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2. Molecular mechanisms of endocrine disruptors: Interference with the endocrine system activity

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Abstract. Endocrine disrupting chemicals (EDCs) are an heterogeneous group of compounds able to interfere with hormonal functions by mimicking the endogenous hormones. This feature makes them able to interact with different cellular and molecular targets that affect all the biological functions of organisms. Many EDCs have a structural similarity with several endogenous hormones and this allows them to interact physically with specific receptors even though with different binding affinities each time. In this review we have collected some of the various and manifold molecular mechanisms activated by EDCs. Of these, the receptor-mediated pathway prevails; it is based on the interaction with estrogen receptors (ERs). However, this is not the only way they can use to determine endocrine interference. Several *in vitro* and *in vivo* studies have shown the existence of non-receptor and non-genomic pathways that are much faster and trigger a number of signal transduction pathways that control multiple cellular functions such as proliferation, differentiation

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and motility. Finally, several EDCs affect the hypothalamus-pituitary axis and the hormonal systems involved in the thyroid and the adrenal glands. Their wide presence in the environment and the multiple exposure paths to which we are constantly subjected, make EDCs a very wide health problem. Determining the specific molecular mechanisms that they are able to activate is an important step in trying to reduce the risk associated with their presence in our daily lives.

Introduction

The endocrine system is formed by different glands producing several hormones which are able to regulate metabolism, growth, development and reproduction in humans and animals (Witorsch, 2002). Endocrine Disruptor Chemicals (EDCs) are exogenous compounds, of natural or synthetic origin, that are able to interfere with different hormonal pathways such as production, transport, metabolism and action of natural hormones. EDCs can act as agonists and/or antagonists of natural hormones. EDCs are characterized by multiple mechanisms: they can function in genomic, epigenomic or non-genomic manner. In this way, EDCs negatively influence homeostasis, reproduction and developmental processes (Sun et al. 2016). EDCs are ubiquitously present in the environment because they are used in different industrial (industrial chemicals, plastic packaging components) and agricultural (pesticides, fungicides, insecticides, herbicides) purposes (Nappi et al. 2016). Other than, EDCs are used for the preparation of detergents, cosmetics, sun lotion for personal care and in the manufacturing of toys. Moreover, they can be presents in the environment as natural compounds like phytoestrogens. EDC classification is complicated but in general they can be divided in short-lived pollutants and persistent organic pollutants (POPs) (Giulivo et al. 2016). The first category includes phthalates and bisphenol A, whereas POPs include the organochorine pesticides dichlorodiphenyltrichloroethane (DDT) and other industrial products as dioxins, flame retardants (Giulivo et al. 2016). Due to their whole diffusion in each matrix (sediments, soils, water, atmosphere), human exposure to EDCs is unavoidable and can mainly occur through the food chain, by the consumption of contaminated tap water and food, by dermal exposure and/or by inhalation of volatile compounds and airborne fine and ultrafine particulate matter (Nappi et al. 2016). Another important EDC peculiarity is their lipophilic nature that allows their persistence in the environment other than biomagnification and bioaccumulation processes. Morevoer, it is important to consider that animals and humans are exposed to

complex mixtures of EDCs. These compounds can have a great complexity of mechanism of action, because their can contemporary act on multiple signaling pathways and targets (Nappi et al. 2016).

