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Review article

Organotins in obesity and associated metabolic disturbances

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ABSTRACT

The objective of the present study was to review the mechanisms of organotin-induced adipogenesis, obesity, and associated metabolic disturbances. Peroxisome proliferator-activated receptor γ (PPARγ) and retinoid X receptor α (RXRα) activation is considered as the key mechanism of organotin-induced adipogenesis. Particularly, organotin exposure results in increased adipogenesis both in cell and animal models. Moreover, transgenerational inheritance of organotin-induced obese phenotype was demonstrated *in vivo*. At the same time, the existing data demonstrate that organotin compounds (OTCs) induces aberrant expression of PPARγ-targeted genes, resulting in altered of adipokine, glucose transporter, proinflammatory cytokines levels, and lipid and carbohydrate metabolism. The latter is generally characterized by hyperglycemia and insulin resistance. Other mechanisms involved in organotin-induced obesity may include estrogen receptor and corticosteroid signaling, altered DNA methylation, and gut dysfunction. In addition to cellular effects, organotin exposure may also affect neural circuits of appetite regulation, being characterized by neuropeptide Y (NPY) up-regulation in parallel with of pro-opiomelanocortin (POMC), Agouti-related protein (AgRP), and cocaine and amphetamine regulated transcript (CART) down-regulation in the arcuate nucleus. These changes result in increased orexigenic and reduced anorexigenic signaling, leading to increased food intake. The existing data demonstrate that organotins are potent adipogenic agents, however, no epidemiologic studies have been performed to reveal the association between organotin exposure and obesity and the existing indirect human data are contradictory.

1. Introduction

Obesity, being characterized by excessive adipose tissue accumulation is considered as a worldwide epidemic [1]. In 2013 one of three adults worldwide was overweight or obese [2], with the highest rate of > 35% both for men and women in the USA [3]. Although being initially observed in the Western countries, the most rapid increase in body mass index (BMI) was recently observed in the developing countries [4]. Particularly, in a period from 1991 to 2011 the prevalence of obesity in China was characterized by a > 4- and 2-fold increase in men and women, respectively [5].

Health effects of obesity epidemics are related not to increased

Abbreviations: AgRP, Agouti-related protein; AMPK, AMP-activated protein kinase; aP2, adipocyte protein 2; AR, androgen receptor; ARC, *arcuate nucleus*; BMI, body mass index; C/EBPa, CCAAT-enhancer-binding protein a; CART, cocaine and amphetamine regulated transcript; DBT, dibutyltin; DMSO, dimethyl sulfoxide; ER, estrogen receptor; FABP, fatty acid binding protein; GLUT, glucose transporter; GR, glucocorticoid receptor; LBD, ligand-binding domain; LHA, lateral hypothalamic area; LPS, lipopolysaccharide; MEHP, mono-(2-ethylhexyl) phthalate; MDI, methylisobutylxanthine, dexamethasone and insulin; METBP, mono-(2-ethylhexyl)tetrabromophthalate; NAFLD, non-alcoholic fatty liver disease; NPY, neuropeptide Y; NTS, *nucleus tractus solitarii*; OTCs, organotin compounds; POMC, pro-opiomelanocortin; PPARγ, Peroxisome proliferator-activated receptor γ; PVN, paraventricular nucleus; Rosi, rosiglitazone; RXRα, retinoid X receptor α; TBBPA, tetrabromobisphenol-a; TBT, tributyltin; TG, triglyceride; TNFα, tumor necrosis factor α; TPT, triphenyltin; Trog, troglitazone; WAT, white adipose tissue

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adipose tissue mass itself, but rather to associated metabolic disorders linking obesity to a wide spectrum of pathologies including cardiovascular [6], renal [7], cerebral [8,9], and reproductive system [10] pathology, and also cancer [11]. Obesity together with diabetes, atherogenic dyslipidemia, and hypertension is clustered in the metabolic syndrome [12]. As a result, obesity is graded as the fifth cause of death with 3.4 million deaths worldwide annually [13].

Positive caloric balance due to increased food intake or reduced energy expenditure is playing a significant role in obesity [14] and was long considered as the only cause of the disease. At the same time, recent data indicate that obesity result from a complex gene-environment interplay [15]. In addition to other factors, environmental pollution was shown to play a significant role in obesity pathogenesis, being first proposed within the chemical theory of obesity by Baillie-Hamilton [16]. Particularly, the association between pollutant exposure and obesity was demonstrated [17]. Persistent organic pollutants play the most significant role in obesity [18–20] due to their endocrine disruptor properties [21]. In addition, perinatal exposure to endocrine disruptors was shown to program obesity [22] through induction of epigenomic changes including altered DNA methylation and other mechanisms [23]. At the same time, heavy metals [24] and metal-based nanoparticles [25] were also considered as endocrine disruptors. In particular, a significant association between obesity, diabetes, adipose tissue dysfunction and mercury [26], arsenic [27] and cadmium exposure [28] has been reported. But in this view, organometallic tin compounds are of particular interest [29].

Although several studies have addressed the mechanisms of organotin-induced adipose tissue dysfunction, epidemiologic studies on the association between organotin exposure and obesity have yet to be carried out [30,31]. An investigation originating from Finland demonstrated that placental tributyltin (TBT) levels are associated with body weight gain during the first three months of life, although no other associations with body weight were revealed [32]. Our earlier study demonstrated a significant association between body mass index and hair tin levels only in men aged 22–35 years, but not in older men and women [33].

The objective of the present study was to review the mechanisms of organotin-induced adipogenesis, obesity, and associated metabolic disturbances.

2. Brief chemical characteristics of organotin compounds

Tin $_{50}$Sn [Kr]$4d^{10}5s^25p^2$ is chemical element of the 14th group of the periodic table. The occurrence of tin in the earth's crust is about 10^{-4}% [34]. A main mineral formed by tin is cassiterite SnO_2. Most often in compounds with other elements tin possesses positive oxidative states of +2 and + 4 [35]. Sn (II) compounds are reducing agents, whereas oxidative properties are characteristic for Sn (IV).

Tin forms a large variety of organotin compounds. Organotin compounds (OTCs) are used in the field of catalysis, production of polymers and biocide agents. Organotin compounds are substances containing at least one Sn – C covalent bond. In the majority of organotin compounds tin has oxidation state of +4. However, organometallic compounds of tin (II) and tin (I) have been obtained currently. The particles like Bu_2SnX_2 (where X = OMe, OEt, OBu, Cl Br, OPh, OOCMe, $OOC(CH_2)_{10}Me$, $SSNEt_2$; X_2 = O, (OH, Cl); $Bu_2XSnOSnXBu_2$ (X = Cl, Br, OOCMe, OBu, n-Bu)) [39] and {4-t-Bu-2,6-[P(O)(O-i-Pr)$_2$]$_2$C$_6$H$_2$Sn}$_2$ [40] may provide an example of such compounds.

