Endocrine Disruptors: From Endocrine to Metabolic Disruption

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Abstract

Synthetic chemicals currently used in a variety of industrial and agricultural applications are leading to widespread contamination of the environment. Even though the intended uses of pesticides, plasticizers, antimicrobials, and flame retardants are beneficial, effects on human health are a global concern. These so-called endocrine-disrupting chemicals (EDCs) can disrupt hormonal balance and result in developmental and reproductive abnormalities. New in vitro, in vivo, and epidemiological studies link human EDC exposure with obesity, metabolic syndrome, and type 2 diabetes. Here we review the main chemical compounds that may contribute to metabolic disruption. We then present their demonstrated or suggested mechanisms of action with respect to nuclear receptor signaling. Finally, we discuss the difficulties of fairly assessing the risks linked to EDC exposure, including developmental exposure, problems of high- and low-dose exposure, and the complexity of current chemical environments.

EDCs: endocrine-disrupting chemicals

Metabolic syndrome: a combination of disorders including impaired glucose tolerance or insulin resistance, dyslipidemia, high blood pressure, and obesity

NRs: nuclear receptors

1. INTRODUCTION

1.1. Endocrine Disruption

Endocrine disruptors are exogenous compounds with the potential to disturb hormonal regulation and the normal endocrine system, consequently affecting health and reproduction in animals and humans (1). Endocrine disruptors can interfere with the production, release, metabolism, and elimination of or can mimic the occurrence of natural hormones (2). Endocrine disruptors may also be derived from natural animal, human, or plant (phytoestrogen) sources; however, for the most part international concern is currently focused on synthetic chemicals and endocrine-disrupting chemicals (EDCs). This concern is further amplified by two factors, the expansion in chemical production, which has now reached 400 million tons globally, and the increased pollution from these chemicals. As such, the impact on human health through known or unknown effects of these chemicals on hormonal systems is great.

The term endocrine disruptors was first coined by Ana Soto and collaborators, who identified a number of developmental effects of EDCs in wildlife and humans (3). Although EDCs can target various hormone systems, a number of observations concerning reproductive development and sex differentiation, together with early embryonic development and puberty, have focused on EDC interference with sex steroid hormones.

1.2. Metabolic Disruption: A Subdivision of Endocrine Disruption

In addition to the developmental and reproductive effects, there is also a growing concern that metabolic disorders may be linked with EDCs. Global obesity rates have risen dramatically over the past three decades in adults, children, and adolescents, especially in developed countries. Obesity is frequently associated with metabolic disorders (including type 2 diabetes, metabolic syndrome, cardiovascular and pulmonary complications, and liver disease) as well as other health issues such as psychological/social problems, reproductive defects, and some forms of cancer.

A combination of genetic, lifestyle, and environmental factors likely account for the rapid and significant increase in obesity rates. Although genetic factors may explain a portion of obesity predisposition, they alone are unable to account for the sudden appearance and progression of the current worldwide obesity epidemic. Modern lifestyles that include excessive energy intake, lack of physical activity, sleep deprivation, and more stable home temperatures appear to be major contributing factors of obesity. However, the increased incidence of metabolic diseases also correlates with substantial changes in the chemical environment resulting from new industrial and agricultural procedures initiated over the past 40 years. This change in the environment has led to the hypothesis that some of the numerous environmental pollutants are EDCs, interfering with various aspects of metabolism and adding another risk factor for obesity (4, 5). This hypothesis is supported by laboratory and animal research as well as epidemiological studies that have shown that a variety of environmental EDCs can influence adipogenesis and obesity (reviewed in References 5–10). Such EDCs have been referred to as environmental obesogens (11). However, because adverse effects by EDCs may also lead to other metabolic diseases such as metabolic syndrome and type 2 diabetes, this subclass of EDCs would be better referred to as metabolic disruptors (12).

