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Full Length Research Paper

Endocrine disruption induced by triorganotin (IV) compounds: Impacts in the reproductive and genetic function

V. S. Delgado Filho[1], C. N. Mancini[1], I. V. Silva[1], D. F. Pedrosa[1,2], A. C. Destefani[1], V. Y. Samoto[3], C. M. Takiya[3] and J. B. Graceli[1]*

[1]Ageing Cell Biology Laboratory, Department of Morphology, Health Sciences Center, Federal University of Espírito Santo, Vitória, ES, Brazil.
[2]Department of Pharmaceutical Sciences, Health Sciences Center, Federal University of Espírito Santo, Vitória, ES, Brazil.
[3]Institute of Biomedical Sciences, Federal University of Rio de Janeiro, RJ, Brazil.

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Organotin compounds, such as tributyltin (TBT) and triphenyltin (TPT), are typical environmental contaminants and suspected endocrine-disrupting chemicals because they cause irreversible sexual abnormality (masculinization) in female mollusks, called "imposex". However, it remains unclear whether organotin compounds also cause crucial toxicities in mammalian, including in human and rodents, in their sexual development and reproductive functions. Moreover, these compounds can act as potential competitive inhibitors of aromatase enzyme or others steroidogenic enzymes and recently, it was identified as agonists for retinoid X receptor (RXR) and peroxisome proliferator-activated receptor (PPAR)γ, which are members of the nuclear receptor superfamily. *Gene* expression of human aromatase is regulated by the activation of PPARγ and/or RXR. In this review, the authors provide a discussion of the cellular, biochemical, and molecular mechanisms by which organotin compounds may cause adverse effects in the modulated *genes* involved in reproductive function.

Key words: Organotin, endocrine disruptor, aromatase, mammalian reproductive function.

INTRODUCTION

Organotin compounds (OT), such as tributyltin (TBT) and triphenyltin (TPT), have been widely used as biocides, agriculture fungicides, wood preservatives, and disinfecting agents in circulating industrial cooling waters, as well as antifouling paints for marine vessels (Fent, 1996; Swennen et al., 2009). Due to its widespread use as an antifouling agent in boat paints, OT are a common contaminant of marine and freshwater ecosystems exceeding acute and chronic toxicity levels (Nakanishi, 2008). OT is one of the most significant pesticides in marine and freshwaters and consequently its environmental level, fate and toxicity are of current concern (Fent, 1996; Nakanishi, 2008).

The OT has the general formula R_nSnX_{4-n}, where R is an alkyl group, X is an anion, and varies between 1 and 4. OT compounds can belong to any of four classes, related to the number of organic groups, namely tetraorganotins, triorganotins, diorganotins and monoorganotins (Davies, 2004). The TBT compounds are organic derivatives of tetravalent tin, which belongs to triorganotin class of OT, they have the general formula $(C_4H_9)_3Sn$-X (where X is an anion). Moreover, the TBT compounds include: tributyltin hydride; tributyltin oxide; tributyltin benzoate; tributyltin chloride; tributyltin fluoride, among others. In sea water and under normal conditions,

*Corresponding author. E-mail: jbgraceli@ccs.ufes.br, jbgraceli@gmail.com. Tel: +55-027-33357369. Fax: +552733357358.

Abbreviations: RXR, Retinoid X receptor; **(PPAR)γ,** peroxisome proliferator-activated receptor; **OT,** Organotin compounds; **TBT,** tributyltin; **TPT,** Triphenyltin.

TBT exists as three species (hydroxide, chloride, and carbonate), which remain in equilibrium (Poller, 1970).