Substances containing both Sn(II) и Sn(IV) ($(Me_3Sn^{IV}C_5H_4)_2Sn^{II}$ ect. [41] as well as atoms of tin and other metal (chromium, palladium, tungsten, ruthenium) [42–44] have also been obtained.

Sn(IV) atom usually exists in tetrahedral hybridization (sp^3) in organotin compounds. The cases of trigonal bipyramidal (sp^3d) and octahedral hybridization (sp^3d^2) have been also reported (Fig. 1).

Similarly to a number of other organic substances organotin compounds are classified into mono-, di-, tri- and tetrasubstituted derivatives of tin. The following types of organometallic tin compounds are known: $RSnX_3$, R_2SnX_2, R_3SnX, R_4Sn, R_3SnSnR_3, $(R_2Sn)_n$ (R is an aliphatic, aromatic or heterocyclic radical, X is alkoxy, mercapto, amino functional group or chloride, fluoride, oxide, hydroxide, carboxylate or thiolate ion). X can also be represented by hydrogen, an alkali metal or an element-organic group (R_3Si, R_3P, R_3As) both bound directly to tin atom and *via* the bridged heteroatom S, Se, O (Table 1).

Most OTCs are liquid or solid substances readily soluble in organic solvents, but water-soluble organometallic tin compounds also exist. Organometallic compounds of tin (diethyltin iodide Et_2SnI_2) were first synthesized by Frankland (1849) and LeVig (1852). A number of methods have been described for the preparation of various types of OTC (halides, oxides, hydroxides, tetrasubstituted derivatives, *etc.*). The methods for the synthesis of various organometallic tin compounds have been systematized and reviewed in a monograph by Davies [67]. Since then the production of organotins has significantly increased worldwide [68].

OTCs were widely used as antifouling agents, as well as fungicides, preservatives, disinfectants, catalysts, stabilizers [69], plastic, foams, and silicone that are used in clothes and other consumer products [70]. The use of organotins as antifouling agents was banned in 2003 [71] due to their high toxicity [72] especially trisubstituted alkyl- and aryl derivatives (*e.g.*, tributyltin and triphenyltin chlorides) (Fig. 2). These limitations resulted in a significant reduction of gastropod OTC levels up to 42.9% for dibutyltin [73], although in some locations these measures were ineffective [74]. Despite the legislative measures and their efficiency, ecotoxicologically relevant organotin levels still exist in the environment [75] possessing significant health risk for humans especially living in the coastal areas [76].

3. Receptor mechanisms of organotin-induced adipogenesis

3.1. Chemical basis of the interaction between OTCs and nuclear receptors and other biomolecules

Modulation of nuclear receptor signaling was found to be the key mechanism of organotin-induced adipogenesis [77]. In particular, the effects of organotins as peroxisome proliferator-activated receptor γ (PPARγ) and retinoid X receptor α (RXRα) agonists mediate a wide spectrum of toxic effects of organotin exposure [78]. It was also proposed that nuclear receptor agonism may be a more potent mechanism of organotin toxicity than inhibition of aromatase [79]. Other mechanisms might include inhibition of ATP synthase, glutamate excitoxicity, Ca^{2+} signaling dysregulation [80], inhibition of aromatase [81], to name a few.

OTCs directly interact with molecules in prokaryotic and eukaryotic cells, including proteins of the nuclear receptor family, intracellular and membrane enzymes, as well as DNA [82,83]. Recent studies in the field of OTC toxicology link the negative effect of these substances (tributyltin and triphenyltin (TPT) in particular) to their ability to compete with biomolecules for peroxisome proliferator-activated receptor γ (PPARγ) and retinoid X receptor (RXRα). Biological activity of organometallic compounds is determined by the nature and number of substituents on the tin atom. Grün proposed a general empirical rule that the toxicity of organotin compounds increases with the increase in the number of substituents, except tetra-substituted tin derivatives with low reactivity [84].

The biphylic structure of organometallic tin derivatives mediates two main types of this interaction. Due to the presence of organic radicals (aliphatic or aromatic), organotin compounds are able to interact with lipophilic structures of biomolecules through Van der Waals forces. Organotin compounds and especially those containing large radicals change the hydration degree of phosphate and carbonyl groups in the composition of phospholipids or proteins, resulting in altered structural organization of membrane proteins and membrane fluidity. The most significant effect is possessed by TBT, being able to penetrate

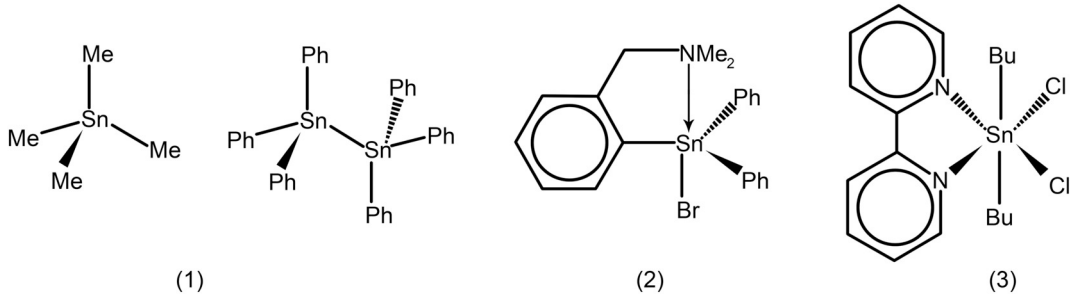

Fig. 1. Examples of structures with different types of Sn (IV) hybridization [38].
1 - tetrahedral, 2 - trigonal bipyramidal, 3 – octahedral.

Table 1
Examples of different types of OTCs.