1.3. A Common Molecular Mechanism for Endocrine Disruption and Metabolic Disruption

Hormones function mainly through interactions with their cognate receptors, which can be classified into two large groups: (*a*) membrane-bound receptors, which respond primarily to peptide hormones such as insulin, and (*b*) nuclear receptors (NRs), which are activated by interaction with small lipophilic hormones such as sex steroid hormones. EDCs may possess multiple mechanisms of action; however, because many EDCs are small lipophilic compounds, one privileged route is through their direct interaction with a given NR, which presumably perturbs or modulates downstream gene expression. For example, most EDC-associated reproductive and developmental defects are thought to result from EDCs interfering with the function of the estrogen receptor (ER) and/or androgen receptor (AR), thereby disrupting the normal activity of estrogens and androgens ligands.

In humans, the NR superfamily encompasses 48 members that share a common structure and, once activated, bind as dimers to specific response elements located near target gene promoters. These dimers may be homodimers or heterodimers with retinoid X receptor (RXR), another member of the NR superfamily. In addition to the sex steroid receptors, the NR superfamily includes transcription factors that play pivotal roles in the integration of the complexities of metabolic homeostasis and development. The ability of EDCs to interact with these NRs is supported by, and explains, the wide range of metabolic perturbations reported in both experimental and epidemiological studies. It also reinforces the concept of associating endocrine and metabolic disruption.

The present review focuses on metabolic disruptors and is organized into three sections. The first section discusses the chemical compounds that are presently considered to be major potential endocrine/metabolic disruptors. Also summarized is the impact of these chemicals on human health and metabolism on the basis of available epidemiological studies. The second section highlights recent advances in established or proposed mechanisms of EDC-mediated metabolic disruption. The last section highlights the main challenges that scientists and regulators face in this field.

2. A MYRIAD OF ENDOCRINE-DISRUPTING CHEMICALS

EDCs encompass a variety of chemical classes, including pesticides, compounds used in the plastic industry and in consumer products, and other industrial by-products and pollutants. They are often widely dispersed in the environment and, if persistent, can be transported long distances; EDCs are found in virtually all regions of the world (13–17). Persistent organic pollutants are prevalent among environmental contaminants because they are resistant to common modes of chemical, biological, or photolytic degradation. Moreover, many EDCs can be stored for years in animal and human fat mass. However, other EDCs that are rapidly degraded in the environment or the human body, or that may be present for only short periods of time, can also have serious deleterious effects if exposure occurs during critical developmental periods.

EDCs can be categorized according to their intended use (e.g., pesticides) or their structural properties (e.g., dioxins). The main categories of chemicals with suspected metabolism-disrupting activity are presented below (see **Tables 1** and **2**). For more detailed information, the interested reader may refer to in-depth reviews focused on specific chemical categories, as discussed below.

2.1. Pesticides

Pesticides are any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest (1, 18). Several hundreds, if not thousands, of different chemicals are used as pesticides, and human exposure to these pesticides is widespread. Prominent chemical families include organochlorine pesticides (OCPs), organophosphates, carbamates, triazines, and pyrethroids. All OCPs are persistent. Even though OCPs such as the insecticide dichlorodiphenyltrichloroethane (DDT) are currently banned in most developed countries and were subsequently replaced in 1975 by organophosphates and carbamates, DDT contamination still exists. OCPs are detected in human breast milk and adipose tissue and may exhibit estrogenic, antiestrogenic, or antiandrogenic activity. Their association with breast cancer is suspected but not yet

Estrogen receptors (ERs): ERα and ERβ are members of the nuclear receptor superfamily. They form homodimers to bind to DNA

Retinoid X receptor (RXR): a member of the nuclear receptor superfamily and a major partner of other nuclear receptors such as PPAR, PXR, and CAR, with which it forms heterodimers

Persistent organic pollutants: chemicals that persist in the environment and bioaccumulate with risks of adverse effects to human health and environment

OCPs: organochlorine pesticides

Table 1 EDCs described as metabolic disruptors and their effects on the metabolism[a]

