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Review article

Obesogens in the aquatic environment: an evolutionary and toxicological perspective

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ABSTRACT

The rise of obesity in humans is a major health concern of our times, affecting an increasing proportion of the population worldwide. It is now evident that this phenomenon is not only associated with the lack of exercise and a balanced diet, but also due to environmental factors, such as exposure to environmental chemicals that interfere with lipid homeostasis. These chemicals, also known as *obesogens*, are present in a wide range of products of our daily life, such as cosmetics, paints, plastics, food cans and pesticide-treated food, among others. A growing body of evidences indicates that their action is not limited to mammals. *Obesogens* also end up in the aquatic environment, potentially affecting its ecosystems. In fact, reports show that some environmental chemicals are able to alter lipid homeostasis, impacting weight, lipid profile, signaling pathways and/or protein activity, of several *taxa* of aquatic animals. Such perturbations may give rise to physiological disorders and disease. Although largely unexplored from a comparative perspective, the key molecular components implicated in lipid homeostasis have likely appeared early in animal evolution. Therefore, it is not surprising that the *obesogen* effects are found in other animal groups beyond mammals. Collectively, data indicates that suspected *obesogens* impact lipid metabolism across phyla that have diverged over 600 million years ago. Thus, a consistent link between environmental chemical exposure and the obesity epidemic has emerged. This review aims to summarize the available information on the effects of putative *obesogens* in aquatic organisms, considering the similarities and differences of lipid homeostasis pathways among metazoans, thus contributing to a better understanding of the etiology of obesity in human populations. Finally, we identify the knowledge gaps in this field and we set future research priorities.

1. Introduction

1.1. Endocrine disruption

The steep increase of chemical production and use since the 1940s coincides with the rise of several endocrine-related disorders in humans and wildlife populations, suggesting a relationship between both events (Bergman et al., 2013; Diamanti-Kandarakis et al., 2009; Grün and Blumberg, 2006; Kabir et al., 2015). The number of studies supporting this hypothesis is growing and it is now established that several of these chemicals have endocrine disrupting properties (Bergman et al., 2013). Endocrine disrupting chemicals (EDC) interfere with the normal

Abbreviations: ACA, Acetyl-CoA Acyltransferase; ACACa, acetyl-CoA carboxylase 1; ACACb, acetyl-CoA carboxylase 2; ACC, Acetyl CoA Carboxylase; ACOX, Acyl-CoA Oxidase; ACS, Acetyl-CoA synthetase; APOA-1, apolipoprotein A-I; BBzP, Butyl benzyl phthalate; BPA, Bisphenol A; BZF, bezafibrate; CA, clofibric acid; C/EBPs, CCAAT/enhancer binding proteins; CPT, carnitine palmitoyltransferase; CYP27a, sterol 27-hydroxylase; CYP4, cytochrome P450 4; DBD, DNA binding domain; DDT, dichlorodiphenyltrichloroethane; DEHP, di-2-ethylhexylphthalate; DiDP, diisodecyl phthalate; ECR, Ecdysone Receptor; EDC, Endocrine disrupting chemicals; ER, estrogen receptor; FA, fatty acid; FABP, fatty acid binding protein; FADS, fatty acid desaturase; FASN, Fatty Acid Synthase; FXR, farnesoid X receptor; GPAT1, glycerol-3-phosphate acyltransferase 1; HL, hepatic lipase; HNF4A, Hepatocyte Nuclear Factor 4 A; HSL, hormone sensitive lipase; IPA, Ingenuity pathway analysis; KSI, kidney somatic index; LBD, ligand biding domain; LPL, Lipoprotein Lipase; LSI, liver somatic index; LXR, liver X receptor; MEHP, Mono-ethyl-hexyl phthalate; NP, nonylphenol; NRs, nuclear receptors; PA, phthalic acid; PAHs, Polycyclic aromatic hydrocarbons; PBBs, polybrominated biphenyls; PCBs, polychlorinated biphenyls; PFOA, perfluorooctanoic acid; PPARs, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; Rosi, Rosiglitazone; RXR, retinoid X receptor; SCD1, stearoyl-CoA desaturase 1; sod1, superoxide dismutase; SREBPs, sterol regulatory element-binding proteins; STA, Steroidogenic Acute Regulatory Protein; t-OP, octylphenol; TAG, Triacylglycerol; TBBPA, Tetrabromobisphenol A; TBT, Tributyltin; TCBPA, tetrachlorobisphenol A; TPT, Triphenyltin; WAT, White Adipose Tissue; ZOT, Zebrafish obesogenic test

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function of the endocrine system by mimicking, blocking and/or altering hormone roles and metabolism (Diamanti-Kandarakis et al., 2009; Kabir et al., 2015; Schug et al., 2011). Although more than 1300 chemicals have been identified to potentially interfere with hormonal metabolism, very few have been screened for their capacity to cause endocrine effects in vivo (Bergman et al., 2013; "TEDX The Endocrine Disrupting Exchange," 2017).

This vast number of compounds identified as EDCs have distinct chemical structures, proprieties and applications. Some of these compounds are used as synthetic hormones (e.g. ethynilestradiol), plastics (e.g. bisphenol A (BPA), phthalates), pesticides and fungicides (e.g.: organotins, methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT), vinclozolin), solvents (e.g.: polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins), pharmaceutical agents (e.g. thiazolidinediones, atypical anti-psychotics, antihistamines, antidepressants) and personal care products (e.g. triclosan). Besides synthetic chemicals, some natural compounds are also known EDCs (e.g. phytoestrogens, including genistein and coumestrol) (Castro and Santos, 2014; Kabir et al., 2015; Schug et al., 2016). Several of these compounds can undergo bioaccumulation and biomagnification through the food-chain, being persistent in the environment. In contrast, others are easily degraded but their continuous release into the environment still makes them a cause of concern (Bergman et al., 2013; Diamanti-Kandarakis et al., 2009; Kabir et al., 2015) (See Fig. 1).

