male reproductive system, research has been mainly focused on three major health endpoints; impaired semen quality and infertility, urogenital tract abnormalities-cryptorchidism and hypospadias- and testicular germ cell cancer. This is probably related to the epidemiologic evidence that suggest a decline in human semen quality over the last 50 years (Carlsen et al., 1992) and temporal increasing trends in the prevalence of urogenital tract malformations such as cryptorchidism and hypospadias (Toppari et al., 2001). Interestingly, it is hypothesized that the above-mentioned abnormalities share a common embryogenic origin as parts of a pathogenic entity coined as "testicular dysgenesis syndrome" (TDS). This hypothesis proposes that a prenatal, synergistic, interaction between environmental, genetic and maternal factors lead to abnormal testis development (dysgenesis) (Skakkebaek et al., 2001) and secondarily to impaired androgen production and germ cell development due to Sertoli and Leydig cells' dysfunction (Sharpe & Skakkebaek, 2003). The existence of TDS as a distinct clinical entity and of possible associations with EDs is an area of active research.

Some substances that have been incriminated to have an aggravating impact on sperm parameters include polychlorinated biphenyls (Dallinga et al., 2002; Hauser et al., 2003), phthalates (Duty et al., 2003; Hauser et al., 2006) and non-persistent pesticides (Juhler et al., 1999; Padungtod et al., 2000). Epidemiologic evidence for EDC exposure and cryptorchidism or hypospadias are limited. Concerning ED exposure and cryptorchidism and/or

hypospadias, the strongest epidemiological data are those suggesting an association between residency in agricultural areas and/or measures of direct parental exposure to non-organochlorine pesticides (Diamanti-Kandarakis et al., 2009).

Overall, the epidemiologic data on the environmental EDs suggest that there may be associations between exposure and adverse health outcomes in men. However, the limited human data highlight the need for further research on these chemicals. Future longitudinal epidemiology studies with appropriately designed exposure assessments are needed to determine potential causal relationships, to identify the most important time windows of exposure, and to define individual susceptibility factors for adverse effects on men's health in response to exposure.

3. Thyroid and endocrine disruptors

Thyroid hormones have been evolutionarily preserved as important regulators of development, tissue growth and metabolism among all vertebrates and in some invertebrate species (Heyland and Moroz, 2005). Given their importance for normal physiological processes, considerable concern has aroused regarding the clinical impact of environmental factors on thyroid function to the extent that human could be affected. This interaction is biologically plausible as a variety of heterogeneous synthetic chemicals has been recognized to interfere with thyroid homeostasis by acting on different points of regulation of thyroid hormone synthesis, release, transport through the blood, metabolism and clearance (Howdeshell, 2002) or directly at the receptor level (Zoeller, 2007).

Polychlorinated biphenyls (PCBs), Polybrominated diphenyl ethers (PBDEs), Bisphenol-A, dioxin, Perchlorate and furans have been incriminated as potential disruptors of thyroid homeostasis through their ability to affect the hypothalamic- pituitary- thyroid axis (Boas et al., 2006; Zoeller, 2010). Correlations between levels of these compounds in the body and circulating thyroid hormone levels, thyrotropin levels, thyroid volume and prevalence of thyroid antibodies have been reported by several researchers, however, inconsistency exists across studies (Hagmar et al., 2001; Langer et al., 2008; Meeker et al., 2007).

Literature on thyroid disrupting chemicals includes human epidemiological studies that indicate a potential association between exposure to endocrine disruptors and disturbance of thyroid function (Persky et al., 2001; Steinmaus et al., 2007; Takser et al., 2005) with most data pointing towards subtle alterations of the thyroid axis within normal ranges which may, in turn, be harmful especially for human fetus (Boas et al., 2006). Fetus' growth and brain development are very sensitive to modifications of thyroid homeostasis with a significant risk of neurological and cognitive deficiencies.