EDCs	Type or source	Legal status	NRs	In vitro/animal studies	Human epidemiological studies	Developmental exposure studies	References
Organochlorines (e.g., DDT)	Pesticides and plasticizers	1970s: DDT banned in most developed countries 2000s: restricted by the Stockholm Convention	ERα, AR		Associated with MetS and diabetes	Associated with children being overweight (humans)	22, 24, 25
Dioxins (e.g., PCB, TCDD)	Environmental pollutants in food	2000s: PCB banned and other dioxins restricted by the Stockholm Convention	Via AhR: PPARγ, ERs	Adipogenesis inhibition	Associated with MetS, obesity, and diabetes		123
Organotins (e.g., TBT, TPTO)	Environmental pollutants in food	Banned worldwide by the International Maritime Organization	RXR: PPARγ	Adipogenesis induction		Control of adipogenesis disruption (mice)	28, 31, 144
PFCs (e.g., PFOA, PFOS)	Plasticizers	2009: restricted by the Stockholm Convention and the EU	ERs, AR, PPARs	Weight loss, anorexigenic effect	Associated with increased cholesterol levels	Weight gain and increased serum insulin and leptin levels (mice)	38, 40, 140–142
BFRs (e.g., PBDE)	Flame retardants	PBDE banned in the EU and some U.S. states 2009: some BFRs banned by the Stockholm Convention	PXR, ERs, TR	Lipolysis increase, glucose oxidation decrease	Associated with MetS and diabetes		95, 122, 155
Alkylphenols (e.g., octylphenol)	Surfactants	Restricted for some uses in the EU	ERs, AR, CAR	Resistin expression upregulation			80
BPA	Plasticizers	2009: Canada becomes the first country to ban BPA in baby bottles; WHO begins assessing BPA safety	ERs, AR, TR, GR	Adipogenesis induction, insulin increase	Associated with diabetes and liver abnormalities	Increased body weight (mice and rats)	60, 82, 85, 156
Phthalates (e.g., DEHP, DBP, DEP)	Plasticizers	Restricted in children's toys in the EU (1999) and the United States (2009) 2010: Australia bans products with >1% of DEHP	PPARs, CAR/PXR, GR	Adipogenesis induction in cells, body weight decrease in mice	Associated with obesity and insulin resistance	DiBP: reduced plasma insulin and leptin levels in mice DEHP: no effect (mice)	6, 9, 73, 133, 136, 138

[a]Abbreviations used: Ahr, aryl hydrocarbon receptor; AR, androgen receptor; BFR, brominated flame retardant; BPA, bisphenol A; CAR, constitutive androstane receptor; DBP, dibutyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEHP, diethylhexyl phthalate; DEP, diethyl phthalate; EDC, endocrine-disrupting chemical; ER, estrogen receptor; EU, European Union; GR, glucocorticoid receptor; MetS, metabolic syndrome; NR, nuclear receptor; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFC, polyfluoroalkyl compound; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PPAR, peroxisome proliferator–activated receptor; PXR, pregnane X receptor; RXR, retinoid X receptor; TBT, tributyltin chloride; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TPTO, bis(triphenyltin) oxide; TR, thyroid hormone receptor; WHO: World Health Organization.

Table 2 Human exposure to EDCs compared with concentrations experimentally used[a]