Radical	$RSnX_3$	R_2SnX_2	R_3SnX	R_4Sn
Alkyl	$iPrSnCl_3 \cdot 2DMSO$ [44] $BuSnCl_3$, $PrSnCl_3$ [43] $(Me)_3SnLi$ [45] $MeSnI_3$ $Cl_3Sn(CH_2)_nSnCl_3$ (n = 3–5, 8) [46]	Me_2SnX_2 $(nC_3H_7)_2SnX_2$ $(nC_4H_9)_2SnX_2$ $(nC_8H_{17})_2SnX_2$ X = Cl, SO_3F, SO_3CF_3, PO_2F_2 [41] Me_2SnX_2 X = 1/2 oxalate; 1/2 malonate, ½ maleate, cyclobutyl dicarboxylate, cyclohexane carboxylate and pivolate [47] Me_2SnI_2 [48] $(Me)_2Sn(o\text{-}O_2C_6H_4)$ $(n\text{-}By)_2Sn(o\text{-}O_2C_6H_4)$ [49]	R_3SnX $(n\text{-}Bu)_3SnH$ $(n\text{-}Bu)_3Sn\text{-}Sn(n\text{-}Bu)_3Sn$ [50] $(Bu)_3SnX$ X = oxide, sulfaminate, naphthenate [51] $Me_3Sn\text{-}SnMe_3$ [52]	$i\text{-}PrSn(Me)_3$, $t\text{-}BuSn(Me)_3$ [52] Me_4Sn Et_4Sn [53]
Aryl	$PhSnCl_3$ [48] $2,4,6\text{-}(CF_3)_3C_6H_2SnCl_3$ $2,4\text{-}(CF_3)_3C_6H_3SnCl_3$ $2,6\text{-}(CF_3)_3C_6H_3SnCl_3$ [54] $PhSnH_3$ [55] $ArSnLi_3$ Ar = 2,6-bis(2,4,6-triisopropylphenyl)phenyl [56]	Ph_2SnL_2 (L = 2-[(9H-Purin-6-ylimino)]-phenol) [57] $Ph_2Sn[OCHMeC(O)NMe_2]_2$ $Ph_2Sn[OCHMeC(O)OPri]_2$ [58]	$(Bn)_3SnCl$ $(Ph)_3SnX$ X = Cl, acetate [50] $Ph_3Sn\text{-}SnPh_3$ [52] Ph_3SnH [53] $(p\text{-}CF_3C_6H_4)_3SnX$ X = OBu, NMe_2 [56]	Ph_4Sn, $(o\text{-}Tol)_4Sn$ $(m\text{-}Tol)_4Sn$ $(p\text{-}Tol)_4Sn$ $(2,4\text{-}Xyl)_4Sn$ $(2,5\text{-}Xyl)_4Sn$ [59]
Heterocyclic	$nBuSnR_1R_2$ R_1 = -SCH_2CH_2OH R_2 = -SCH_2CH_2O- [60]	$(n\text{-}C_4H_9)_2SnR_2$ $(C_6H_5)_2SnR_2$ *R* = 3-methyl-2-mercaptobenzothiazole [61] nBu_2SnR R = -SC(CN) = C(CN)S- [62] *R* = 1,3,4-thiadiazol-2,5-dimercaptide, nOc_2SnR R = 1,3,4-thiadiazol-2,5-dimercaptide [63] *R* = 2,3,4,5- tetraaza-6-diphenylstannyl][3.4]bicyclonona-1,3-diene [64] Bu_2SnO_2R R = uridine, cytidine, adenosine [65]	nBu_3SnR R = 1-tributylstannyl-4,5-di-ethoxycarbonyl-1,2,3-triazole [66]	–

deeply into hydrophobic formations. Organotin compounds can also disrupt the membrane functions, affecting the solvolysis and hydrolysis equilibria in biosystems. The trisubstituted OTCs in solution promote the formation of the weak bases acting as proton carriers and the lipophilic cations that behave like anion exchange agents towards chloride and hydroxide ions, disrupting their equilibrium. These

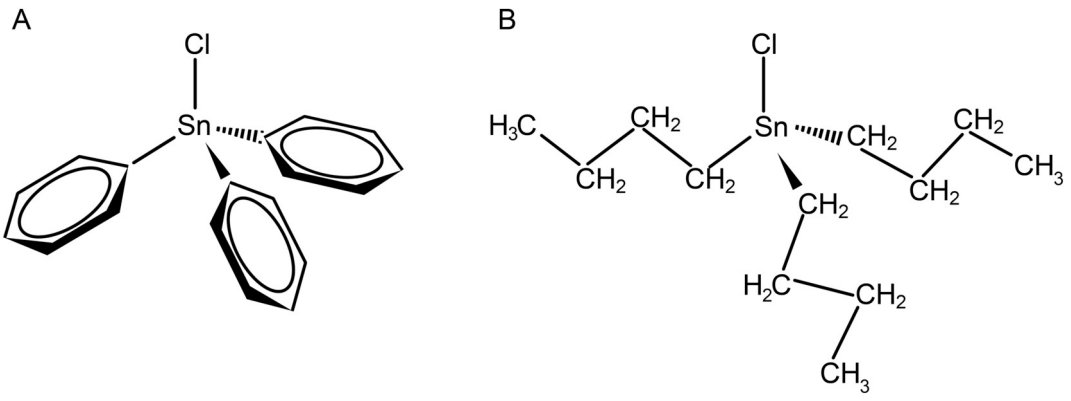

Fig. 2. Structure of triphenyltin (A) and tributyltin (B) chlorides.

properties at least partially mediate the ability of OTC to affect electrochemical ion gradients of membrane organelles and mitochondria [84].

Through the radical chain mechanism OTCs also contribute to lipid peroxidation, being enhanced by the parallel process of phospholipid complex formation by the dative Sn—O—P bonds [85]. Non-selective lipid peroxidation leads to a wide spectrum of electrophilic reactive lipid species (RLS), for example, 4-hydroxynonen-2-al and cyclopentenone isoprostanes. Like OTCs these RLS tend to form covalent bonds with soft nucleophiles, including low-molecular antioxidants, and SH-groups of proteins [84].

On the other hand, to explain the causes of the toxicity of OTC one should turn to the tin coordination chemistry. Sn (IV) compounds, including organometallic compounds, belong to the group of Lewis acids. Vacant 5 s, 5p and 5d orbitals of tin (IV) predetermine its ability to form complexes through bonds with charged or uncharged electron-donor functional groups (O-, N-, S-, P-donor ligands).

For Sn binding with sulfur-containing molecules (mainly with cysteine residues) is typical as for other heavy metals (for example, Hg, Cd, Pb). The resulting complexes can have a bipyramidal and tetrahedral structure. The fact that tin is preferentially bound to sulfur atoms of bioligands is confirmed by the studies of Munguia et al. [86], Buck et al. [87,88], Ali et al. [89].