Other the way of exposure, particularly important is the consideration of the time of in order to evaluate the next impact of EDCs on biological systems. Specifically, the fetal life represents a period of special attention, since important processes such as organogenesis and tissue differentiation must occur through a series of well-regulated molecular, biochemical and cellular events (Prusinski et al. 2016). Any perturbation of only one of developmental key point can cause adverse effect in the "tomorrow" person. It has been demonstrated that environmental exposures during specific "window of susceptibility" can permanently reprogram normal physiology of polluted organisms. In this view, prenatal and early postnatal developmental processes are more susceptible to EDC action since each minimum change of timing and/or activation/inhibition pathways can alter all the other cellular events. However, humans are continuously exposed to EDCs daily during all the life, hence all stages of body physiology are potential targets of endocrine disruption. Moreover, EDCs differ from other environmental pollutants since they are able to function at small doses but inducing subtle changes at cellular and tissue levels that finally evoke pathophysiological effects (Prusinski et al. 2016). At today, all human body systems are negatively influenced by EDCs: cardiovascular system (Roseboom 2012), nervous system (Nesan and Kurrasch 2016), reproductive system (Crews and McLachlan 2006, Maqbool et al. 2016), digestive system (Janesick and Blumberg 2016; Nappi et al. 2016) and obviously endocrine system. Moreover, EDCs are linked to carcinogenes, teratogenesis and transgenerational inheritance of phenotype (Bernal and Jirtle 2010; Prusinski et al. 2016). In the last twenty years, the study of EDCs have completely revolutionized the concept of teratological compounds, in fact from substances inducing structural abnormalities at birth they have been transformed in molecules and/or mixtures of chemicals involved in the developmental origin of adult diseases (McLachlan 2016). Among all the well known substances acting as teratological compounds, a pioneer of EDCs that has contributed to the modification of endocrine disruption view in the teratology, was diethylstilbestrol (DES) that for the first time had been demonstrated as the cause of transplacental carcinogenesis: DES took by the mother during pregnancy was able to induce cancer later in the life of the daughters (McLachlan 2016).

Multiple compounds for multiple molecular mechanisms

As written above, EDCs can have many different molecular behaviour and they can act on multiple cellular targets. However, the more important EDC targets are the nuclear receptors such as estrogen (ER), progesterone (PR) and androgen (AR) receptors, steroid (mineralcorticoid, glucocorticoid) receptors, thyroid receptors (TR) and peroxisome proliferator-activated receptors (PPAR) (Wuttke et al. 2010; Yang et al. 2015; Giulivo et al. 2016;). Due to the broad involvement of these receptors in many different cell and tissue functions, it is evident the attention needed to EDC role in biological interference at several points. Recent studies have demonstrated that EDCs can also act with membrane receptors like estrogen receptor GPER or other ER splice variants. Moreover, EDCs interfere with enzyme activity such as hormone metabolizing enzymes like aromatase (Sanderson, 2006), 5-reductase (Kalfa et al. 2009), 3-hydroxysteroid dehydrogenase (Ye et al. 2011) and 11-hydroxysteroid dehydrogenases (Odermatt et al. 2006; Guo et al. 2012; Giulivo et al. 2016).

Among EDCs there are numerous compounds that exert an estrogenic effects. It is well known that estrogen is a female hormone but its role is not only to regulate female reproductive cycle but also to influence non reproductive organs regulating lipid metabolism, protein synthesis and behaviour (Kiyama and Wada-Kiyama 2015). So, estrogenic chemicals that mimick this endogenous female hormone are able to interfere with normal body homeostasis through different mechanisms. In fact, estrogenic signaling can be divided in intracellular and extracellular mechanism. The intracellular pathway involves genomic activation such as transcription of specific target genes, and non-genomic pathway through the activation of transduction signals mediated by membrane receptors (Kiyama and Wada-Kiyama 2015). The extracellular pathway, on the contrary, involves other hormones, growth factors and cytokines (Kiyama and Wada-Kiyama 2015). It is very difficult to identify all chemicals that act as estrogenic compounds since other EDCs can have multiple effects including estrogenic actions (For a list of several estrogenic chemicals, see Kiyama and Wada-Kiyama 2015 review). Considering the estrogenic compounds, it is important to specify that they have contradictory effects since they can behave as estrogen or anti-estrogen, agonist or antagonist of ERs. Often, it has been pointed out a biphasic activity, better depending of the dose they show an estrogenic or antiestrogenic activity. Anyway, they can show different cellular pathways (Kiyama and Wada-Kiyama 2015). This mechanism of action is often shared among different EDCs.

In order to describe a view of different molecular mechanisms, we have subdivided their targets in genomic, non genomic and non-receptorial pathways.

