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Current Opinion in Toxicology

Role of mixtures of organic pollutants in the development of metabolic disorders *via* the activation of xenosensors

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Abstract

Environmental pollutants, particularly persistent organic pollutants but also widespread short-lived ones (bisphenol family and phthalates), also may be endocrine disruptors. These molecules are emerging in the etiology of the world-wide epidemic of chronic diseases such as obesity, diabetes and the metabolic syndrome. These pollutants mainly bind either xenosensors or endocrine receptors, which then act as transcription factors. On the one hand, recent epidemiological studies have pinpointed the association between human exposure to mixtures of such contaminants and metabolic disorders. On the other hand, numerous studies in animal and *in vitro* models have described the consequences of exposure to individual pollutants in terms of modifications of the transcriptome or the metabolome implicating diverse signaling and metabolic pathways linked to obesity or the metabolic syndrome. The objectives of this commentary are 1) to give an overview of the potential role of organic pollutant mixtures on metabolic dysfunction, with a focus on obesity, type 2 diabetes and the metabolic syndrome in humans, as assessed by epidemiological studies; 2) to assess the state of art of *in vitro* and *in vivo* models to address this question, since most studies focus on the effects of single pollutants and 3) to evaluate the limits of the various models, in relation to the epidemiological studies.

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Current Opinion in Toxicology 2018, **8**:57–65

This review comes from a themed issue on **Mechanistic toxicology: Metabolic Disruption**

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cotox.2018.01.001

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Keywords

Xenosensor, Mixture, Endocrine disruptor, Pollutant, Metabolic disorder.

1. Introduction

Living organisms are exposed to various xenobiotics (xeno: foreign, biotics: living). During the course of time, they have been and continue to be produced naturally, for example by fires and volcanoes. During the course of human evolution and, especially, during the last two centuries with the occurrence of the industrial revolution, there has been an exponential increase in the number of chemical compounds, some of which are toxic. Among them are the persistent organic pollutants (POPs) and the endocrine disrupting compounds (EDCs). POPs are defined by the Stockholm Convention as compounds that have a slow rate of biodegradation, long distance transportation, high lipophilicity and, thus, bioaccumulation in fat tissues. Although most POPs have been banned, their study is still of interest for understanding their effects on health. EDCs are defined as interfering with any aspect of hormonal action [1]. Some molecules are both POPs and EDCs and, therefore, may disrupt cell physiology.

The WHO has declared obesity (defined as BMI$\geq$30 kg/m^2 for adults by the WHO, and for children as a weight-for-height greater than 3 (age<5 years) or 2 (age>5 years) standard deviations above the WHO Child Growth Standards or Reference median) and its related diseases, diabetes, cardiovascular diseases, musculoskeletal disorders and some cancers, as a worldwide epidemic burden [2]. Xenobiotics, especially EDCs, have multiple deleterious effects, among which carcinogenicity and alterations of the reproductive system have been the most studied ([3] for a review). Many epidemiological studies now have reported associations between the levels of various contaminants, mainly POPs, and metabolic disorders. Thus, an increasing number of studies now focus on metabolic disruption by pollutants. For example, Toxicant-Associated Fatty Liver Disease (TAFLD) has been described as a form of NAFLD (Non-Alcoholic Fatty Liver Disease) associated with exposure to industrial chemicals, such as vinyl chloride in workers [4] or various polychlorobiphenyls (PCBs) and heavy metals in the NHANES cohort [5]. The liver, one of the main metabolic regulators, participates in the control of the levels of blood glucose, lipids, amino acids, lactate and ammonia. Other tissues also regulate metabolism: adipose tissue (triglyceride storage, adipokine secretion), the pancreas (hormone release), smooth muscle (glycogen storage) and the kidney (blood filtration). We will focus, mainly, on the metabolic syndrome (hypertension, dyslipidemia, hyperglycemia) which is often linked to obesity and type 2 diabetes and which

has been associated with exposure to organic pollutants, alone or in combination.

