Toxicology in Vitro 27 (2013) 978–990

Contents lists available at SciVerse ScienceDirect

Toxicology in Vitro

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

Review

Toxicity of organotin compounds: Shared and unshared biochemical targets and mechanisms in animal cells

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ARTICLE INFO

Article history:
Received 12 April 2012
Accepted 3 December 2012
Available online 8 December 2012

Keywords:
Organotin toxicity
Biochemical targets
Action mechanisms
Commonalities
Discrepancies
Animal cells

ABSTRACT

Most biochemical effects of organotin compounds leading to toxicity are astonishingly similar in different animal species. *In vitro* tests, designed to explore organotin action modes at cell level by minimizing interfering factors, point out akin responses to these man-made environmental pollutants from prokaryotes to mammals. On the other hand, a broad susceptibility range to organotin toxicants of animal cells and variegated action mechanisms of these compounds have been reported both *in vitro* and *in vivo* studies. Endocrine and lipid homeostasis perturbations span from mollusks to mammals, in which organotins mainly favor fat accumulation. Lipid changes were also found in Bacteria. Organotin are immunotoxic both in invertebrates and humans. Mitochondria and membrane functions seem to be a preferred target of these lipophilic pollutants. The inhibition of key membrane-bound enzyme complexes such as Na,K- and F_0F_1-ATPases, accompanied by perturbation of hydromineral balance, membrane potential and bioenergetics, has been widely reported. Highly conserved mechanisms could be involved in organotin binding to nuclear receptors, membrane components and intracellular proteins as well as in promoting DNA damage, all widely shared action modes of these toxicants. Accordingly, the different responsiveness/refractoriness to organotins, here overviewed, may mirror the biochemical-physiological selectivity of biomembranes, signalling pathways and intracellular protein components.

Contents

Abbreviations: AR, androgen receptor; CYP, cytochrome P_{450}; DBT, di-butyltin; DMT, dimethiltin; DPhT, diphenyltin; DHA, 5α-dihydroandrostenedione; DHT, 5α-dihydrotestosterone; DTT, dithiothreitol; EDC, endocrine-disrupting chemicals; EI, enzyme-inhibitor complex; ER, estrogen receptor; ESI, enzyme–substrate-inhibitor complex; GABA, gamma-aminobutyric acid; CSH, reduced glutathione; GR, glucocorticoid receptor; 11β-HSD2, 11β hydroxysteroid dehydrogenase 2; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 11KT, 11-ketotestosterone; MFO, mixed-function oxidase(s); MAPK, mitogen-activated protein kinase; MBT, mono-butyltin; MMT, monmethyltin; MR, mineralocorticoid receptor; NCCs, natural cytotoxic cells; NK, natural killer; NRs, nuclear receptors; NMDAR, N-methyl-d-aspartate receptor; OTCs, organotin compounds; Plictran, tricyclohexyltin hydroxide; PPAR, peroxisome–proliferator-activated receptor; RAR, retinoid acid receptor, RXR, retinoid X receptor; ROS, reactive oxygen species; SER, smooth endoplasmic reticulum; TBT, tributyltin; TBTO, tributyltin oxide; TET, triethyltin; TMT, trimethyltin; TPhT, triphenyltin; TPhTA, triphenyltin acetate; TPhTC, triphenyltinchloride; TPhTH, triphenyltinhydride.

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0887-2333/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tiv.2012.12.002

1. Introduction

Approximately one century after the first organotin synthesis (Frankland, 1853), the subsequent organotin chemistry development and the exponential industrial exploitation of organotin compounds (OTCs) has soon unraveled the dark side of these eclectic chemicals (Nicholson, 1989; Appel, 2004). Unfortunately, the widely exploited OTC versatility (Nath, 2008) is dramatically counterbalanced by toxicity to biota (Fent, 1996; Appel, 2004; Meador, 2011), especially in the case of trisubstituted compounds such as tributyltin (TBT) and triphenyltin (TPhT) (Snoeij et al., 1987; Fent, 1996; Hoch, 2001). Poor literature data are available for the far less toxic monosubstituted tin compounds (Meador, 2011). Soon OTC turned into a matter of worldwide concern as environmental toxicants of global impact (Fent, 1996, 2004; Antizar-Ladislao, 2008; Meador, 2011). According to Goldberg (1986) and Maguire (1987), TBT is the most toxic substance ever deliberately introduced into the environment. Due to the coexistence of lipophilic and polar moieties and their structural complexity, OTC interact by both covalent and non-covalent bonds with biomolecules and membrane structures (Pagliarani et al., 2010) and their biological effects have often been linked to the chemical reactivity (Saxena, 1987; Appel, 2004). However, in spite of the wealth of studies, the intimate nature of the toxicity mechanisms still remains partially obscure. One of the most astonishing features of OTC toxicity is the wide spectrum of responsive animal species, the similarity of the responses in far taxa counterbalanced by apparently inexplicable peculiarities in different cell types and species. *In vitro* approaches, powered by recent advances in cell culture, allow to compare effects on different biological matter by testing comparable contaminant concentrations and minimizing overlapping factors. Interestingly, when assayed under *in vitro* conditions, preparations from different Phyla often depict a similar scenario, even if the extension of *in vitro* results to the biological damage *in vivo* should be carefully evaluated (Salazar, 1989; Tabb and Blumberg, 2006).