Genomic pathway

The genomic pathway is the main target of EDCs. This pathway starts with the binding of chemicals with the nuclear estrogen receptors (ERs). There are two different ERs: ERα and ERβ, both involved as transducer. They are encoded by different genes, respectively *ESR1* located at 6q25.1 and *ESR2* located at 14q23.2-q23.3 on human chromosomes. Even so, the receptor proteins share a common structural organization based on the presence of three functional domains: the A/B domain at the N-terminal region, involved in the transcriptional activation of ER target genes; the C domain responsible for the receptor dimerization and DNA binding; the E/F domain at the C-terminal region involved in the ligand binding, nuclear translocation and transactivation of target gene expression (Nilsson et al. 2001; Kiyama and Wada-Kiyama 2015). Both *ESR1* and *ESR2* show splice variants that are responsible of differences in the expression at cell or tissue level, in the specificity and/or affinity for a ligand, in the localization and function in the cells (Taylor et al. 2010; Kiyama and Wada-Kiyama 2015). Co-regulators and other transcriptional factors, such as Sp1 and AP1, are often needed for the transactivation of target genes (Kiyama and Wada-Kiyama 2015). The complex (endogenous or not) ligand - ER binds the DNA at specific site acting as transcription factor in order to up-regulate or down-regulate the transcription of target genes (generally bringing the Estrogen-Responsive-Elements) (Kiyama and Wada-Kiyama 2015). The change in ER conformation depending on the ligand bound, renders ERs more or less prone to the transcriptional coactivators or corepressors recognition (Acconcia et al. 2015). Very large amount of estrogenic chemicals (fungicides, herbicides, insecticides, several pharmaceutical estrogens, plasticizer, pollutants) use ERs as dealer to induce endocrine interference (Kiyama and Wada-Kiyama 2015). Among these, BPA has structural features that confer it the ability to bind to the both ERα and ERβ (Bolli et al. 2008; Bolli et al. 2010; Acconcia et al. 2015). BPA binding to ERs produces a displacement of α-helices of LBD of ERα due to a not proper accommodation in the hormone-binding site; so BPA can function as ERα agonist. On the contrary BPA is not able to bind the LBD of ERβ, acting as antagonist (Ascenzi et al. 2006; Acconcia et al. 2015). These

differences in the binding of the two ERs induce a varied regulatory activity on gene expression (Acconcia et al. 2015). Many other EDCs are able to bind ERs. It has been demonstrated that nonylphenol (NP) is able to induce cytoplasm to nucleus translocation of ERα but not ERβ in human epithelial prostate cells (Forte et al. 2016). This translocation induced ERα activation of transcription of specific genes such as cyclin D1 and ki67 that allow cell proliferation (Forte et al. 2016). Recently, another nuclear receptor family has been identified as part of estrogen signaling. This family includes some nuclear estrogen-related receptor such as ERRα, ERRβ and ERRγ. These "alternative" receptors act as ligand-dependent transcription factors but their natural ligand is still unknown. Several compounds prefer ERR pathways such as genistein and resveratrol, as well as chlordane, diethylstilbestrol and toxaphene that are ERR antagonists. In some case it is possible a crosstalk between ER and ERRs as demonstrated for resveratrol (Kiyama and Wada-Kiyama 2015). That's why nuclear receptor pathway is more complex and interlaced.

Non-genomic pathway

Estrogen or xenoestrogens can also bind to the membrane receptors stimulating signaling cascade through different protein involvement. Generally, the non-genomic pathway is very fast and rapidly occurs. Canonical ERα and ERβ can translocate to the membrane after the modification. Here, they bind to caveolin-1 after palmitoylation, after that they are translocated to the membrane and anchored as a dimer (Soltysik and Czekaj 2013; Kiyama and Wada-Kiyama 2015). It has been shown that this pathway is used by the cells to rapidly respond to hypothalamic stimulation (Micevych and Kelly 2012; Kiyama and Wada-Kiyama 2015). Endogenous estradiol (E2) activates ERα-mediated extracellular regulated kinase/mitogen-activated protein kinase (ERK/MAPK) and phosphatidyl-inositol-3-kinase/AKT (PI3K/AKT) pathways, as well as the ERβ-mediated p38/MAPK signaling (Acconcia and Marino 2011; Acconcia et al. 2015). It has been demonstrated that xenoestrogenic compounds such as BPA can activate ERK/MAPK and AKT phosphorylation (Bolli et al. 2008; Marino et al. 2012; Acconcia et al. 2015). Another EDC such as Arsenic (As) is able to interfere with estrogen signaling pathways (Watson and Yager 2007; Bae-Jump et al. 2008; Chatterjee and Chatterji 2010; Sun et al. 2016). Particularly, it has been shown that As interacts with the MAPK pathway (mitogen-activated protein kinase), which plays a crucial role in different cell functions such as cell growth, differentiation, survival, and death