Like inorganic tin (IV) halides, organotin compounds with the Sn-Hal bond are subjected to hydrolysis already in a weakly acidic media [90], and after the elimination of the halide ion the Sn cation can interact with the electron-donor atom of the biomolecule. The structure and thermodynamic characteristics of the resulting adducts were studied by Hiromori et al. [91], Harada S. et al. [92], Pagliarani A. et al. [93]. Hiromori et al. [91] performed a Scatchard analysis of PPARγ with purified recombinant PPARγ. The obtained dissociation constant of the PPARγ-tertbutyltin complex is 66.6 ± 5.2 nM that is close to the dissociation constant of the PPARγ complex with the typical antagonist [^{3}H] rosiglitazone (Rosi) (46.2 ± 2.5 nM). It has been shown that tributyltin, triphenyltin, diphenyltin and tetrabutyltin block binding of [^{3}H]Rosi to PPARγ, as evidenced by the higher value of the dissociation constant. Hiromori et al. noted that trialkylated and triarylated tin compounds are the most likely potential PPARγ agonists, and the phenyl radical at the tin atom enhances the effect of organotin compounds as PPARγ antagonists to a greater degree than the butyl radical [91].

To clarify the mechanism underlying the activation of PPARγ by organometallic tin compounds, Harada S. et al. [92] analyzed the interactions of the ligand-binding domain (LBD) of PPARγ with TPT and TBT by X-ray crystallography and mass spectrometry. PPARγ forms complexes with TPT and TBT of equimolar composition. It was shown that the specific binding of organotin compounds was achieved through ionic interactions between the sulfur atom Cys285 and the tin atom [92]. In order to clarify the problem of understanding how tritbutiltin activates the RXRα-PPARγ signaling pathway, the structure of the RXRα - TBT complex was analyzed [94]. It was shown that organotin compounds form covalent bonds between the tin atom and the cysteine residue Cys432, located in the helix (H11) of RXRα (retinoid X receptor). The authors concluded that the binding of organotin compounds to single PPARγ does not cause the necessary transactivation, due to the absence of a cysteine residue in the corresponding position in PPARγ.

Sn binding to functional groups and donor atoms of biomolecules was analyzed in detail by Pagliarani et al. [93]. These authors underline a special role of strong covalent Sn—S bonds, which contribute to further coordination with the donor nitrogen atoms of the biomolecules in addition to the binding of the organotin compound. Organotin compounds can bind with one or two sulfur atoms, being determined by the spatial arrangement of the -SH groups [93]. In this case, dealkylation is possible for trisubstituted OTC in the presence of two vicinal mercapto-groups of the bioligand, ultimately resulting in the formation of two Sn—S covalent bonds instead of one. Tetrahedral hybridization of Sn (IV) atom in OTC is preserved when tributyltin binds to a single nucleophilic atom, *e.g.* sulfur atom of an isolated cysteine residue. In the case when tin forms bonds with two ligands (S-donor and N-donor) the conformation changes to trigonal-bipyramidal, which requires a certain three-dimensional spatial distribution of amino acid residues. Because of steric hindrances, massive phenylalanine, tyrosine and tryptophan residues tend to be located equatorially due to the rearrangement of the molecule geometry in the region of OTC binding. Consequently, OTCs can significantly alter structural arrangement of functional groups of polypeptide chains. When the cysteine residues that are bound to the tin atom are included in the critical domains, adverse effect of tin compounds on the protein function may take place.

In addition to sulfur, tin can bind to phosphorus in the structure of ATP, nucleic acids, phosphoproteins, phospholipids, ultimately leading to disruption of the synthesis of phospholipids and intracellular transport, as well as DNA structure [93]. OTCs directly interact with nucleic acids *in vitro* [95] by forming complexes with a coordination number of 5, in which the central metal atom can bind to phosphorus, oxygen, nitrogen and sulfur atoms, resulting in the condensation of DNA [95–97].

The existing data demonstrate the efficiency of organotin-induced PPARγ signaling and adipogenesis varies significantly depending on the particular organotin compound, although the potential reasons were insufficiently discussed. Hypothetically, increasing the number of radicals enhances OTC lipophilicity, thereby facilitating the transport of these particles through hydrophobic membranes of the cell and nucleus thus increasing toxic effect of these OTC, being in agreement with Grün [84]. Another potential reason for the observed differences in variation in molecule hydration. Particularly, compounds with the lower number of substituents are generally characterized by better solubility in water and higher hydration rate that may have a significant impact on protolytic equilibria in biological media. One can also propose that lower toxicity of mono- and disubstituted OTC may be explained by the lack of structural similarity between these compounds and target molecule.

3.2. Induction of adipogenesis: organotins as PPAR and RXR agonists

Existing studies demonstrate that organotin compounds are capable of adipogenesis induction. PPARγ is a key regulator of adipocyte biology (adipogenesis, differentiation, lipid metabolism) [98]. PPAR binds RXR to form heterodimers, being obligate for direct DNA binding and subsequent modulation of transcription [99]. Although PPARγ agonists are widely used in treatment of obesity-associated insulin resistance and other metabolic disorders [100], ectopic excessive PPARγ stimulation may induce adipogenesis [101].

Multiple studies have shown that effects of organotin in adipose tissue are mediated *via* PPAR and RXR (Fig. 3), although this effect is species-specific. In particular, a pioneer study by Kanayama et al. [102] demonstrated that both TBT and TPT induced adipocyte differentiation in different differentiation media, as well as increased adipocyte protein 2 (aP2) and PPARγ mRNA expression. The authors have also demonstrated a strong agonistic effect of TBT and TPT on RXRa and PPARγ, respectively. Moreover, the effect of organotin compounds was as potent as that of the well-known ligands, 9-cis retinoic acid and Rosi [102]. It has been shown recently that dibutyltin compounds are partial RXRa agonists in contrast to TBT, being a full agonist. Dibutyltin (DBT) compounds also induced adipogenesis in 3T3-L1 preadipocytes associated with increased Fabp4, Adipoq, and Glut4 expression, although the effect was less pronounced than that of TBT and ROSI. Proadipogenic effect of these organotin compounds was prevented by specific PPARγ antagonist. Moreover, DBT exposure also induced proinflammatory response in adipocytes (Vcam1, Dcn, Fn1, S100a8, Lgals9), as well as altered lipopolysaccharide (LPS)-induced tumor necrosis factor α (TNFα) expression in macrophages [103].