The TPT compounds also belong to triorganotin class of organotin compounds, with the general formula $(C_6H_5)_3Sn$-X, where X is an anion or an anionic group, such as chloride (TPTCl), hydroxide (TPTH), and acetate (TPTA) (Poller, 1970). There are many reports of the biological effects of OT, which vary in their toxic effects on eukaryotes (Fent, 1996; Takahashi et al., 1999; Lahbib et al., 2008; Meng et al., 2009). These compounds are potent endocrine disrupters in marine invertebrates (Costa, 2008a, b; Limaverde et al., 2007), mainly, but not exclusively, in gastropod mollusks. For example, very low concentrations of TBT and TPT induce irreversible sex-organ alterations in females, a phenol-menon known as "imposex" (Mathiessen and Gibbs, 1998). These endocrine abnormalities are the result of a masculinization process by which male sex organs are developed, notably a penis and a vas deferens, in female animals, that could lead to sterility and death of affected females (Shi et al., 2005). In certain species, growth of a vas deferens disrupts the structure and function of oviducts, impairing normal breeding activity and causing population decline (Nakanishi, 2008). In addition, it had been reported in more than 190 marine species (Shi et al., 2005; Nakanishi, 2008) and has been considered as the most important endocrine disruption effect derived from a specific class of compounds (Snoeij et al., 1987; Mathiessen and Gibbs, 1998). This high specificity makes this syndrome a useful biomarker of organotin pollution (Snoeij et al., 1987; Fernandez et al., 2002; Fernandez et al., 2005a; b). Besides gastropods, organotins have been implicated in inducing hormonal alterations in bivalve mollusks (Alzieu, 1986; Morcillo and Porte, 2000; Siah et al., 2003), in crustaceans (Tang et al., 2009; Aono and Takeuchi, 2008) and fish (Mortensen et al., 2007).

Based on *in vitro* studies, human choriocarcinoma cell lines exposure to 300 nM TBT chloride or TPT hydroxide markedly decreased protein synthesis, due to cytotoxicity (Nakanishi et al., 2002). Another study performed by the same group confirms the noncytotoxic concentration ranges of 17 tin compounds. DNA synthesis was evaluated by [^{3}H] thymidine incorporation. Trialkylated and triarylated tin compounds were highly toxic and exposure to > 100 - 300 nM significantly inhibited [^{3}H] thymidine incorporation and the comparison between different fourth functional groups on the tin of TBT and TPT showed similarity in toxicity. Tin chloride ($SnCl_4$) and Butyltin trichloride ($MBTCl_3$) showed no effect, even at concentrations of 10 mM (Nakanishi et al., 2006). The toxicity of organotin compounds varies considerably with the number and nature of organic groups and usually decreases in the order tri-(R_3SnX)> di-(R_2SnX_2) > mono-($RSnX_3$) organotins, while tetraorganotins (R_4Sn) have low toxicity, as also showed by another group (Godoi et al., 2003). The number of Sn-C bonds has a large effect on the properties of OTs and the increase in toxicity may be related to the insolubility of the compounds in water and the maximum biological activity occurs in the triorganotin class (Godoi et al., 2003; Xanthopoulou et al., 2003).

Unfortunately, these OT are also suspected to cause endocrine-disrupting effects in mammals (Konstanze et al., 2006), including humans (Kannan, 1995; Keithly et al., 1999) and rodents (Grote et al., 2004; Grote et al., 2006), due to part of the possibility of transferring through marine food chains by consumption of contaminated sea-food (Tanabe, 1999; Dorneles et al., 2008). At 300 nM concentration range, TPT also inhibit the catalytic activity of human aromatase (Takayanagi and Nawata, 2001; Lo et al., 2003) and others steroidogenic enzymes, affecting sexual development in male (Omura et al., 2001; Grote et al., 2004) and female rats (Ogata et al., 2001). Therefore, OT clearly has many complex actions in endocrine system at both genders, which explains the information on their relative dangers.

ORGANOTINS AS ENDOCRINE-DISRUPTING CHEMICALS

The production of sex hormones steroids from cholesterol requires trafficking between mitochondria and smooth endoplasmic reticulum, and involves many enzymatic steps (Whitehead and Rice, 2006). Most of these pathway use cytochrome P450 (CYP) haem-containing enzymes are abbreviated to CYP (Figure 1). Some OT are known as encoding-disrupting chemicals to change steroid hormone biosynthesis (Bettin et al., 1996; Matthiessen and Gibbs, 1998). As mentioned above, these OT have been suspected to masculinize reproductive organs in vertebrates because, in some gastropods, very low concentrations of these organotins induce "imposex" (Horiguchi et al., 1997; Matthiessen and Gibbs, 1998). Some evidences have theorized that these OT act as a specific inhibitor of aromatase enzyme which con-verts androgen to estrogen (Bettin et al., 1996; Matthiessen and Gibbs, 1998). For example, exposure to OT increase testosterone levels in female gastropods and organotin-induced imposex can be mimicked by specific inhibitor of aromatase (Bettin et al., 1996). In addition, TBT was reported to be catalyzed to dibutytin, which is a metabolite of TBT, by aromatase enzyme (Lee, 1985). However, it remained unclear whether OT especially inhibits catalytic activity of aromatase in vertebrates.