(Chatterjee and Chetterji 2010; Sun et al. 2016). Moreover, it has been demonstrated that As suppresses the interaction of ERs with some transcription factors like Sp-1, AP-1 and NF-κB (Watson and Yager 2007; Sun et al. 2016).

Different membrane ERs (mERs) have already been identified such as G-protein coupled estrogen receptor (GPER). The mERs GPER, previously known as G-protein-coupled receptor 30 (GPR30), is encoded by the *GPER* gene located at chromosome 7p22.3. GPER is a 7-membran-spanning protein highly expressed in the hypothalamus, pituitary gland, adrenal medulla, renal pelvis and ovary (Hazell et al. 2009; Soltysik and Czekaj 2013; Kiyama and Wada-Kiyama 2015). GPER shows a high affinity for the endogenous estrogens and other hormones such as aldosterone (Kiyama and Wada-Kiyama 2015). GPER can be located at the membrane of endoplasmic reticulum, Golgi apparatus and can be also present in the nucleus (Soltysik and Czekaj 2013; Kiyama and Wada-Kiyama 2015). GPER activation induces rapid non-genomic signaling (Kiyama and Wada-Kiyama 2015). Different xenoestrogenic compounds have been demonstrated bind to the GPER such as BPA, diethylstilbestrol, genistein, NP and many others (Kiyama and Wada-Kiyama 2015). These compunds act as agonists to the GPER. Moreover, it has been demonstrated that GPER in involved in the signaling pathways mediated by other receptors like serotonin 1A receptor (Li et al. 2013c; Kiyama and Wada-Kiyama 2015). Particularly, it acts inhibiting serotonin 1A receptor (Xu et al. 2009; McAllister et al. 2012; Akama et al. 2013; Kiyama and Wada-Kiyama 2015). Moreover, GPER crosstalks with other signaling pathways involved in different cell functions such as proliferation (Ma et al. 2014), migration (Li et al. 2014a), collagen expression (Li et al. 2013a), NO synthesis (Rowlands et al. 2011), and inflammatory response (Luo et al. 2012; Santolla et al. 2014; Kiyama and Wada-Kiyama 2015). It seems evident that due to involvement of GPER in many different cell pathways involved in any stage of proliferation, differentiation and migration, that all the chemicals able to bind this receptor can deeply interfere with many cell and tissue important processes.

Other receptors, such as estrogen-related receptors (ERRs) that are variants of ERα and ERβ (for example ER-X and ER-α36) have been recently identified showing the broad complexity of estrogen responsive signaling (Kiyama and Wada-Kiyama 2015). Specifically, ER-X is a ERα splice variant; it is a 62-63 kDa membrane protein (Soltysik and Czekaj 2013; Kiyama and Wada-Kiyama 2015). Binding of estrogen to ER-X is associated in particular to the brain, uterus and heart functions. It has been

demonstrated that after binding, ER-X activate MAPK and ERK signaling (Toran-Allerand et al. 2002; Toran-Allerand et al. 2005; Ullrich et al. 2008; Kiyama and Wada-Kiyama 2015). Another ERα splice variant is ER-α36 is located at the membrane. This receptor lacks both AF-1 and AF-2 domais but present DNA-binding domain and partial ligand domain. It has been shown that ER-α36 is able to inibit both ERα and ERβ in a dominant-negative manner. This ability allows it to be involved in different carcinogenesis pathways such as testosterone carcinogenesis (Lin et al. 2009) and breast cancer (Rao et al. 2011; Kiyama and Wada-Kiyama 2015). Different cascade proteins can activated by ER-α36 such as MAPK/ERK, Akt, and c-SRC (Kang et al. 2011; Zhang et al. 2014c; Wang et al. 2013b; Kiyama and Wada-Kiyama 2015).