EDCs	Human exposure	Levels in the human body	Biological half-life	Concentrations experimentally used	References
Organochlorines (e.g., DDT)	Banned Soil half-life: 22 to 30 years	DDE: very variable range from <5 to >15,000 mg (kg BW)$^{-1}$	5 years	In cells: 20 μM *p,p′*-DTT	20, 24, 157
Dioxins (e.g., TCDD)	TDI: 1–4 pg (kg BW)$^{-1}$ (WHO)	In adipose tissue: 3.6 pg (g lipid)$^{-1}$ In blood: 2.2 ppt	7–11 years	In mice: doses of 5–500 ng (kg BW)$^{-1}$ day^{-1} affect energy metabolism	17, 119, 158
Organotins (e.g., TBT)	TDI: 1.6 mg (kg BW)$^{-1}$ (Welfare Ministry of Japan)	In serum: 27 nM In human tissue: 3–100 nM	From 23 to 30 days	In mice: induce adipogenesis at 0.05–0.5 mg (kg BW)$^{-1}$ In vitro: EC_{50}: 3–10 nM for RXR/PPARγ	11, 28
PFCs	Indoor air levels: PFOS: 5 ppm PFOA: 3.7 ppm	Serum-level medians: PFOS: 19.9 μg liter^{-1} PFOA: 3.9 μg liter^{-1}	PFOS: 5.4 years PFOA: 3.8 years	In rodents: PFOA prenatal exposure effects in a range of 0.01–5 mg (kg BW)$^{-1}$	10, 14, 40, 141, 142
BFRs (e.g., PBDE)	Exposure through diet: 37–97 ng day^{-1} Exposure through house dust: Adults: 16.7 ng day^{-1}; children: 191.3 ng day^{-1}	Mean levels in adipose tissue: Europe and Asia: <5 ng (g lipid)$^{-1}$ North America: >200 ng (g lipid)$^{-1}$ In fetal liver: range of 4–98.5 ng (g lipid)$^{-1}$ (in the United States) In breast milk: range of 1.57–73.9 ng (g lipid)$^{-1}$ (worldwide)	In serum: from weeks to months In fat: several years	In rats: exposure to 14 mg (kg BW)$^{-1}$ day^{-1} for four weeks alters lipolysis and glucose oxydation	13, 67, 95
Alkylphenols	NP's TDI: 7.5 mg day^{-1} (Germany)	In urine: range of 0.4–13.9 ng ml^{-1} In adipose tissue: median level of 57 ng g^{-1} (Spain)	NP in blood: 2–3 h	In vitro: lowest effect concentrations in the 10–1000-nM range	52, 55, 56
BPA	TDI: <50 μg (kg BW)$^{-1}$ day^{-1} (U.S. Environmental Protection Agency)	Range of 0.1–10 ng ml^{-1} in blood, urine, fat, and fetal tissue	6 h	In vitro: lowest effect concentrations in the 0.1–1-nM range In mice: weight increase correlated with in utero exposure to 2.4–500 μg (kg BW)$^{-1}$ day^{-1}	55, 67, 89, 156
Phthalates	DBP's TDI: 10 mg (kg BW)$^{-1}$ day^{-1} (European Food Safety Authority)	Range of prenatal phthalate metabolite mean levels in urine of mothers: 2.54–816 μg liter^{-1} Monoesters of DEHP in children's urine: 91.3 μg liter^{-1} (NHANES)	From hours to days	In cells: 50-μM DEHP, DBP, and metabolites In mice: DEHP: 1,000 mg kg^{-1} day^{-1}; DBP: 2,000 mg kg^{-1} day^{-1}	32, 67, 134

[a]Abbreviations used: BFR, brominated flame retardant; BPA, bisphenol A; BW, body weight; DBP, dibutyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEHP, diethylhexyl phthalate; EDC, endocrine-disrupting chemical; NHANES, National Health and Nutrition Examination Survey; NP, 4-nonylphenol; PBDE, polybrominated diphenyl ether; PFC, polyfluoroalkyl compound; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PPAR, peroxisome proliferator–activated receptor; ppt, parts per trillion; RXR, retinoid X receptor; TBT, tributyltin chloride; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TDI, tolerable daily intake; WHO, World Health Organization.

NHANES

The National Health and Nutrition Examination Survey (NHANES) is the American food consumption database program conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. This program was designed to collect data and to assess the health and nutritional status of adults and children in the United States. The program began in 1960, but in 1999 NHANES was changed to include the testing of blood and urine for an extensive number of chemicals and to monitor roughly 5,000 to 10,000 nationally representative persons per year. All NHANES surveys are cross-sectional and contain a core set of physical examinations, clinical and laboratory tests, and personal interviews. Information about disease and health status, diet, sociodemographics, occupation, and education is collected. In addition, tests are conducted for a variety of materials, such as micronutrients, disease markers, and environmental pollutants. NHANES's partnership with the Environmental Protection Agency has also allowed for the implementation of longitudinal studies of many important environmental influences on health [NHANES I Epidemiologic Follow-Up Study (NHEFS)]. NHANES and NHEFS data are public and available for researchers at **http://www.cdc.gov/nchs/nhanes.htm**.