In others experiments, butyltins were demonstrated to exhibit structure-related inhibition of the catalytic human aromatase protein from human placenta cell line (Heidrich et al., 2001) or transfected cells (Cooke, 2002). However, at effective concentrations (micromolar level) for the inhibition of aromatase, TBT and TPT are gene-rally toxic to mammalian cells because they cause apop-tosis or necrosis (Saitoh et al., 2001; Nakanishi et al.,

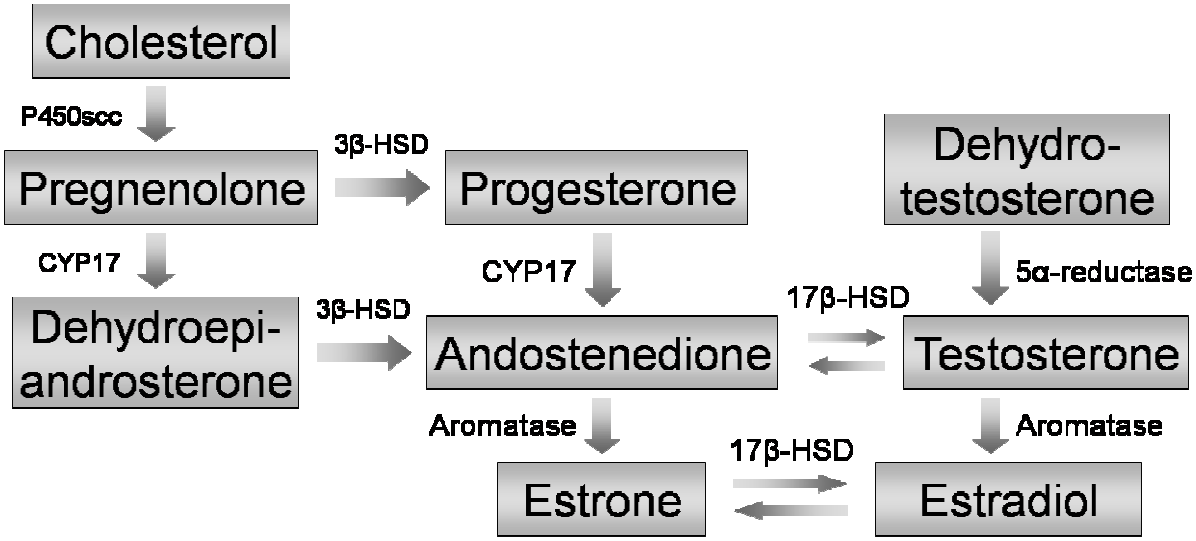

Figure 1. Pathway of steroid hormone biosynthesis whose enzymatic actions can be altered by organotin compounds. Cholesterol side-chain cleavage enzyme complex (P450scc); Cytochrome P450 (CYP, as 17α-hydroxylase and 17,20-lyase, respectivaly); 3β-hydroxysteroid dehydrogenase (3β-HSD); 17β-hydroxysteroid dehydrogenase (17β-HSD). Figure modified from Ref. Nakashima et al. (2008).