In mesenchymal stem cells TBT exposure also induced lipid

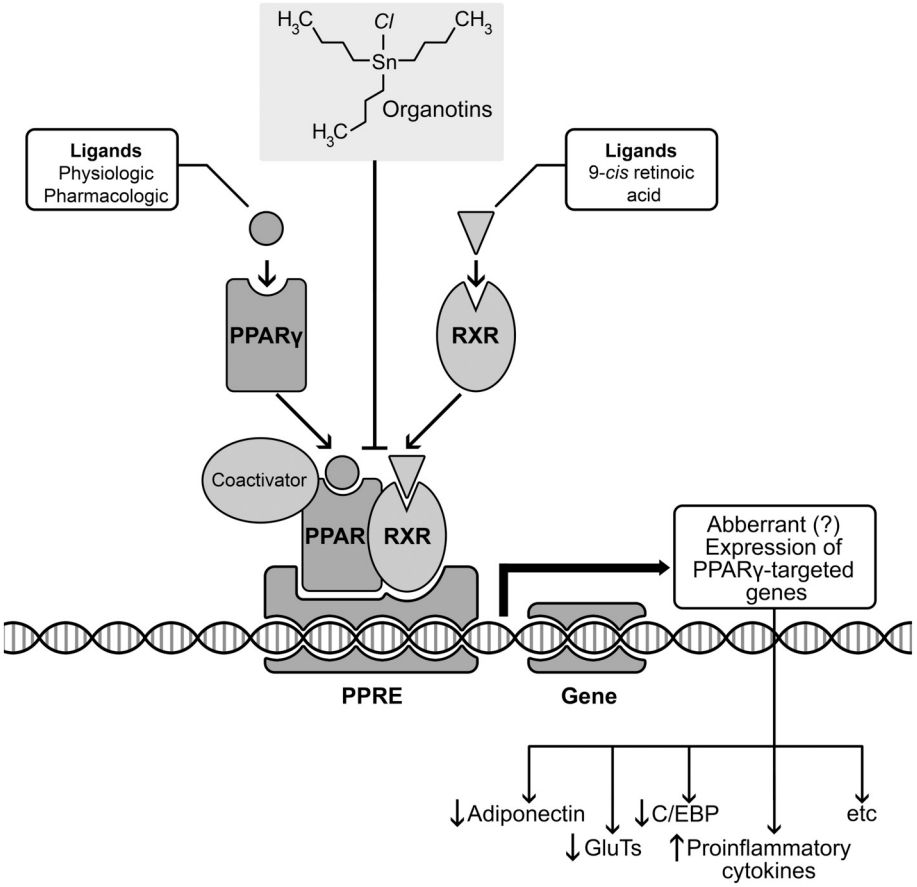

Fig. 3. Organotins as PPARγ and RXR agonists in adipogenesis.
Under normal conditions PPARγ binds physiologic (unsaturated fatty acids and their metabolites) and pharmacologic (rosiglitazone, troglitazone, *etc.*) ligands [112], whereas 9-cis retinoic acid is a natural ligand for RXR [113]. Organotins are dual agonist ligands for RXR-PPARγ heterodimer [84,113]. Agonistic effect of organotin exposure on PPARγ and RXR significantly affects expression of PPARγ-targeted genes, including adipokines (adiponectin, leptin), glucose transporters (GluT), genes involved in lipid and carbohydrate metabolism, proinflammatory cytokines [114]. However, other studies have demonstrated aberrant expression of PPARγ-targeted genes upon organotin exposure [109,110]. Organotin-induced aberrant expression of PPARγ-targeted genes may result in development of obesity and associated metabolic disturbances in contrast to pharmacologic PPARγ agonists that are protective against insulin resistance and inflammation [84].

accumulation, as well as PPARγ2 and fatty acid binding protein 4 (FABP4) expression, with an efficiency between rosiglitasone (PPARγ agonist) and bexarotene (RXR agonist). The use of PPARγ antagonist significantly but not completely reduced TBT-induced adipogenesis. In addition, TBT and bexarotene induced TGM2 (an RXR target) and ABCA1 (a liver X receptor target) [104]. Similarly, in transfection experiments it has been also demonstrated that TBT acts as an activator of RXR-PPARγ heterodimer even in presence of PPARγ antagonist (GW9662) [105].

It has been also demonstrated that RXR plays a significant role in TBT-induced inhibition of osteogenesis in bone marrow stromal cells and induction of adipogenesis [106]. A combination of bisphenol A, diethylhexylphthalate, and TBT also induced adipogenesis in mesenchymal stem cells, being also characterized by increased FAPB4 and adiponectin expression [107]. However, both TBT and TPT activated PPARγ1 and PPARγ2 similarly to rosiglitasone, being more potent activators in comparison to other endocrine disruptors including mono-(2-ethylhexyl) phthalate (MEHP), tetrabromobisphenol-a (TBBPA), and mono-(2-ethylhexyl)tetrabromophthalate (METBP) [108].

It has been also noted that despite evidence for adipogenesis induction in rainbow trout, organotins (TBT, TPT) exposure does not promote complete adipocyte maturation, resulting in dysfunctional cell formation. It has been also noted that organotin exposure may have synergistic effect with lipid overload in alteration of adipocyte phenotype, being characterized by TNFα, abca1, and cebpa expression [109]. These findings corroborate those by Regnier et al. [110] who compared the effects of TBT exposure with troglitazone, PPARγ agonist. In particular, TBT and troglitazone differentially affected metabolic phenotype of adipocytes. Upon stimulation with MDI (methylisobutylxanthine, dexamethasone and insulin) TBT exposure significantly reduced adiponectin, perilipin, and CCAAT-enhancer-binding protein a (C/EBPa) adipocyte expression in comparison to troglitazone (Trog). These findings were confirmed by analysis of gene expression. While some genes were up-regulated by both TBT and Trog exposure (PPARγ, SCD1), multiple genes were up-regulated only by Trog but not TBT (HK2, IR, OLR1, adiponectin, C/EBPa, Glut4). Moreover, TBT treatment decreased Trog-induced stimulation of certain gene expression (PPARγ, SCD1, adiponectin, OLR1, C/EBPa, Glut4). In addition, TBT also induced basal glucose uptake during differentiation [107].

Other mechanisms may be also involved in endocrine-disrupting effects of organotins. Inadera and Shimomura demonstrated that the use of PPARγ antagonist (GW9662), as well as dihydrotestosterone or 17-estradiol did not affect expression of aP2 in TBT-exposed 3T3-L1, being indicative of PPARγ- and aromatase-independent effects of TBT on adipogenesis [111]. However, whether their role in tin-induced adipogenesis is more significant than that of RXR/PPARγ agonism remains questionable.