Overall, the literature on thyroid-disrupting effects of individual chemicals is rapidly increasing, as animal exposure studies and in vitro tests reveal a multitude of potential mechanisms of action. Quick and robust tools should be developed to identify potential thyroid disrupting chemicals and their multiple mechanisms of action. Furthermore, a better understanding of the mechanisms underlying disruption of the thyroid function may lead to changes in public policy in order to limit adverse outcomes for future generations.

4. Obesity epidemic and endocrine disruptors

A potential role of environmental contaminants on the escalating rates of human obesity has been hypothesized as an exogenous factor that may impair body's natural weight-control

mechanisms (Baillie-Hamilton, 2002). As the current epidemic in obesity cannot be solely explained by alterations in food intake, physical activity and/or genetic predisposition, the contribution of environmental factors becomes suspicious.

Research on this field has been mainly focused on the identification of environmental “obesogens”, molecules that inappropriately regulate lipid metabolism and adipogenesis and also on the molecular mechanisms underlying these metabolic alterations (Grün et al., 2006; Tabb & Blumberg, 2006). After all, recent epidemiology studies indicate that exposure to EDs during development is associated with overweight and obesity later in life. In a cross-sectional analysis of six urinary phthalates metabolites in a total sample of 4369 participants, positive correlations were observed between body mass index (BMI) and waist circumference and most of the metabolites in adult males (Hatch et al., 2008). High serum Polychlorinated Bisphenyls levels have been associated with high levels of total serum lipids and BMI in a Native American cohort (Goncharov et al., 2008) and prenatal and early life PCB exposures were associated with increased weight in boys and girls at puberty (Gladen et al., 2000).

So far, several experimental data have pointed to the effect of endocrine disrupting chemicals on lipid metabolism suggesting that adipocyte *per se* may represent a cell vulnerable to disruption. A characteristic example of such interaction is provided by the organotin tributyltin (TBT) that has been shown to modulate adipocyte differentiation by acting as an agonist for retinoid X receptor (RXR) and peroxisome proliferators-activated receptor γ (PPAR γ), the nuclear receptors that play important roles in lipid homeostasis and adipogenesis (Grün & Blumberg, 2006; Kanayama et al., 2005). Therefore, as it is speculated by Tabb & Blumberg, chronic life-time or developmental exposure to TBT could activate RXR and/or RXR:PPAR- γ signalling leading to long-term alterations of the total adipocyte number and/or a lipid haemostasis (Tabb & Blumberg, 2006).

Another chemical showed to display “obesogenic” properties *in vivo* is diethylstilbestrol. Female mice neonatally exposed to both low and high doses of this estrogenic compound exhibited increased body weight in adulthood. The low dose did not affect body weight during treatment but was associated with a significant increase in body weight in the adult animal by 4 to 6 months of age while the highest dose resulted in a significant decrease in mice weight during treatment followed by a “catch-up” before puberty and consecutively elevated body weight during adulthood (Newbold et al., 2008). Further studies indicated that the increase in body weight in DES-exposed mice was associated with an increase in the percent of body fat as determined by mouse densitometry (Newbold et al., 2007).

Bisphenol A is also postulated to play a role in the development of obesity by interacting with lipid homeostasis and body weight control mechanisms through pleiotropic modes of action. Micromolar concentrations of BPA were shown to enhance adipocyte differentiation and lipid accumulation in target cells in a dose-dependent manner (Masuno et al., 2002, 2005; Wada et al., 2007). From a molecular perspective, these effects are linked with up-regulation of gene expressions involved in lipid metabolism and adipogenic transcription factors (Phrakonkham et al., 2008; Wada et al., 2007). *In vivo* studies confirm the above observations. Perinatal exposure to low doses of BPA increases adipose storage in rodents in adult life (Rubin et al., 2001; Somm et al., 2009). A similar effect is observed when exposure takes place during gestation (Nikaido et al., 2004).