2006). In human choriocarcinoma cell lines, Jar, JEG-3 and BeWo, exposure to be greater than 300 nM TBT or TPT markedly decreases DNA and protein synthesis (Nakanishi et al., 2002; Nakanishi et al., 2006). Concentrations under 1 µM of either OT did not significantly affect aromatase activity in microsomes isolated from human choriocarcinoma cells (Nakanishi et al., 2002). In addition to aromatase, at above 1 µM, TBT inhibit the catalytic activity of human 5*α*-reductase I and II (5*α*-R I and II) (Doering et al., 2002), rat 3*β*-hydroxysteroid dehydrogenase (3*β*-HSD) (McVey and Cooke, 2003) and pig 17*β*-hydroxysteroid dehydrogenase I(17*β*-HSD I; Ohno et al., 2005). At same concentrations ranges, TPT also inhibit the catalytic activity of human aromatase, 5*α*-R II, 17*β*-HSD I and III (Lo et al., 2003). These observations suggest that these OT at micromolar level not specifically inhibit the catalytic activity of aromatase and they have to consider the toxicity of OT in distinguishing between nonspecific toxicity to cells and the specific inhibition of steroidogenic enzymes.

In addition, gonadal steroid receptors and steroidogenic enzymes for sex steroid hormones have not yet been identified in gastropods, and it remains unclear whether sex steroid hormones are critical factors for sexual maturation in gastropods. Furthermore, homologues of both the estrogen receptor (ER) and androgen receptor (AR) have not been found in invertebrates (Escriva et al., 2000) and the composition of nuclear receptor family members is very different between vertebrates and invertebrates (Escriva el al., 1997). Therefore, there are some doubt as to whether OT function as inhibitors of enzyme that metabolize androgens in gastropods and this doubt led us to suspect that organotin compounds affect other target molecule in mammals.

ORGANOTINS AFFECT ENDOCRINE FUNCTIONS IN MAMMALIAN GONADAL SYSTEM

Sexual differentiation is a sequential process beginning with the establishment of chromosomal sex at fertilezation, followed by the development of gonadal sex, and culminating in the development of secondary characteristics, collectively termed the male and female phenotypes (Filicore et al., 1986). The endocrine system reflects deeply at the reproductive morphophysiology most likely due to specifics *genes* and gonadal steroids actions and endocrine/paracrine pathways (Figure 2) on the gonadal system (Lim and Hawkins, 1998; Piprek, 2009). Moreover, it also been shown that exerts different effects on either males or females (Piprek, 2009), that are time and dose dependents of exposure to toxic effect of OT. Studies suggested that potential toxicity of OT in mammalian, that include human and rodents, are endocrinophatic, as well as potential toxicity reproductive, teratogenic and developmental (Nakanishi, 2008), in both genders (Omura et al., 2001; Grote et al., 2004, Grote et al., 2006).

Female reproductive system

The production of germ cells is essential for the continuation of a species. This function, in the female, is accomplished by the ovaries. In addition, the ovaries secrete steroidal (mainly progesterone and estradiol) and nonsteroidal hormones, as relaxin, that not only stimulate

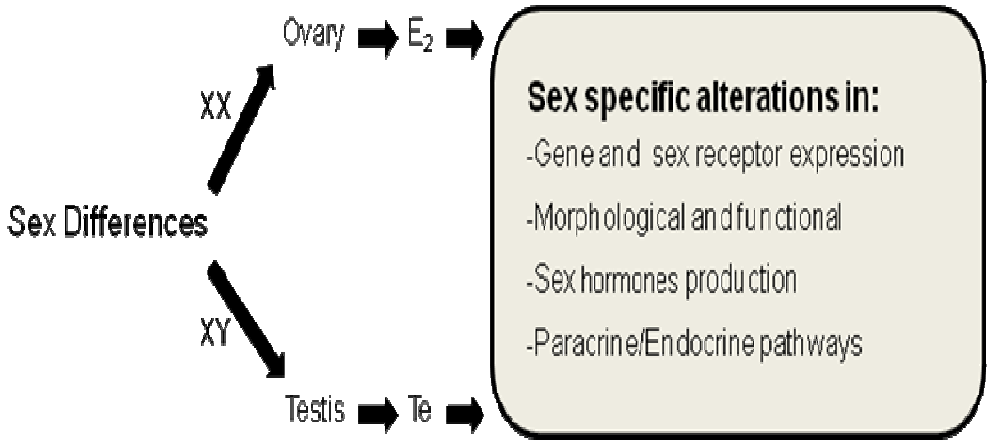

Figure 2. Mechanisms underlying sexual dimorphism by genetic, gonadal sex and differences actions the sex hormones. The sex steroids (estradiol and testosterone) can be alterations directly in gene expression, endocrine/paracrine pathways, morphologic development and functional, and ultimately phenotype, specifically; whereas changes directly influence physiological function, with sex development. X, Y: sex chromosomes; E_2: estradiol; Te: testosterone