3.3. Estrogen receptor (ER) signaling

Modulation of estrogen signaling was shown to play a significant role in adipose tissue physiology [115]. In particular, it has been demonstrated that estrogen inhibits adipogenic differentiation in ERα-expressing bone marrow stromal cells [116], with the potential inhibitory effect on PPARγ signaling [117]. Correspondingly, ERα knockout mice are characterized by obese phenotype due to reduced energy expenditure [118].

It has been demonstrated that acute TBT exposure up-regulates ERs activity in a dose-dependent manner in epididymal and renal WAT, as well as in BAT and pancreas. In contrast, ER downregulation was detected in liver in response to acute TBT treatment. Long-term experiments showed that TBT acts as ER activator, although being less potent than 17β-estradiol. It is also notable that at low-dose exposure TBT significantly increases adipogenesis, as demonstrated by total body fat

and aP2 expressoin, and inhibited ER basal activity. In turn, at higher doses TBT activated ER with no effect on body mass. In 3T3-L1 ERE-transfected cells TBT exposure directly targeted ERα in undifferentiated cells and ERβ in differentiating adipocytes, with all effects being inhibited by ER-antagonist ICI-182,780 [119].

It is noteworthy that modulation of ERβ activity was shown to be a regulator of PPARγ activity, thus providing an additional link between organotin exposure and PPARγ signaling in metabolic disorders [120].

3.4. Corticosteroid signaling

Activation of glucocorticoid receptor signaling as well as increased levels of glucocorticoids in adipose tissue due to modulation of 11β-hydroxysteroid dehydrogenases 1 and 2 were shown to play a significant role in obesity [77].

In a HEK-293 (human embryonic kidney) cell model, organotins were shown to inhibit 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme of glucocorticoid catabolism, resulting in elevated tissue levels of glucocorticoids [121].

Modulation of glucocorticoid receptor (GR) activity by endocrine disrupting chemicals (tolylfluanid) was shown to affect adipocyte biology including alteration of insulin signaling [122]. However, data on the role of GR modulation in organotin-induced obesity are insufficient. Moreover, a study by Sargis et al. [123] demonstrated that unlike certain other chemicals (bisphenol A, dicyclohexyl phthalate, endrin, tolylfluanid) TPT exposure did not cause significant GR activation in 3T3-L1 cells [123].

Concomitantly, it has been demonstrated that DBT but not other organotins inhibited ligand binding to glucocorticoid receptor and its subsequent activation, ultimately leading to altered cytokine response [124]. It has been also demonstrated that mineralocorticoid and glucocorticoid receptor differentially mediate trimethyltin toxicity [125].

4. Adipogenic effect of organotin exposure *in vivo*

Results of *in vivo* studies on the adipogenic effect of organotin exposure generally correspond to those noted *in vitro*, demonstrating significant increase in adiposity and adipose tissue dysfunction in experimental animals treated with tin species. In particular, in male mice TBT exposure resulted in obesity and fatty liver, which were associated with increased circulating leptin (leptin resistance) and insulin (insulin resistance), as well as reduced adiponectin levels. Moreover, both hepatic adiponectin and resistin were reduced in TBT-exposed mice [126]. Oral administration of TBT (1, 10, and 25 mg/kg body weight) to female rats resulted in adipogenic transformation of thymus, being characterized by increased adipogenic markers (aP2, PEPCK, and CD36). TBT also induced thymocyte apoptosis and reduction of thymus-specific gene (EVA, KGF, AIRE, and IL-7) expression [127].

It is noteworthy that maternal organotin exposure results in prenatal programing of obesity [128]. It has been demonstrated that maternal TBT exposure (0.1 mg/kg gavage) resulted in a significant activation of lipogenesis in maternal liver, being accompanied by up-regulation of fatty acid synthase, fatty acid transport protein, acetyl-CoA-carboxylase, and sterol response element-binding protein 1c expression. At the same time, prenatal TBT exposure promoted adipogenic differentiation in offspring adipose-derived stromal stem cells, and was associated with a nearly 2-fold increase in lipid accumulation, *Fapb4* and *leptin* expression. The effect of TBT exposure was similar to that of Rosi, PPARγ agonist. In addition, *in vitro* studies of the authors also demonstrated that TBT exposure efficiently reduced expression of *Pref-1*, adipogenesis inhibitor [129].

Similarly to other obesogens, tributyltin exposure results in transgenerational inheritance of obese phenotype [130]. In particular, *in vivo* effects of prenatal TBT exposure on three generations of animals were studied by Chamorro-García et al. [131], demonstrating that adipogenic effect of oral TBT exposure in F0 persists at least to F3, being characterized by increased white adipose tissue (WAT) mass, adipocyte number and size without alteration of body mass. Notably, TBT-induced increase in WAT mass was more pronounced than that in the case of ROSI exposure. Mesenchymal stem cells from F1, F2, and F3 generations were also characterized by increased *PPARγ*, *Fapb4*, *Zfp423*, and *LPL* expression, as well as down-regulation of Pref-1, and osteogenic markers *ALP* and *Runx2* expression. Moreover, prenatal TBT exposure induced fatty liver disease, being characterized by increased hepatic lipid accumulation, and up-regulation of lipogenic (*PPARγ2*, *SREBP1c*, *GyK*, *FASN*), lipolytic (*PPARα*, *ACOX*), and lipid droplet (*Fsp27*, *FATP*) markers [131].

These mechanisms may underlie the association between tributyltin exposure and non-alcoholic fatty liver disease (NAFLD) development [132,133].

Taken together, *in vivo* animal studies have demonstrated that not only postnatal but also prenatal exposure of animals to organotin species results in obese phenotype. Moreover, the observed effects were considered to be transgenerational and persisted up to the third generation in experimental laboratory animals.

4.1. Central effects of organotin: regulation of appetite

In addition to direct effects on adipose tissue through interference with nuclear receptor signaling, organotin compounds were also shown to have central hypothalamic effects that may play a significant role in adipogenesis [134]. Experimental studies demonstrated that organotin compounds readily accumulated in brain [135] and induced c-fos activation in hypothalamic arcuate nucleus [136]. Therefore, certain adverse effects may be mediated through direct influence of organotins on brain in general and neural circuits of appetite regulation in particular (Fig. 4).