As widely known, the unmasking of the Janus face of OTC by the quite unexpected toxicity to non-target species, represented the main stimulus to limit by law the worldwide OTC exploitation (Delgado Filho et al., 2010), even if probably late since law restrictions reduced OTC diffusion but did not eradicate worries. In spite of bans, the chemical–physical features of OTC favor their harmful persistence especially in water environments (ECHA, 2008; Eklund et al., 2008). Besides, a variety of causes embracing illegal uses, toxicant leaching from old paints and resuspension from sediments concur to make OTC a threat to biota spanning from microorganisms to higher vertebrates, even for the future generations (Fent, 1996; Belfroid et al., 2000; Hoch, 2001; Antizar-Ladislao, 2008; ECHA, 2008; Meador, 2011).

The main toxicity mechanisms of OTC are here reviewed on the basis of literature data and our findings in this field, aware of the limits of reporting studies in which different molecular forms and different ways of specifying the dose of the compound tested were reported (Aschner and Aschner, 1992).

The intriguing perspective is to attain an improved understanding of the link between biological and biochemical effects of OTC up to perceive some of the the reasons for differences and analogies between taxa. Therefore, this review does not aim at all at being exhaustive, but only at highlighting some spots. *In vitro* studies, allowing a deep insight in the molecular mechanisms, deserve a special focus. The knowledge of the still poorly studied variables modulating OTC toxicity may help to counteract OTC biological impact, plan bioremediation and food safety strategies and forecast the duration of harmful effects.

2. The biological damage

The most toxic OTC, namely TBT and TPhT, are well known to have the main biological impact on the hormonal asset (Iguki and Katsu, 2008; Delgado Filho et al., 2011), where they act as endocrine-disrupting chemicals (EDC) (Tabb and Blumberg, 2006). Endocrine perturbations, often associated with widespread metabolic shifts (Swedenborg et al., 2009), span from the aquatic species, deeply studied for the impressive biological and ecological impact (Alzieu, 2000; Nakayama et al., 2004), to terrestrial organisms (Delgado Filho et al., 2011). The most striking *in vivo* effect of trisubstituted OTC at very low concentrations (1 ppb) is imposex, namely the irreversible masculinization of female gastropods, a recognized biomarker of organotin pollution (Iguki and Katsu, 2008; Delgado Filho et al., 2010). Beside gastropods, OTC at very low tissue concentrations act as EDC in a variety of taxa (Meador, 2011) including bivalve mollusks (Morcillo and Porte, 2000), tunicates (Mansueto et al., 2011), crustaceans (Tang et al., 2009), echinoderms (Sugni et al., 2010), fish (McGinnis and Crivello, 2011) and mammals (Nakanishi et al., 2006; Delgado Filho et al., 2011). The endocrine damage by TBT extends to the thyroidal status in amphibians (Cao et al., 2011), fish (Zhang et al., 2009) and rats (Cooke et al., 2004). Quite surprisingly, the endocrine impact is somehow discontinuous and even contradictory, being closely related species, even within susceptive taxa, often differently affected. This is the case of gastropod prosobranchs, one of the most organotin-sensitive taxon (Sternberg et al., 2010), which embraces imposex-prone and refractory species (Ketata et al., 2008). Moreover, in spite of an overall masculinizing effect shown in gastropods (Iguki and Katsu, 2008; Sternberg et al., 2010) and fish (McGinnis and Crivello, 2011), TBT at nM concentrations may display estrogen-like effects on mammalian adipocytes (Penza et al., 2011).

Among the wealth of studies on endocrine effects, focus on sex steroids was quite obvious (Delgado Filho et al., 2010). Accordingly, OTC-driven changes in the expression and/or the activity of steroidogenic enzymes and steroid receptors have been widely explored (Sanderson and Den Berg, 2003; Tabb and Blumberg, 2006; McGinnis and Crivello, 2011; Penza et al., 2011), even if the well established role of sex steroids in vertebrates, is still controversial in invertebrates (Lafont and Mathieu, 2007; Janer et al., 2006; Delgado Filho et al., 2010). In lower Phyla vertebrate-type steroids may even be not endogenous (Ketata et al., 2008), in spite of the recognized metabolic steps in some mollusks (Delgado Filho et al., 2010), echinoderms (Lafont and Mathieu, 2007) and crustaceans (Verslyke et al., 2002; Summavielle et al., 2003).

The great diversification of endocrine systems (Delgado Filho et al., 2010), steroidogenic pathways and enzymes, not only among species, but also among cell types (Luu-The and Labrie, 2010) complicates the overall pattern of OTC endocrine effects. Many steps of steroid biosynthesis from cholesterol (Fig. 1), with a complex interplay between mitochondria and smooth endoplasmic reticulum (SER) (Sanderson, 2006), are performed by the membrane-bound