The effects of different EDCs in non-target organisms have been well documented (Ferreira et al., 2009; Liu et al., 2014; Melvin, 2016; Rodrigues et al., 2006; Schug et al., 2016). Two well-known examples targeting the reproductive system are organotins that cause imposex in gastropods mollusks (a condition characterized by the development of male secondary sexual characteristics in females) (Abidli et al., 2009; Lima et al., 2011; Pascoal et al., 2013), and ethinylestradiol that alters the fecundity and sex ratio of fish (Runnalls et al., 2015; Soares et al., 2009). Alterations in gene and protein expression, as well as physiological and behavioral changes are also observed frequently as a consequence of EDC exposure (Brander, 2013; Sária et al., 2013). More recently, evidences emerged regarding disruption in lipid homeostasis by EDCs. Since lipid metabolism dysregulation is related with several important diseases in the human population, the mode of action of these compounds - also known as *obesogens*- is now under strong scrutiny (Castro and Santos, 2014; De Cock and Van de Bor, 2014; Diamanti-Kandarakis et al., 2009; Grün and Blumberg, 2006; Ouadah-Boussouf and Babin, 2016; Santos et al., 2012). These compounds can increase the number of fat cells and/or the amount of fat stored in each cell by altering the pathways of energy metabolism and food intake (Holtcamp, 2012; Janesick and Blumberg, 2011). Several mechanisms of action have been suggested, including epigenetic changes that will be inherited by the future generations (Holtcamp, 2012). However, only a small portion of chemicals has been tested so far for their potential to disrupt lipid homeostasis and a considerable amount of those fall in the *obesogens* category, such as organotins, BPA, perfluorooctanoic acid (PFOA), phthalates and some pharmaceuticals (Bašić et al., 2012; Bergman et al., 2013; Legler et al., 2015).

1.2. Lipid homeostasis

Lipid homeostasis is vital for the normal development, maintenance and reproduction of metazoans, given their transversal involvement in a great variety of metabolic processes, such as energy storage, membrane composition, as intracellular signaling molecules, enzyme cofactors and several others (Birsoy et al., 2013). In vertebrates, lipid metabolism is tightly regulated so that the organism can meet its physiological needs (Castro et al., 2016; Mello, 2010; Santos et al., 2012) (see Fig. 2). This metabolic regulation involves three major forms (Desvergne et al., 2006):

a. Allosteric control of enzyme activity along a metabolic pathway through the binding of an activator (for example, the enzyme-substrate);
b. Post-translational modifications, which activate/deactivate the enzyme;

One example is the phosphorylation/dephosphorylation of Acetyl CoA Carboxylase (ACC). Low glucose levels cause the dephosphorylation of ACC down-regulating the fatty acid synthesis, while high glucose levels cause the opposite response. This regulation is essential in the balance between β-oxidation and fatty acid (FA) synthesis. (Berg et al., 2002; Nelson et al., 2005).

c. Transcriptional regulation;

This regulation of lipid metabolism occurs through the action of several transcription factors, including nuclear receptors (NRs), sterol regulatory element-binding proteins (SREBPs) and CCAAT/enhancer binding proteins (C/EBPs) (Desvergne et al., 2006). The transcription factors can up or down-regulate the transcription of specific genes and protein synthesis (Lempradl et al., 2015; Lyssimachou et al., 2015). NRs include peroxisome proliferator-activated receptors (PPARs), pregnane X receptor (PXR), liver X receptor (LXR), farnesoid X receptor (FXR), all

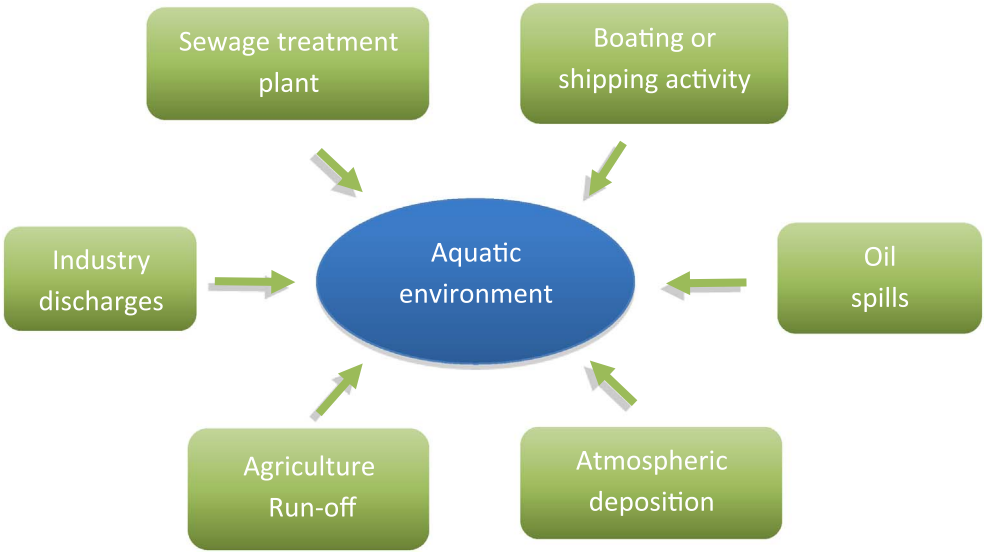

Fig. 1. Schematic illustration of EDCs input in the aquatic environment (lakes, rivers and sea) (modified from Pait and Nelson, 2002; Sumpter, 2005).