Both genomic and non-genomic pathways can be considered as direct signaling mechanisms that differently can induce many functional outcomes such as apoptosis, cell growth, differentiation, inflammation and carcinogenesis (Kiyama and Wada-Kiyama 2015). However, each pathway can influence other cellular outcomes by crosstalk and/or bypassing. Moreover, the direct signaling mechanisms also induce the secretion of autocrine/paracrine or endocrine factors enlarging the range of targets involved.

Epigenetic pathways

EDCs can also act through epigenetic mechanisms. Epigenetic mechanisms are particularly important to address the potential health effects of lower-level exposures within the general population; moreover it is useful to explain how EDC exposure during the development can cause adverse effects in the adult (Prusinski et al. 2016). It has been shown, for example, that genistein is able to induce epigenetic changes of non-genomic estrogen receptor (ER) signaling through the activation of the PI3K/AKT pathway (Prusinski et al. 2016). This phosphorylates histone methyltransferase Enhancer of Zeste Homolog 2 (EZH2), a potent epigenetic regulator of gene expression (Sandovici et al. 2013). Finally, this epigenetic pathway increases the overall expression of estrogen-responsive genes (Cook et al. 2005; Prusinski et al. 2016). Likewise, also BPA increases EZH2 that in turn increases histone H3 trimethylation at lysine 27 (Doherty et al. 2010; Santangeli et al. 2017). Furthermore, BPA was demonstrated to alter methyltransferase 1 and 3A which are epigenetic regulators of expression of genes encoding estrogen receptors (Kundakovic et al. 2013; Santangeli et al. 2017). BPA induces hypermethylation of estrogen promoter region in rat

testis (Doshi et al. 2011; Santangeli et al. 2017). Other studies have shown that BPA strongly increases the expression of the secretaglobin gene, *Scgb2a1*, by way of the increased enrichment of acetylated H3K9 and hypomethylation of DNA for a CpG island upstream of the transcription start site of *Scgb2a1* (Wong et al. 2015; Prusinski et al. 2016). SCGB2A1 is being an interesting marker of carcinogenesis, since its gene and protein overexpression is linked to endometrial, breast and lung cancers (Li and Richardson 2009; Prusinski et al. 2016).

Non receptorial pathways

Recently, different studies highlight other non nuclear receptor mediated pathways involved in estrogenic and xenoestrogenic actions. In fact, it is well known that natural hormones and xenoestrogens can also act by enzymatic and binding protein pathways (Mueller and Korach 2001; Sheikh et al. 2017). Particularly, sex steroids interact with plasma sex hormone-binding globulin (SHBG) that is a circulatory protein secreted by liver important in maintaining the balance between bioavalable and not avalaible hormones (Anderson 1974; Sheikh et al. 2017). Particularly, it has been demonstrated that the free portion of steroid hormones represents a small percentage, about 1-3% of the total steroids. Despite this low amount represents the bioactive portion for the target tissues (Hammond, 2011; Laurent and Vanderschueren 2014; Sheikh et al. 2017). The SHBG binds both androgens and estrogens with nanomolar affinity. SHBG has two subunits each containing two laminin G-like domains: the N-terminal domain presents the steroid-binding pocket and calcium and zinc binding sites; the C-terminal domain shows residues for glycosylation (Hammond 2011; Sheikh et al. 2017). It regulates hormonal free portion able to bind receptors that is important in clinical practice. Moreover, SHBG influences hormonal metabolic clearance (Hammond 2011; Sheikh et al. 2017). Alteration of SHBG function and/or amount has been associated with various human diseases such as ovarian dysfunctions, male and female infertility, endometrial cancer, diabetes, cardiovascular diseases (Cherkasov et al. 2005; Sheikh et al. 2017). Many different EDCs can bind SHBG, among these some alkylphenols such as BPA, NP, octylphenol (OP) have been shown binding ability (Dechaud et al., 1999; Jury et al., 2000; Cherkasov et al., 2008; Hong et al., 2015; Sheikh et al. 2017). Recently, it has been demonstrated that BPA, NP and OP have high structural similarity with endogenous hormones and for this they can strongly bind SHBG (Sheikh et al. 2017). Among three alkylphenols Sheikh et colleagues (2017) have seen that NP is the more potent endocrine disruptor of androgen and