demonstrated by epidemiological studies (19). A well-documented case study in the United Kingdom listed 127 pesticides identified as having endocrine-disrupting properties (16). Despite confounding issues stemming from the multifactorial causes of disease and the challenges in monitoring pesticide exposure, this study underscores the link between medical problems and pesticide exposure (16). With respect to metabolic disorders, a large number of epidemiological studies have also linked pesticide exposure with obesity, diabetes, insulin resistance, and metabolic syndrome (9, 20). For example, an association was discovered between prenatal exposure to the DDT breakdown product dichlorodiphenyldichloroethylene (DDE) and increased body mass index in adult women (21). Similarly, cord blood levels of the OCP hexachlorobenzene correlated with a two- to threefold-higher risk of an elevated body mass index and obesity in children (22). Another study used the National Health and Nutrition Examination Survey (NHANES) database and carried out a cross-sectional analysis of 1,721 adults (see NHANES and Observational Studies sidebars); the study reported a positive association between diabetes and the levels of 19 different persistent pollutants (including OCPs) measured in serum (21). Other epidemiological studies find a significant association between pesticide exposure [mostly OCPs such as heptachlore epoxide, oxychlordane, or β-hexachlorocyclohexane (β-HCH)] and higher incidences of metabolic syndrome, insulin resistance, and diabetes (23, 24). A higher prevalence of diabetes is also associated with DDE exposure (25).

PVC: polyvinyl chloride

2.2. Dioxins

Dioxins consist of a group of organochlorines that include the polychlorinated dibenzodioxins (PCDDs), the polychlorinated dibenzofurans (PCDFs), and the polychlorinated biphenyls (PCBs) and other related compounds. Dioxins can be produced from natural sources such as volcanoes and forest fires but are created mostly by human activity as by-products in organochloride production, in incineration of chlorine-containing substances such as polyvinyl chloride (PVC), and in bleached paper production. The PCDD 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the most toxic of all dioxins. This dioxin was a major contaminant in the Seveso catastrophe and in the Vietnam War (Agent Orange); it was also used as a poison in the attempted assassination of Viktor Yushchenko (17).

Dioxins are fat soluble and readily climb the food chain via their bioaccumulation in fat tissues. They are neither readily metabolized nor excreted, and TCDD has a half-life of approximately 8 years in humans. Several epidemiological studies have evaluated the toxic effects of TCDD and others dioxins on the general population as well as heavily exposed subgroups such as Vietnam War veterans (reviewed in References 17 and 26). These studies demonstrate a cause and effect between dioxin exposure, with an increase in cancers, nervous system degeneration, immune damage, thyroid disease, and reproductive and sexual development disorders. With respect to metabolism, exploration of the NHANES database indicated that PCDDs and PCDFs are weakly associated with metabolic disorders, whereas PCBs are strongly associated with type 2 diabetes (27). Several cross-sectional investigations further supported these correlations (reviewed in Reference 25).

OBSERVATIONAL STUDIES

Different types of observational studies are detailed at **http://www.vetmed.wsu.edu/courses-jmgay/glossclinstudy.htm**. A summary is presented below.

Clinical studies aimed at evaluating the effects of EDC exposure rely mainly on observational studies, which interpret experiments of nature and are exposed to large confounding biases. However, such studies provide preliminary evidence to be used as a basis for hypotheses.

Cross-sectional studies examine the relationship between diseases and other factors (such as EDC levels) at one point in time in a defined population. Cross-sectional studies lack any information on timing of exposure and include only prevalent cases. They can suggest a link between a disease and the factor of interest.

In longitudinal studies, or cohort studies, a panel of individuals is interviewed repeatedly over a period of time. This allows a prospective and analytical study of a group in which some individuals have had, currently have, or will have the exposure of interest to determine the association between that exposure and an outcome. Cohort studies are stronger than cross-sectional and case-control studies when well executed, but they are more expensive.

Case-control studies are a retrospective comparison of the proportion of cases with a potential risk factor to the proportion of controls (individuals without the disease) with the same risk factor. Due to the potential for many forms of bias in this study type, case-control studies provide relatively weak empirical evidence, even when properly executed.

2.3. Organotins

Organotins, including tributyltin chloride (TBT) and bis(triphenyltin) oxide (TPTO), are persistent organic pollutants that have been widely used as agricultural fungicides, as rodent repellents, as molluscicides, and in antifouling paints for ships and fishing nets. Organotin compounds such as PVC are also used to stabilize plastics.

