Toxicology 311 (2013) 41–51

Contents lists available at SciVerse ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Evidence of reproductive disruption associated with neuroendocrine changes induced by UV–B filters, phtalates and nonylphenol during sexual maturation in rats of both gender

Osvaldo J. Ponzo*, Carbone Silvia

Laboratorio de Endocrinología, Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 22 February 2013
Received in revised form 27 May 2013
Accepted 28 May 2013
Available online 15 June 2013

Keywords:
Sunscreens
Nonylphenol
Phthalates
Gonadotropins
GnRH
Amino acids

ABSTRACT

Endocrine disruptors (EDs) are exogenous substances or xenoestrogens natural or synthetic, capable of interacting with different systems and altering their normal hormonal regulation, being the reproductive system one of the most affected. EDs produce their effects not only by acting on nuclear steroid receptors, but also on membrane receptors, steroidal and non-steroidal synthetic enzymatic pathways and/or metabolism. The incorporation to the body depend on each EDs, which are liposoluble and easily deposited in the tissue; thus ensuring a prolonged accumulation and release, even when the exposure is not continuous. In addition to cross the placenta, EDs may act in the offspring during the reproductive system formation and maturation key stages and its regulatory mechanisms. The effects of EDs can be multiple, but most acts mediating estrogenic and/or antiandrogenic effect. Three groups of EDs are widely used: in plastics (phtalates), sunscreens (cinnamate and methylbenzylcamphor), and detergents (nonylphenol). In this paper we review the effects of the exposure to these environmental chemicals on the reproductive system and the possible mechanisms by which they occur, focusing in the hypothalamic–pituitary neuroendocrine mechanisms that regulate the reproductive system.

1. Introduction

Environmental pollution had and has a major impact on biological systems. In the last few decades huge amounts of chemicals of different origin, structure and use coming from industrialization have been released into the environment as chemical waste, causing changes to the exposed living organisms. These substances are generically considered endocrine disrupters (EDs) (Schug et al., 2011). They have been also called xenoestrogens or xenobiotics as they have the capacity to alter hormonal homeostasis through the same biological paths used by endogenous steroids (Akingbemi and Hardy, 2001; Sharpe, 2001), modifying the endocrine system, like the reproductive and the thyroid axis (Danzo, 1998; Heindel, 2006; Schmutzler et al., 2004; Zoeller, 2007) and causing adverse health effects in an organism or its progeny. One decade ago, Krimsky suggested a new hypothesis known as "Endocrine Disruption" (Krimsky, 2000), (see Table 1). At present, the US Environmental Protection Agency (EPA) defines them as: "Exogenous agents that interfere with synthesis, secretion, transport, metabolism, binding action or elimination of natural blood-borne hormones that are responsible for homeostasis, reproduction and developmental process".

There is increasing interest and research on effects of EDs on neuroendocrine systems (Dickerson and Gore, 2007; Gore, 2010). Most studies have focused on the effects of chemicals known for several years as EDs (pesticides, phytoestrogens, dioxins, etc.) on gonadal and thyroid neuroendocrine systems. This article will primarily discuss the literature on neuroendocrine alterations induced by substances used to manufacture products used daily, such as plastics (phthalates), sunscreens and cosmetics (cinnamate and methylbenzylcamphor) as well as detergents (nonylphenol), focusing in their effects on the hypothalamic–pituitary-gonadal axis and the sequelae on reproductive function.

1.1. Characteristics and mechanism of action of EDs

EDs include substances with estrogenic and/or antiestrogenic, androgenic and/or antiandrogenic actions (Carbone et al., 2010; Carou et al., 2008; Rivas et al., 2002) and mimetizers or antagonists of the thyroid hormones (Brucker-Davis, 1998; Schmutzler et al., 2004). Also EDs can interference with hormonal feedback regulation and neuroendocrine cells. Along with the direct influence of EDCs on estrogen or androgen actions, they can affect endogenous steroid production through negative and positive feedback,

* Corresponding author at: Laboratorio de Endocrinología, Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, (1121), Piso 7, Buenos Aires, Argentina. Tel.: +54 11 59509500 2147.
E-mail address: oponzo@fmed.uba.ar (O.J. Ponzo).

0300-483X/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tox.2013.05.014

Table 1
Endocrine disruption hypothesis.

The effects occur through mechanisms of different action, all of them related to the hormonal action
There is no exposure limit without effect. It is shown a relation dose-effect not necessary lineal, which in some cases is apparently paradoxical with U or inverted U curve types. May have effect in low doses (parts per billion) while not showing manifestation at high doses. While the limits of exposure are measured in parts per million (ppm), the body concentrations of some of them exceed that limit
Most of the effects are persistent and bioaccumulative and have a latency period of decades
Their effects are specifically evident in critical development periods or in moments of particular susceptibility
Their effects may be the result of the combine action of different compounds that may trigger a synergic, antagonic and/or additive response
The expression of the effects may appear late in life in the exposed individual, and even appear over generations

effects that may differ depending on developmental stage, leading to perturbations in neuroendocrine systems function (Gore, 2010).