Ishikura et al. (2002) demonstrated that trimethyltin exposure significantly increases *hippocampal* NPY immunoreactivity and mRNA expression [137]. It has been shown that TBT (0.5 μg/kg body weight) exposure for 54 days resulted in a significant increase in food intake and body mass, being associated with up-regulation of brain NPY, and reduced POMC, AgRP and CART expression. These changes were also associated with increased hepatic cholesterol and triglyceride (TG) content [138]. At the same time, a recent study demonstrated a significant increase in feed efficiency, which were associated with reduced circulating leptin levels and hypothalamic neuropeptide Y and Y1 receptor expression [139].

It has been also demonstrated that oral tributyltin (100 ng/kg/day) administration resulted in a significant alteration of hypothalamic-pituitary-gonadal axis, accompanied by hyperleptinemia, increased body weight, and insulin resistance [140].

In a goldfish (*Carassius auratus*) model, TBT exposure (2.44 and 24.4 ng/L) resulted in a significant up-regulation of NPY and apelin, as well as reduced POMC, ghrelin, cocaine and amphetamine-regulated transcript, and corticotropin-releasing factor in association with increased food intake [141].

4.2. Lipid and energy metabolism

Organotin compounds were shown to have a significant effect on lipid metabolism in adipocytes as well as other tissues. In particular, in male mice TBT exposure (0, 0.5, 5 and 50 μg/kg) resulted in increased hepatic total lipid, cholesterol, and triglyceride levels, that may be associated with lipogenic effects including up-regulation of acetyl-CoA carboxylase-1, acetyl-CoA carboxylase-2, and stearoyl-coenzyme A desaturase 1 activity. It is expected that the observed changes may be associated with TBT-induced modulation of nuclear receptor (retinoid X receptor α, PPAR receptor γ, PPAR receptor β/δ and PPAR receptor γ coactivator 1α) signaling [145]. In rare minnow, Zhang et al. [146] have demonstrated a significant increase in total lipid, cholesterol, triglyceride and fatty acid content in muscles in response to TBT

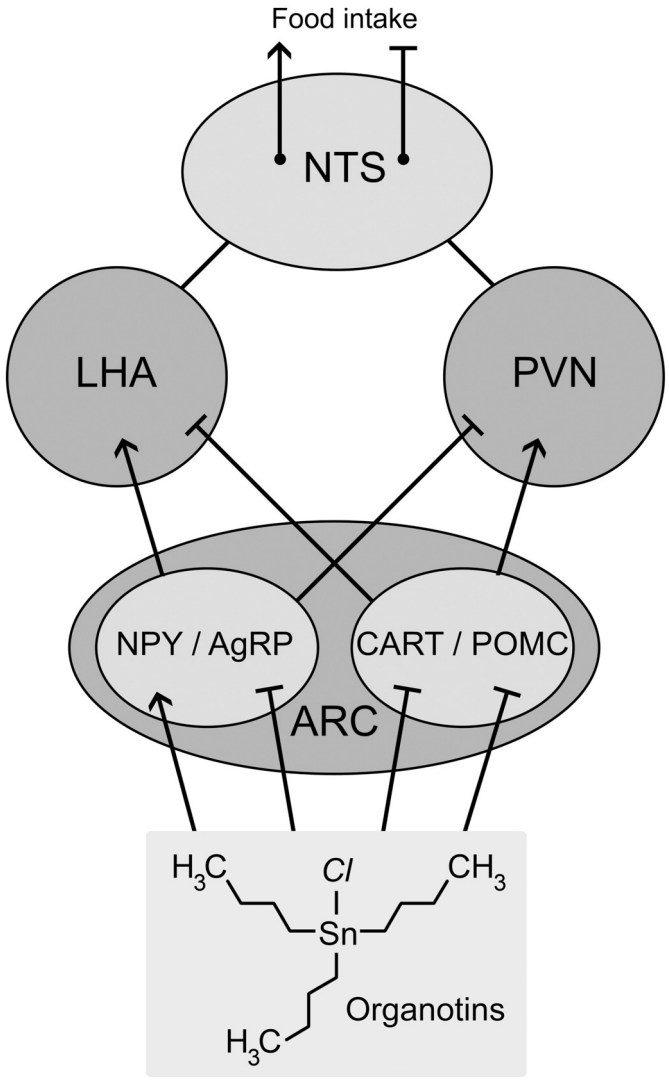

Fig. 4. Central effects of organotin compounds on food intake neural circuits
Organotin up-regulates expression of NPY in parallel with down-regulation of POMC, AgRP and CART expression in the arcuate nucleus (ARC) [142]. The resulting NPY overproduction stimulates lateral hypothalamic area (LHA) with subsequent orexigenic signaling [143]. Both orexigenic and anorexigenic signals are integrated in NTS (*nucleus tractus solitarii*) [144]. In turn, anorexigenic impacts from paraventricular nucleus (PVN) are reduced by oranotin exposure, resulting in increased food consumption as a net effect of organotin.

exposure. It is notable that organotin exposure increased the level of unsaturated fatty acids, being associated with elevated hepatic fatty acid desaturase 2 and stearoyl-CoA desaturase activity [146]. TBT-induced hepatic steatosis in *Danio rerio* was also associated with up-regulation of lipid transport (slc25a10, Fapb6), lipid storage (LPIN1, ACAT-2, LDLR), and lipogenesis (Acc1, Fas, SCD1, DGAT2, SREBP-1C, PPARγ, C/EBP-a) genes expression. Moreover, induction of caspase 3 activity and up-regulation of apoptotic and stress-response genes (Gadd45aa, Casp2, Bik, Mmp9, Decr9) was also observed in livers [147]. These data generally correspond to a recent study by Lyssimachou et al. (2015) who demonstrated up-regulation of hepatic PPARγ, SREBP1, FASn, IGF-IIa in parallel with down-regulation of RXRa/a, C/EBPb, DGAT2, 11b-HSD2 gene expression in male zebrafish. In female zebrafish only hepatic PPARγ and IGF-IIa expression were up-regulated in response to TBT *in vivo* exposure. Alteration of lipogenic genes was also observed in brain [148]. Finally, TBT exposure in ramshorn snail (*Marisa cornuarietis*) resulted in alteration of fatty acid profile [149].