the secretion of anterior pituitary hormones but also act on various targets on female reproductive system´s organs (Filicore et al., 1986). A number of studies have showed that exposure to OT and sea food contaminated by organotin cause reproductive disrupting in mammalian reproductive female system (Harazono et al., 1996; Ema et al., 1997; Ema et al., 1999; Ema, 2000; Omura et al., 2001; Ogata et al., 2001; Nakanishi et al., 2002; Grote et al., 2004; Hirose et al., 2004; Nakanishi et al., 2005; Grote et al., 2006; Konstanze et al., 2006). After treatment with organotin in pseudopregnant rats, decreased in uterine weight and serum progesterone levels were shown. It is correlated with decreased of pregnancies rate and number of embryologic implantations (Ema et al., 1997; Ema et al., 2000; Ema et al., 2002).

In mammalian, others works have shown that *in utero* exposure to high doses of TBT led to decreased on maternal weight gain and fetal weights, induced pre- or post-implantation losses (Adeeko et al., 2003; Ema et al., 1995; Harazono et al., 1998), and caused fetal toxicity (Itami et al., 1990), altered anogenital distance in both postnatal day 1 female pups (Ogata et al., 2001), gestational day 20 male rat fetuses (Ema et al., 1997) and reduced, in the ovaries of fetal female rats (20 mg/kg, days 0 - 19; 10 mg/kg, days 8 - 19), the number of germ cells by 44 and 46%, respectively (Kishta et al., 2007).

Based on genetic analysis, the TBT and the TPT increased the catalytic activity of aromatase and 17*β*-HSD I enzymes, which converts low-activity estrone to high-activity estradiol in human choriocarcinoma cells (Nakanishi et al., 2006) along with their mRNA expression in a dose-dependent fashion following exposure to nontoxic concentration ranges (Nakanishi, 2008), indicating the regulation of mRNA levels of both steroido-genic enzymes, not of enzyme complex. However, the TBT and the TPT suppressed both activity and *gene* ex-pression of aromatase enzyme in the human ovarian granulose-like cell line (Saitoh et al., 2001). This discre-pancy in the action of OT on the *gene* expression of human aromatase is due to the tissue-specific expression of aromatase, which is strictly regulated in each type cell (Nakanishi, 2008).

Male reproductive system

Several studies addressing the effect of TBT on male reproductive functions that have been reported (Adeeko et al., 2003; Chen et al., 2008; Grote et al., 2004; Konstanze et al., 2004; Kim et al., 2008; Kishta et al., 2007; Makita and Omura, 2006; Omura et al., 2001; Wang et al., 2006; Yu et al., 2003a; b; Zhang et al., 2009a; b). A study conducted during two generations showed that weight of the testis, epididymis and ventral prostate weights decreased in all groups, but mainly in the 125 ppm. However, no reduction was observed in weight of the seminal vesicle in F1 generation. Unfortunately, the effects on F2 generation compared with those in the F1 generation are greater (Omura et al., 2001). Despite this effect, some studies showed significant decreased in weight of the seminal vesicle (Yu et al. in 2003b; Grote et al., 2004) and in all weights of repro-ductive organs at 15 mg TBT/Kg bw (Grote et al., 2004). The caudal epididymal and testicular sperm (Yu et al., 2003a) and homonization-resistent spermatid (Omura et al., 2001) counts were decreased, and some of motion kinematic parameters of sperms from vasa deference were reduced too (Yu et al., 2003a).