Humans (as well as entire ecosystems) were and still are increasingly exposed to POPs. The rapidity with which these molecules have appeared has not permitted living organisms to modify their arsenal of proteins to combat potentially toxic effects. At present, three proteins, called xenosensors, are known to respond to xenobiotics which an organism might encounter: the Aryl Hydrocarbon Receptor (AHR), the Pregnane X Receptor (PXR) and the Constitutive Androstane Receptor (CAR) (Table 1). These intracellular receptors bind the xenobiotics and transactivate the expression of target genes, mainly xenobiotic metabolizing enzymes. These enzymes modify the molecules to permit their elimination from the body and allow the survival of the cells. In addition to exogenous ligands, endogenous ligands, such as tryptophan derivatives, also bind the xenosensors, as described recently for the aryl hydrocarbon receptor [6]. Moreover, endocrine receptors and other nuclear receptors can bind some pollutants. Presumably, endocrine receptors were not initially destined to perform such an activity and cellular dysfunctions result. Today, about 15 receptors, which can bind various xenobiotics, have been described (Table 1).

Given the number of xenobiotics (more than 100,000 referenced chemicals), the possible combinations, which represent the exposure of a human organism from conception throughout its life (defined as the exposome by C. Wild [7]), are vast. Since current research technologies are incapable of testing all the possible combinations of compounds, alternate approaches need to be employed. Two complementary approaches that have been developed are: i) the study of the effects of authentic exposures as determined by measurements from blood, urine or hair samples from cohorts or known mixtures (mixtures of polychlorobiphenyls (PCBs) such as Arochlor®, ClophenA60® or Phenoclor® sold by several companies [8]) and ii) the study of intra-cellular signaling pathways that are dysregulated following the activation of one or several xenosensors by prototypical ligands in *in vivo* and *in vitro* models. However, cross-talks between several receptors or their pathways, such as the interaction between the AHR and ERα [9], have been documented which may complicate interpretation of the experimental results. A role *via* the binding to xenosensors of many contaminants is now well documented in *in vitro* cellular models and in various animal species, especially rodents. However, extrapolation of the results obtained in these models to the potential effects found in human populations is not

Table 1 List of receptors which bind xenobiotics. For each, examples of endogenous and exogenous ligands are given [10–15]. *considered as hormones by some authors (bile acids [16]; 9-*cis* RA [17]). For abbreviations of xenobiotics, see Table 2.

Acronym	Approved symbol (nuclear receptor family)	Receptor name	Example(s) of xenobiotics	Example(s) of endogenous ligand(s)
Xenobiotic receptors (xenosensors)				
AHR	AHR	Aryl hydrocarbon receptor	Dioxins, DPCBs	Indol and tryptophan derivatives
PXR (=SXR)	NR1I2	Pregnane-X-receptor	NPCBs (PCB-153), several drugs	5 β-cholestane-3α 7α, 12α-triol, steroids, bile acids*
CAR	NR1I3	Constitutive androstane receptor	NPCBs (PCB-153), several drugs	Androstane and derivatives
Endocrine nuclear receptors				
ER α, β	ESR1 (NR3A1), ESR2 (NR3A2)	Estrogen receptor	Bisphenol A (BPA), pesticides (DDT)	β-17-estradiol
AR	AR (NR3C4)	Androgen receptor	*p,p'*-DDE	Testosterone
PR	PGR (NR3C3)	Progesterone receptor	Musk compounds	progesterone
TR α, β	THRA (NR1A1), THRB (NR1A2)	Thyroid hormone receptor	Hydroxylated Polybrominated Diphenyl Ethers	Thyroid hormones
GR	NR3C1	Glucocorticoid receptor	Tolylfluanid, DPCBs, PCB methyl sulphones	cortisol
VDR	NR1I1	Vitamin D receptor	Curcumin	1,25-dihydroxy-vitamin D (calcitriol)
Other nuclear receptors				
PPAR α, δ, γ	PPARA (NR1C1), PPARD (NR1C2), PPARG (NR1C3)	Peroxisome Proliferator-activated Receptor	Phthalates, organotins	Arachidonic acid derivatives, linoleic acid derivatives
FXR	NR1H4	Farnesoid X Receptor	Pyrethroids	Bile acids*
RXR α, β, γ	RXRA (NR2B1), RXRB (NR2B2), RXRG (NR2B3)	Retinoid X Receptor	Organotins (tributyltin)	9-*cis*-retinoic acid*
RAR α, β, γ	RARA (NR1B1), RARB (NR1B2), RARG (NR1B3)	Retinoic acid receptor	Organochlorine pesticides, alkylphenols, phthalate esters	All *trans* retinoic acid
LXR α/β	LXRA (NR1H3), LXRB (NR1H2)	Liver X receptor	PFOA	oxysterol

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