In 3 T3-L1 cells TBT-induced adipocyte differentiation, lipid accumulation, and adipocyte specific protein 2 (aP2) expression were associated with profound changes in gene expression, with greater statistical significance at later periods and higher exposure levels (50 nM TBT, 10 days). In particular, TBT exposure was associated with up-regulation of TCA cycle (*Aco2*, *Idh3a*, *Ogdh*, *Suclg1*, *Mdh2*, *Csl*, *Pcx*, *Phdb*), fatty acid β-oxidation (*Acox1*, *Acadvl*, *Acadm*, *Acadl*, *Hadha*, *Hadh*, *Acaa2*, *Hadhb*, *Cpt2*), fatty acid and TG synthesis (*Acaca*, *Agpat9*, *Agpat3*, *Agpat2*, *Dgat1*, *Dgat2*), PPAR signaling (*Rxrg*, *Scd1*, *Scd3*, *Dbi*, *Fabp3*, *Fabp5*, *Cd36*, *Acsl1*, *Acsl3*, *Nr1h3*, *Scp 2*, *Angptl4*, *Plin1*, *Fabp4*, *Adipoq*, *Sorbs1*, *Pck1*), adipokine signaling (*Adipor2*, *Cfd*, *Agt*, *Rarres2*, *Retn*), as well as uncoupling protein (Ucp2) genes. It was also noted that from all studied pathways, only PPAR signaling pathway was significantly enriched after 1-day exposure, being indicative of the target role of PPAR modulation in TBT-induced adipogenesis [150].

Finally, it has been demonstrated that in thymoma cells tributyltin oxide significantly affects proliferation and energy sensing pathways, including modulation of pyruvate dehydrogenase, acetyl-CoA carboxylase isoform 1, and glutamine: fructose-6-phosphate amidotransferase [151]. Of note, immunotoxic effects of TBT to thymus cells were also characterized by alteration of lipid metabolism gene (*Aldh1a7*, *Cidea*, *Cnbp1*, *Fabp3*, *Nr1h3*, *Pck1*, *Ppap2a*, *Rpe65*, *Ugt8*) expression [152].

4.3. Glucose metabolism

In addition to adipogenesis, organotin exposure may also contribute to metabolic syndrome through alteration of glucose metabolism and its regulation. In particular, an earlier study by Manabe and Wada [153] demonstrated that triphenyltin fluoride significantly reduced pancreatic insulin secretion in response to glucose, glucagon, or arginine, as well as decreased plasma and adipose tissue LPL activity. These changes resulted in increased fasting blood glucose and triglyceride levels [153]. Correspondingly, TPT exposure reduced insulin secretion in response to glucose and acetylcholine stimulation by alterating of intracellular calcium levels in pancreatic β-cells [154].

Further studies have highlighted the particular mechanisms of organotin-induced alteration of carbohydrate metabolism. In particular, oral TBT exposure (0.5, 5, or 50 μg/kg every 3 days) for 60 days resulted in a significant increase in plasma glucose, as well as decreased insulin and glucagon levels, which were associated with reduced pancreatic islet β-cell count and islet cell apoptosis. These changes in pancreatic structure were associated with reduced ERα but not ERβ expression, and up-regulation of androgen receptor (AR) in pancreas [155]. Oral TBT exposure (0.1 mg/kg/day) was shown to increase blood glucose and insulin levels, altered glucose tolerance and insulin stimulation test, and led to a significant increase in islet numbers. Adipocyte hypertrophy was also associated with increased expression of ERα and PPARγ in WAT, whereas fatty liver was accompanied by increased hepatic PPARγ and decreased ERα expression. Taken together with TBT-induced reduction in circulating estrogen levels, the authors propose that dysregulation of the relationship between liver, WAT and pancreas may be the cause of organotin-related metabolic risks [156].

Further studies by the same authors demonstrated hyperglycemia in rats treated with TBT for both 45 or 60 days. Shorter periods of exposure with organotin compound resulted in a significant dose-dependent increase in serum insulin, adiponectin, and reduction in glucagon levels. After 60 days of TBT exposure no significant group differences in serum insulin or glucagon were noted. However, in contrast to the shorter exposure period, 60-days TBT exposure significantly reduced circulating adiponectin levels. The authors further documented decreased IR-IRS1-PI(3)K-Akt-Glut4 signaling in liver and muscles [157]. In addition, TBT treatment resulted in a significant reduction in GLUT1 levels in human pluripotent embryonic carcinoma cell line NT2/D1, whereas the use of AMP-activated protein kinase (AMPK) activator significantly improved glucose uptake by stimulating GLUT1 translocation [158].

5. Other potential contributing mechanisms

5.1. Gut dysfunction

It has been shown that pollutant exposure may also affect gut microbiota, thus contributing to obesity [159]. In particular, a recent study demonstrated that TBT exposure results in increased body weight and adiposity, which are associated with altered gut biodiversity [160]. These data generally correspond to the findings of inflammatory intestinal cytokine and transcription factor expression (TNF-α, IL-1β, IL-6, NF-κB p65) in response to TBT exposure (1–100 ng/L) [161].

5.2. Methylation

Organotins were shown to affect DNA methylation and histone acetyltransferase activity [162]. *In vitro* studies demonstrated that treatment of 3T3-L1 adipocytes with TBT resulted in a significant increase in adipocyte differentiation and decrease in cell global methylation status, including PPARγ methylation, although no alteration in methylation of CpG rich regions was noted [163].

6. Conclusion

In conclusion, the existing data demonstrate that organotins are potent adipogenic agents. Adipogenic effects of organotin exposure may be mediated by cellular mechanisms, with PPARγ and RXRα agonism being the key ones, as well as central effects being characterized potentiation of orexigenic signals. At the same time, organotin exposure induces aberrant expression of PPARγ-targeted genes resulting in altered adipogenesis and metabolic profile of the adipocytes ultimately resulting in proinflammatory effects, leptin and insulin resistance, and other disturbances.

Generally, these findings indicate a unique position of organotin compounds in a wide spectrum of organic and inorganic pollutants possessing adipogenic effects. Particularly, although being metal-based pollutants, organotins induce adipogenesis predominantly *via* PPARγ signaling similarly to organic pollutants like mono-ethylhexyl phthalate, butylparaben, *etc.* [164]. At the same time, data on the role of other metals including cadmium and mercury in induction of adipogenesis *via* modulation of PPARγ signaling are scarce, being indicative of the involvement of other mechanisms [26,28]. Therefore, it is proposed that organotin compounds may share similar properties both with organic and inorganic metal-based pollutants.

Despite the presence of rich laboratory data, human data on the role of organotin exposure on the prevalence of obesity are extremely insufficient. Further studies are strongly required to assess the potential adipogenic effects of environmental organotin exposure in humans, including analysis of the contribution of organotins and other pollutants into the human obesity epidemics.

Conflict of interest

The authors declare no conflict of interest.

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