estrogen signaling since it shows the most high binding affinity with SHBG (Sheikh et al. 2017). Binding of xenoestrogens to SGBG displaces endogenous testosterone and estradiol from SHBG steroid pocket in native plasma from men and women (Dechaud et al. 1999; Sheikh et al. 2017). In an other study, 125 structurally diverse compounds have been tested in competitive binding assay for SHBG and it has been shown that BPA, OP, and NP have a potential competing function (Hong et al. 2015; Sheikh et al. 2017). Xenoestrogenic binding to SHBG induce a lower clearance rate that allows a major accumulation of EDCs in the body. Moreover, in children during the prepubertal period (Apter et al., 1984; Belgorosky and Rivarola, 1986) and in women during pregnancy (Anderson 1974), SHBG levels are higher whereas testosterone and estradiol concentrations remain lower. Under such conditions, BPA, NP and OP ability to bing SHBG may affect the metabolism and tissue availability of natural steroids (Sheikh et al. 2017). This "new" EDC molecular target of endocrine disruption open a broad scenario of interference with steroid homeostasis in the human body.

EDCs and hypothalamus-pituitary axis

Thyroid gland

Another important field to consider in EDC pollution is the involvement and activation of other hormonal pathways, such as thyroid and adrenal glands. EDCs can impair thyroid system through different mechanisms: disruption of TH serum transporters such as transthyretin (TTR) and thyroxine-binding globulin (TBG), aberrant binding to TH nuclear receptors, or disruption of TH-metabolizing enzymes such as deiodinases (DIO) and sulfotransferase (SULT) (Aufmkolk et al. 1986; Meerts et al. 2000; Schmutzler et al. 2004; Kitamura et al. 2008; Kojima et al. 2009; Szabo et al. 2009; Butt et al. 2011; Butt and Stapleton 2013; Leonetti et al. 2016). Particularly, it has been demonstrated that different EDCs are able to negatively influence thyroid hormone levels (Zhou et al. 2002; Sciarrillo et al. 2010; Noyes et al. 2013; de Coch et al. 2014; Eisenreich and Rowe 2014; Yost et al. 2016). Several studies have demonstrated that prenatal exposure to thyroid hormone endocrine disruptors affect birth weight, can cause preterm births, other than affect the glucose and lipid metabolism (Molehin et al. 2016; Shah-Kulkarni et al. 2016). Infact, THs are known to be particularly important for fetal growth and development (Costa et al. 2014; Leonetti et al. 2016). Different interference pathways can be activated in alteration of thyroid functions.

For example, it has been hypothesized that perfluorinated compounds (PFCs) may increase the hepatic production of TBG (Knox et al. 2011). Other PFCs like perfluorooctane sulfonate (PFOS) may increase the thyroidal conversion of T4 to T3 via type 1 deiodinase (Yu et al. 2009; Shah-Kulkarni et al. 2016). Polybrominated diphenylethers (PBDEs) and other halogenated compounds (Butt et al. 2011; Butt and Stapleton 2013; Leonetti et al. 2016) are able to inhibit the activities of TH-metabolizing enzymes so impacting the placental TH concentrations and fetal TH delivery (Leonetti et al. 2016). Other compounds such as As alters thyroid hormone production. Particularly, it has been shown that after consuming diet containing As for 15 weeks, plasma levels of T3 and T4 are decreased while the ratios of T4/T3 are increased (Meltzer et al. 2002; Sun et al. 2016). Moreover, Ciarrocca et al. (2012) have shown an increase of the levels of thyroid stimulating hormone (TSH) and thyroglobulin and a decrease of free T4 and T3 contents (Ciarrocca et al. 2012; Sun et al. 2016). Opposite effects were seen in rats where feeding food containing As increases T3 levels and decreases T4/T3 ratios (Glattre et al. 1995). As thyreotoxicity is related to alteration of TR-related gene expression. Particularly, AsIII inhibites the activity of thyroid peroxidase, a major enzyme involved in the synthesis of T4 and T3 (Palazzolo and Jansen 2008; Sun et al. 2016). Thyroid disruption has been demonstrated also in different animal models. It has been shown that PBDEs are able to disrupt thyroid hormone signaling in *Xenopus laevis* tadpole (Yost et al. 2016). Specifically, Yost and colleagues have demonstrated that 2,2',4,4'-tetrabomodiphenyl ether (BDE-47) specifically alterate transcriptomic expression of thyroid hormone-related genes (Yost et al. 2016). BDE-47 reduces expression of *trα, trβ* and *tshβ* and decreases thyroid hormone plasma levels (Yost et al. 2016). Moreover, BDE-47 influences also thyroid hormone transport; in fact it suppresses expression of two thyroid hormone transporters *mct8* and *oatp1c1* (Yost et al. 2016). In fish, AsIII significantly increases the levels of T4 (Sun et al. 2015; Sun et al. 2016). On the contrary, in *Podarcis sicula* lizards, NP induced a significant decrease of TSH, T4 and T3 plasma levels and affected histological features of lizard thyroid (Sciarrillo et al. 2010).