Many other environmental chemicals are suspected to be candidate obesogens including pesticides; for example, organochlorines such as DDT, endrin, lindane, and

hexachlorobenzene; organophosphates; carbamates; polychlorinated biphenyls; other plastic components such as phthalates; perfluorooctanoic acid (PFOA); heavy metals such as cadmium, lead, and arsenic; and solvents (Newbold, 2010). Although the epidemiological link between specific obesogen exposure and obesity is highly suggestive, causality and overall significance currently remain ambiguous. New detailed longitudinal studies are merited as a high-priority investigative goal to establish the magnitude of the contributing risk by individual obesogens.

5. Metabolic disorders and endocrine disruptors

The issue of potential ED interference with metabolic imbalances is very timely especially in light of a recent cross-sectional study in the general adult population of the United States that reported an association between higher urinary BPA concentrations with diabetes, cardiovascular diagnoses and clinically abnormal concentrations of the liver enzymes γ -glutamyltransferase (Lang et al., 2008). An analysis of the posterior data from the US National Health and Nutrition Survey (NHANES) conducted by Melzer et al. confirmed the association between urinary BPA levels with coronary heart disease (Melzer et al., 2010).

These adverse effects of BPA on humans' metabolism appear to be confirmative of previously reported actions in animal models. Indeed, a series of studies by Alonso-Magdalena et al. have illustrated the potency of this estrogenic compound to directly affect pancreatic cells' function and to favor metabolic disorders (Alonso-Magdalena et al., 2005, 2006, 2010). Low doses of BPA acutely induced a change in glycemic balance characterized by a decrease in glucose levels that correlated with a rise of plasma insulin in adult male mice (Alonso-Magdalena et al., 2006). Furthermore, long term administration of BPA in β -cells from these rodents resulted to an increase in the insulin content and insulin secretion of the islets of Langerhans while BPA-treated mice appeared to be insulin resistant (Alonso-Magdalena et al., 2006). Pancreatic α -cells have also been implied as potential targets for endocrine disruption given that low doses of Bisphenol A were shown to impair the molecular signaling that leads to secretion of glycagon by suppressing intracellular calcium ion oscillations in α -cells in response to low blood glucose levels (Alonso-Magdalena et al., 2005).

Interestingly, gestational exposure to BPA has been recently linked to impaired glucose tolerance and reduced insulin sensitivity in adult mice' life when compared with non-exposed male offspring. Pregnant mothers were also affected as indicated by the aggravated insulin resistance during pregnancy and post-partum in this population in comparison to non-treated mothers (Alonso-Magdalena et al., 2010). As demonstrated in these rodent studies, BPA may contribute to metabolic disorders relevant to glucose homeostasis and, therefore, this altered blood glucose homeostasis may subsequently enhance the development of type 2 diabetes. Interestingly, human studies have also implied BPA to favor metabolic syndrome development through an inhibitory effect on adiponectin release from adipose depots of patients with morbidity obesity undergoing gastric bypass surgery (Hugo et al., 2008).

Other compounds that have been correlated with alterations in blood glucose homeostasis in humans are dioxins (Bertazzi et al., 2001; Henriksen et al., 1997) and arsenic (Lai et al., 1994; Meliker et al., 2007).

In conclusion, accumulating data are pointing to the potential role of endocrine disrupting chemicals either directly or indirectly in the pathogenesis of adipogenesis and diabetes, the major epidemics of modern world.

6. Conclusion

Accumulative evidence from experimental and human studies imply that exposure to endocrine disruptors may have significant impact to all hormone-sensitive endocrine systems. The catalogue of endocrinopathies possible related to EDs is expanding to include a broad spectrum of disorders from reproductive function to metabolic regulation (see Table 1).