At the molecular level EDs can act through different mechanism (De Coster and van Larebeke, 2012): (a) activation of the classical nuclear receptors ERα and ERβ, which bind estrogen responsive elements (EREs) in the promoters of target genes, regulating its expression (Levin, 2005), (b) activation of membrane-bound estrogen receptors: mERα, mERβ, and GPR30 (non nuclear steroid hormone receptors), inducing rapid nongenomic responses and acting through second messenger-triggered signal cascades (Watson et al., 2007), (c) binding to cytosolic ER receptors, activating the kinases and leading to the activation of the Src/Ras/ERK signaling cascade (Nadal et al., 2001), (d) cross-talk between genomic and nongenomic pathways (Silva et al., 2010), (e) activation of estrogen-related receptors (ERR), which are orphan nuclear receptors (Takayanagi et al., 2006), (f) changes in DNA Methylation or Histone-Modifications, that produced epigenetic modifications (Ho et al., 2006). Also early life exposures to EDs may alter gene expression in hypothalamic nuclei via nongenomic epigenetic mechanisms (Gore, 2008), modifying the phenotype expression and explaining the fact that multi and trans-generational exposure to EDs may promote the development of a disease over future generations (Hoshino et al., 2005; Anway and Skinner, 2006), (g) acting on the enzymatic pathways involved in steroid biosynthesis and/or metabolism of hormones, such as the enzymes 3b-HSDs and 17b-HSDs, aromatase, sulphatases (Whitehead and Rice, 2006).

EDs may be transferred through placental circulation and breast secretion (Campoy Folgoso et al., 2004; Nishikawa et al., 2010; Rogan et al., 1987;Wickizer and Brilliant, 1981; Schlumpf et al., 2010).), disturbing sexual differentiation and development of exposed offspring during early prenatal or postnatal stages (Colborn et al., 1993). Most of the EDs are lipid-soluble substances and they tend to be deposited especially in adipose tissue, in a dose-dependent manner, causing a very important cumulative effect (Schlumpf et al., 2004). In addition, simultaneous exposure to several EDs produced an additive or synergic effect (Crews et al., 2003). Exposure to EDs minimum doses may cause even more drastic effects than the ones appearing in high doses exposure. This occurs because EDs exert their effects following a non classic response dose curve: in inverted U or U shape (Vandenberg et al., 2012; vom Saal et al., 2007). This would explain the fact that EDs may alter the normal function of the endocrine system even at doses that could be considered, from toxicological point of view, as "safe dose" or "safety margin".

EDs are released in the environment and can be found in natural water courses and in fish (Poiger et al., 2004). In humans, exposure occurs through air, contaminated water or food intake, dermal contact and even through medical consumables and devices such as catheters, breathing and respiratory equipment and blood bags. It is also possible that the disruptive endocrine action may come from food ingestion with some hormonal action per second. For example, it has been demonstrated that urinary concentration of the estrogenic ED genistein was about 500 times higher in the soy milk formula-fed infants than in the cow milk formula-fed infants (Cao et al., 2009).

1.2. Impact of EDs on male and female reproductive peripheral organ

Many decades ago some researchers observed the loss of reproductive capacity, malformation in the reproductive organs and abnormal sexual behavior in animals of the ecosystem (Carson, 1962).

One of the more important variable to take into account to evaluate the impact of EDs on the reproductive system is the period of exposure, being more relevant during early fetal and neonatal developmental, when the programming of the endocrine system is carried out. In males, exposure to EDs during gestation and early stages of life has been related with the presence of genital malformations as cryptorchidism, hypospadia and decreased anogenital distance (Boisen et al., 2001; Gray Jr. et al., 2000; Skakkebaek et al., 2001; Swann et al., 2005), decreased sperm quality and increased testicular cancer incidence (Landrigan et al., 2003; Olea Serrano and Zuluaga Gómez, 2001; Paulozzi, 1999). Skakkebaek et al. (2001) described the testicular dysgenesis syndrome (TDS), characterized by the presence of testicular cancer, hypospadia, cryptorchidism and low semen quality as a consequence of exposure to environmental contaminants. The reduction of the anogenital, distance parameter used as biomarker of reproductive effects, has been related with, higher levels of phthalates in urinary excretion and in the amniotic fluid in exposed gestational mothers (Huang et al., 2009; Swann et al., 2005). The decrease in sperm count in human, would be related with gonadal atrophy attributable to chronic exposure from fetal development to xenoestrogens (Sharpe et al., 1993; Toppari et al., 1996), similar to that produced by dietary 17 β-estradiol exposure (10 and 50 ppm) in adult rats (Cook et al., 1998).

In females the early contact with EDs during development has been related to an acceleration of pubertal development, polycystic ovary syndrome and cystic endometrial hyperplasia, endometriosis, uterine fibroids, premature, thelarche, early menarche, irregular menstrual cycle and a higher risk regarding breast and cervical cancer (Crain et al., 2008). It is well known the high incidence of ovarian, breast and vaginal carcinoma observed in daughters born form women treated with diethylstilbestrol (DES) during pregnancy (Blatt et al., 2003; Titus-Ernstoff et al., 2010). Direct exposure to EDs during woman reproductive stage was related to implantation failure, miscarriages and premature birth (Crain et al., 2008).

1.3. Neuroendocrine control of sexual maturation and reproduction. Possible interference by EDs

During the last two decades, an earlier onset of puberty was described (Herman-Giddens et al., 1997; Lee et al., 2001). It was not related to improvement in health and nutritional status, because they not always are accompanied by an increase of fat mass and leptin (Aksglaede et al., 2009). Thus, other factors including EDs could be involved in this early puberty (Teilmann et al., 2002). Puberty is a phenomenon that is initiated and regulated at neuroendocrine level. The control of the reproductive neuroendocrine regulation involves neurons in the basal hypothalamus that synthesize and release the decapeptide GnRH, which drives reproduction throughout the life cycle and also is the primary stimulus to the pituitary and gonadal axis. It is known that sexual hormones regulate the