Based on histopathological analysis, TBT causes changes in testes, included vacuolization of seminiferous epithelium, delayed spermiation, spermatide retention in

the epithelium and germ cell degeneration near the basement membrane Frequencies were low in F1 generation, but in F2 generation these are greater and considered abnormal (Omura et al., 2001). Increase of detached debris and sloughed cells were observed in the tubules of epididymis, and seminal vesicle was narrowed and become occupied with epithelial cells (Yu et al., 2003b). A large number of evidences indicate that *in utero* exposure to OT (Adeeko et al., 2003; Makita and Omura, 2006; Kishta et al., 2007) has a different pattern of response by pre- and postnatal offspring. There was reduce in number of Sertoli cells and gonocytes, a large intracellular space between those cells and an increased abundance of lipid droplets in the Sertoli cells (Kishta et al., 2007). Furthermore, in the intertubular region between adjacent interstitial cells, this study revealed abnormally dilation on endoplasmatic reticulum in Sertoli cells and gonocytes; immunostaining for connexin 43, the gap junctional protein, was reduced or absent in treated rats (Kishta et al., 2007).

Additionally, the body weights of the male offspring were decreased, and growth retardation and delayed ossification on the fetal skeleton were found after TBT *in utero* exposition of rats, without direct effects on male reproductive system (Adeeko et al., 2003; Makita and Omura, 2006). However, decreased concentrations of thyroxine and triiodothyronine (Adeeko et al. 2003) in serum, was also observed in another study (Zhang et al., 2009a), and associated with large damage on thyroid gland, and low expression of thyroid hormone receptor alpha in marine fishes' testes. Also, exposure has caused interstitial fibrosis and pyknotic nuclei. Results implied that inhibition of thyroidal status induced by TBT possibly affect testicular development. Similarly, after contact of TBT, the gonadosomatic index had decreased in a dose-dependent manner (Zhang et al., 2009b). Furthermore the level of 17β-estradiol was decreased and result in a down-regulation of estrogen receptor alpha mRNA, which in addiction with enlargement of lipid droplets, may contribute for Sertoli cells dysfunction, leading to disrupted spermatogenesis (Zhang et al., 2009b).

In the same line of investigation, *in vitro* analysis demonstrated that TBT enhanced the chance of occur apoptosis on Leydig cells, in a time- and dose-dependent manner (Wang et al., 2006). It's probably mediated by increase of Ca^{2+} cytoplasmic concentration. Immature male mice given a simple administration of TBT presented lumen formation in seminiferous tubule delayed and increased number of apoptotic germ cells inside tubules, whereas was not signal of apoptotic Leydig cells (Wang et al., 2006). Reduced serum testosterone concentration (Wang et al., 2006; Zhang et al., 2009a,b; Grote et al., 2004) and down-regulated expressions of the mRNAs for P450 scc (Cholesterol side-chain cleavage enzyme complex), P450 (For example, 17α-hydroxylase), 3β-HSD and 17β-HSD were also observed (Kim et al., 2008; Chen et al., 2008). Indeed, others works had related increase of serum testosterone (Omura et al., 2001).

POTENTIAL TOXICITY BY ORGANOTINS THROUGH AROMATASE *GENE* AND PPARY OR RXR RECEPTOR MODULATION IN MAMMALIAN

Nuclear receptors play important roles in maintenance of endocrine system, regulation of organ differentiation, fetal development, stimulate the cell growth and modulate the synthesis of specific proteins (Carson-Jurica et al., 1990; Glass, 1994; Norman et al., 2004). Reproductive abnormalities in wildlife can be associated with exposure to environmental pollutants capable of mimicking the action of natural hormones or cause changes in their enzymatic pathways (Nakashima et al., 2008).