Human exposure to EDs is well-documented to occur through multiple sources, however, several parameters considerably complicate the assessment of EDs' interaction with human health. For instance, it is important to keep in mind that humans are continuously exposed to a multitude of pollutants which can act together, and lead to effects that are different from those of the individual pollutants that are usually studied in the laboratory. Furthermore,

the multiplicity of targets and the fact that many targets can be disrupted at the same time within an organism make difficult to truly evaluate the affect of an endocrine disrupting chemical to many endocrine systems. In addition, humans are not usually exposed to a single compound but to a mixture of EDs and as these chemicals may interact additively or antagonistically, the final clinical outcome may be variable. After all, human disorders are more likely the additive result of chronic exposure to low amounts of mixtures of EDs.

Another important parameter is timing of exposure as the biological effects of a compound vary depending not only on the nature of the chemical and dose, but on the susceptibility of the individual to this. The timing of exposure appears as a determining factor in the developmental programming hypothesis, which proposes that exposure of the developing tissues/organs to an adverse stimulus or insult during critical or sensitive times of development can permanently reprogram normal physiological responses leading to hormonal disorders later in life (Gluckman et al., 2005). In other words, when estimating the effect of a compound on human health the time of exposure may determine the clinical outcome. Importantly, the consequences of an exposure may not be apparent at the actual time of exposure, but may manifest later in life. Indeed, the potential lag between exposure to EDs and the manifestation of an endocrine disorder in humans may be years or decades after initial exposure.

Although direct causal links between exposures to EDs and disease states in humans are difficult to draw, results from basic research and epidemiological studies make it clear that more screening for exposures and targeting at-risk groups is a high priority. Innovative technologies designed to improve the assessment of human exposure and reproductive and endocrine health endpoints should be applied. Furthermore, scientific community should adopt a united approach with collaboration between different professional groups and government policy to prompt precautionary actions against excess exposure. After all, endocrine disruption is on the agenda of many experts' groups, steering committees and panels of governmental organizations, industry, and academia throughout the world.

Endocrine systems	Endocrine Disorders Possibly Related To Endocrine Disruptors' Exposure
Male reproductive system	Testicular Dysgenesis Syndrome Altered semen quality Hypospadias/ cryptorchidism Testicular cancer Prostate cancer
Female reproductive system	Precocious/delayed puberty Impaired fertility/fecundity Reproductive tract anomalies Endometriosis Menstrual and Ovarian dysfunction Pregnancy complication (Preterm delivery/Pregnancy lost) Premature menopause Impaired mammary gland differentiation / Breast cancer
Thyroid	Altered thyroid hormones
Adipose tissue	Promote adipogenesis Altered body weight Disturbed adipokine secretion
Pancreas	Diabetes mellitus Disturbed insulin secretion Disturbed glycagon secretion

Table 1. Endocrine system as a target for disruption: The potential impact of endocrine disruptors on endocrine system based on experimental and human data.

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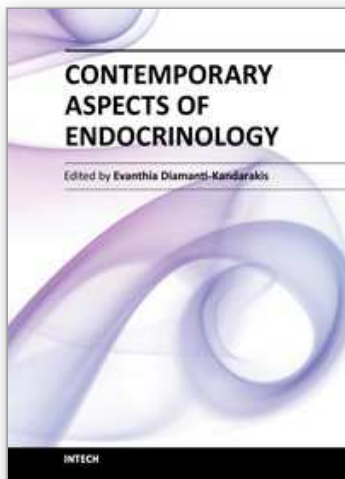
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This book aims to provide readers with a general as well as an advanced overview of the key trends in endocrine disorders. While covering a variety of topics ranging from thyroid carcinogenesis and pituitary adenomas to adrenal tumors and metabolic bone disease, this book also focuses on more specific issues not yet fully elucidated (e.g. the molecular pathways involved in thyrotropin beta gene regulation or monogenic phosphate balance disorders). Readers of different fields and background will have the opportunity to update their knowledge and more importantly to clarify areas of uncertainty and controversies in several topics of endocrine disorders.

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