Adrenal gland

Another important organ in the control of endocrine homeostasis is the adrenal gland. Adrenal gland plays a role in the body response mechanisms

to stress, maintaining the homeostasis of the organism (De Falco et al. 2014). Despite its relevance in the body physiology, relatively few studies have investigated the possible/existing links between endocrine disruptors and the HPA axis (De Falco et al. 2007; De Falco et al. 2010). Recently, it has been demonstrated that As significantly increases ACTH and corticosterone levels in rodents (Jana et al. 2006; Sun et al. 2016). Particularly, it has been shown that As is able to reduce levels of corticotropin-releasing factor receptor 1 and to potentiate binding between serotonin and serotonin 5-hydroxytriptamine receptor (Martinez et al. 2008). Moreover, As acts on glucocorticoid receptors (GRs). Specifically, it has been demonstrated that AsIII can modify GR activity blocking steroid binding to GRs (Lopez et al. 1990; Kaltreider et al. 2001; Sun et al. 2016). Recently, Ahir et al. (2013) have demonstrated that AsIII has a biphasic effect on GR function depending of its dose. At low dose, AsIII enhances glucocorticoid induction of GR-regulated genes, whereas at high dose it disrupts GR gene transcription interfering with hormone receptor binding (Ahir et al. 2013; Sun et al. 2016). Other EDCs are able to interact with GR system. For example, it has been demonstrated that polychlorinated biphenyls (PCBs) downregulate brain GR expression in fish (Aluru et al. 2004; Nesan and Kurrasch 2016). Other compounds have seen to act on HPA axis. Among EDCs, NP was shown to strongly stimulate the whole HPA axis inducing a time-dependent stimulation of CRF, ACTH and corticosterone release in reptile bioindicator *Podarcis sicula* lizards (De Falco et al. 2014). Moreover, NP was able to induce histological changes of adrenal glands with the presence of totally degranulated chromaffin cells (De Falco et al. 2014). Another class of potent environmental pollutant are dioxins that comprises 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This compound has shown to reduce CRH mRNA in hypothalamus of monkeys (Shridhar et al. 2001; Nesan and Kurrasch 2016).

Conclusion

EDCs are compounds of different chemical nature and are widely disseminated in the environment in which we live. This causes the exposure of human and animal populations to occur at any time of life and at different doses. One characteristic of EDCs is their ability to act at very low concentrations, interacting with hormone systems and altering the homeostasis of different organs and systems. It is also evident that a precise and unambiguous classification is practically impossible since many of them

have biphasic behaviors and are capable of activating different molecular pathways depending on the cellular system considered. This particular feature focuses on the behavior of EDCs that we are constantly exposed to in which individual compounds may be present, each with different activity, which in combination can trigger synergies that lead to complete and profound endocrine destruction and all systems connected to it. For this reason, the understanding of the molecular mechanisms that EDCs can activate is of paramount importance to orient themselves in the endocrine interference they have determined and to try to stem the large amount of related pathologies.

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