The hormones exert theses actions on target cells after binding to specific receptors (Carson-Jurica et al., 1990; Glass, 1994; Norman et al., 2004). As the nuclear recaptors of intrinsic hormone systems are likely to be targets of industrial chemicals, information on their ability to bind these chemicals is valuable for environmental risk assessment (Nakanishi, 2008). All nuclear receptors members are consist as ligand-activated transcription factors with a conserved domain structure: (1) DNA binding domain (DBD) for anchoring the protein to specific DNA sequences, hormone response elements (HREs), (2) ligand-binding domain (LBD) for binding of small lipophilic molecules and (3) transactivation domain for activating the basal transcriptional machinery (Mangelsdorf and Evans, 1995; Evans, 1988). Retinoid receptors belong to the family of nuclear hormone receptors, which includes steroid hormone, vitamin D receptors, receptors activated by intermediary metabolites: for example, peroxisome proliferator-activated receptor (PPAR) by fatty acids, and pregnane X receptor (PXR) by xenobiotics (Hollenberg et al., 1985; Green et al., 1986; Issemann et al., 1993). There are three important play roles' RXR in nuclear signaling. First, they can bind to their own response element (RXR response element) as a homodimer and activate transcription in response to their ligands, and on the other hand, they serve as partners for other nuclear receptors (Giguere, 1994; Chambon, 1996; Aranda and Pascual, 2001). Second, the RXR/ retinoic acid receptor (RAR) heterodimer exhibits conditional permissively because a full response to RXR agonists occurs only in the presence of an RAR agonist (Westin et al., 1998; Germain et al., 2002). Third, the nonpermissive heterodimer, such as the RXR/thyroid hormone receptor and RXR/vitamin D receptor, which cannot be activated by RXR agonists regardless of the presence (or absence) of the agonist of its partner receptor; formation of the heterodimer is thought to actually preclude the binding of the ligand to RXR (Forman et al., 1995).

A large number of evidences indicate that TBT and

TPT were potential agonists of RXR and PPARγ (Sun et al., 1998; Kanayama et al., 2005; Nakanishi et al., 2005; Kanayama et al., 2005). The effectiveness of each OT was comparable to that of the natural ligand of RXR, 9-cis retinoic acid (9cRA) or the well-known PPARγ ligand rosiglitazone (Kliewer et al., 1992; Kanayama et al., 2005). The dose ranges of TBT and TPT that induced transactivation were from 10 - 100 nM, which do not cause significant apoptosis or necrosis of mammalian culture cells in general (Nakanishi, 2008). Moreover, the characterization of OT as RXR agonists has shown that binding of these OT to RXR and the responsiveness of the receptor depends on both the number and structure of the alkyl and aryl groups (Nakanishi et al., 2005). To understand how the toxicity of OT occurs via nuclear receptor signaling, researchers investigated the structure dependent binding of TBT and TPT compounds to PPARγ and their ability to activate the receptor. In competition assays, both TBT and TPT competed with [^{3}H]Rosiglitazone (Rosi, a PPARγ agonist drug), and [^{14}C]TPT, but TPT was more competitive for both [^{3}H]Rosi and [^{14}C]TPT than TBT; an approximately 10-fold lower concentration of TPT (10nM) than of TBT (100nM) was needed to elicit similar responses (Hiromori et al, 2009). The di and monosubstituted organotins DBT and MBT provided no significant activation, whereas DPT and MPT were moderately active in the micromolar range (Hiromori et al, 2009). Those results indicate that phenyltins are more potent for both binding and activating PPARγ than butyltins. Results also suggest that the presence of a fourth alkyl group on the tin atom decreases the potency of the organotin compounds for PPARγ, and, as with RXR, the order of potency is tri> tetra>di> mono-substituted (Hiromori et al, 2009).

In addition, OT simulated the transactivation of an RXR homodimer and PPARγ/RXR heterodimer at non-toxic concentration ranges (10-100 nM), whereas they had no effect on the transactivation of RXR/TR and RXR/RAR heterodimers (Nakanishi et al., 2005). Although the effects of OT on the transactivation of permissive RXR heterodimers other than PPARγ/RXR have not been determined, it is probably possible to stimulate the transactivation of other heterodimers because these compounds function as RXR agonists Nakanishi, 2008). Previous studies have demonstrated that gene expression of human aromatase is regulated by the activation of PPARγ and/or RXR (Sun et al., 1998; Mu et al., 2000; Nakanishi et al., 2005; Fan et al., 2005). In the human placenta, a selective RXR ligand stimulates aromatase *gene* expression and increase mRNA expression of aromatase in human choriocarcinoma cells; however, a selective PPARγ ligand has little or no effect on aromatase gene expression (Sun et al., 1998; Nakanishi et al., 2005).

Distinct in the placenta, both RXR- and PPARγ-selective ligand suppress aromatase gene expression in the ovary (Mu et al., 2000; Fan et al., 2005). However, it was suggested that PPARγ/RXR may inhibit promoter II lying upstream of the ovarian major exon I (PII) by an indirect mechanism because of the absence of a PPARγ/RXR response element in promoter II of aromatase (Mu et al., 2001). A transcriptional factor, nuclear factor-κB (NF-κB), interacts with the ovarian promoter II sequence of aromatase and up-regulates its gene expression in the human ovary. Besides, activation of the PPARγ/RXR heterodimer interferes with the interaction between NF-κB and promoter II sequence of aromatase (Fan et al., 2005). The PPARγ/RXR´s relationship, in the ovary, may regulate aromatase gene expression via the NF-κB signaling pathway (Nakanishi, 2008). In light of these findings, human aromatase expression regulated by OT may involve the activation of PPARγ/RXR and/or RXR (Saitoh et al., 2001; Nakanishi et al., 2002; Nakanishi et al., 2005), because the aromatase expression pattern induced in the human placenta and ovary by activations of PPARγ/RXR and/or RXR is similar to that induced by OT (Nakanishi et al., 2005).

The PPARγ is activated by a variety of fatty acids and a class of synthetic antidiabetic agents, thiazolidinediones (Lehmann et al., 1995). PPARγ agonists are used to treat type II diabetes and reverse insulin resistance in the whole body by sensitizing the muscle and liver tissue to insulin. In addition, PPARγ also serves as an essential regulator of adipocyte differentiation and lipid storage in mature adipocytes (Tontonoz et al. 1994). Unfortunately, the adipogenic activity of PPARγ may result in undesirable effects such as obesity. RXR agonists also activate the PPARγ/RXR heterodimer and act as insulin-sensitizing agonists in rodents (Mukherjee et al., 1997), underscoring the potencial effects of both PPARγ and RXR agonists on diabetes and obesity. For example, the OT stimulates the differentiation of pre-adipocyte 3T3-L1 cells into adipocytes (Kanayama et al., 2005). These results suggested that OT are a potential obesogen. A recent study, *in vivo,* showed that, acute exposure to TBT in adult mice resulted in coordinate regulation of lipogenic PPARγ/RXR target gene expression in adipose tissue and liver, and modulated adipocyte differentiation factors and sterol regulatory element-binding protein (Grün et al., 2006). Furthermore, developmental exposure *in utero* led to a fatty liver (hepatic steatosis) phenotype and enhanced lipid staining of neonatal fat deposits, and resulting in a significant increase in the epididymal fat pad size of mice later in life (Grün et al., 2006). Whether this occurs through increased lipid storage, an increase in adipocyte number, or a combination of both is currently unresolved. However, activation of PPARγ/RXR induced by OT represents a compelling mechanistic example of a class of environmental pollutants that have the ability to impact key adipogenic factors, fat deposit size and function.

On the other hand, the RXR agonist bexarotene cause clinically significant hypothyroidism in patients with cutaneous T-cell lymphoma (Duvic et al., 2001), and experimental exposure of rats (a selective RXR agonist)

induces the acute phase of hypothyroidism (Liu, et al., 2002). Yamabe et al. reported that TBT and TPT enhance the proliferation of androgen-dependent human prostate cancer cells and the transactivation of AR (Yamabe et al., 2000) and those OT does not function as AR agonists in a yeast two-hybrid system.

Conclusions

Several studies revealed that exposure to OT alters development and sexual parameters of reproductive system in gastropods, acting as endocrine disruptors, influencing the steroidal metabolism, mainly inhibiting the enzymatic activity of aromatase. These endocrine abnormalities are known as imposex. The OT induced in endocrine system toxic effects in mammals changing the *gene* expression of aromatase in different cell lines and animals models. Moreover, there are others steroidogenic enzymatic pathways that can be impaired by OT. These OT´s effects were associated a both gender-specific alterations in reproductive organs. In addition to these, the organotin-induced change in PPRAγ and/or RXR may cause a lot of toxic effects in gastropods, suggesting novel mechanism for organotin-induced toxic effects in human cells and experimental animals.

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