TBT and TPTO provide one of the clearest examples of environmental endocrine disruption: Exposure of marine gastropods to very low concentrations of these compounds induces an irreversible sexual abnormality in females termed imposex, resulting in impaired reproductive fitness and possibly sterility (28). Concerns over the toxicity of these compounds led to a worldwide restriction and a ban on marine uses. Currently, human exposure may come from dietary sources, such as fish and shellfish, or through contaminated drinking water and food. However, no epidemiological data are available concerning human exposure, although TBT has been reported to have modest adverse effects on mammalian male and female reproductive tracts (29, 30). Nonetheless, recent experimental studies revealed proadipogenic activity of TBT and TPTO (11, 31).

2.4. Plastics

Owing to their variety, robustness, and extremely low costs, plastics are fundamental in modern life, public health, and medicine; plastic production exceeded 300 million tons in 2010 (32). After more than five decades of debate and research, controversy still surrounds the risks that plastics may cause in humans, particularly with respect to endocrine-disrupting properties. Adverse effects can stem from the various components of plastics, the additives used, or a combination of both. Laboratory animal and epidemiological studies have studied the effects of several of these substances on human health. A few examples are provided below.

2.4.1. Polyfluoroalkyl compounds. Polyfluoroalkyl compounds (PFCs) are synthetic fluorinated organic compounds used in a wide range of industrial applications and consumer products, including paper, leather, textile coatings, and fire-fighting foam, and in the polymer

PFCs: polyfluoroalkyl compounds

BFRs: brominated flame retardants

industry. Among them, perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are widely detected in the environment. PFCs are classified as persistent organic pollutants, even though they are not stored in fat tissue but instead form chemical adducts with liver and serum proteins. Laboratory rodents exposed to PFCs exhibit developmental effects such as reduced birth weight and increased neonatal mortality (33–35). In addition to hormonal perturbations with decreased testosterone levels and increased estradiol levels in adult rats (36), reductions in serum cholesterol and/or triglyceride in mice and rats exposed to high doses of PFOS and PFOA (37) suggest that these chemicals disturb normal lipid metabolism.

Inverse relationships were observed between PFOS and PFOA concentrations in cord blood and birth weight, ponderal index, and head circumference in children (38; reviewed in Reference 15). Numerous studies have evaluated the possible associations of blood PFC levels with metabolic parameters; the most consistent result is the positive association between PFC exposure and increased cholesterol, particularly high-density lipoprotein (HDL) (39–44). The same reports discounted any association with metabolic diseases such as type 2 diabetes and metabolic syndrome (39–44) and suggested a complex positive correlation of PFC levels with hyperglycemia but an inverse correlation with metabolic syndrome in adolescents (45). Most of these studies are cross-sectional and as such fail to provide a causal link but rather draw attention to the potential effects of PFCs on human physiology.

2.4.2. Brominated flame retardants. Brominated flame retardants (BFRs), particularly polybrominated diphenyl ethers (PBDEs), are additives used as flame retardants in a great number of consumer products such as house electronic equipment, clothing, and furniture. Although these compounds have decreased fire incidences, they are highly prevalent, ubiquitous, and persistent pollutants. The main sources of human exposure come from indoor environments, diet, and occupational exposure (13, 46, 47). Despite their beneficial effects, these chemicals are also thought to adversely affect human health through endocrine disruption and developmental neurotoxicity (48). In addition, increased incidences of hepatocellular carcinoma and thyroid adenoma have been observed in rodents, albeit with relatively high exposure doses (49). Taken together, these observations have led to the recent ban of PBDEs in several American states and in the European Union, where a ban on all BFR use is being contemplated. Meanwhile, PBDEs are still present in environmental samples and are detected in milk, serum, and adipose tissue in animals and humans.

Published studies addressing the consequences of human BRF exposure remain scarce, and the effects of BFR exposure on sex steroid hormone systems are still poorly understood. One study demonstrated a correlation between PBDEs in breast milk and congenital cryptorchidism, although confounding factors may have been present (50). Only a few epidemiological studies have addressed the possible impacts of these persistent pollutants on metabolic parameters in humans. The most telling study revealed that, among six different BFRs, PBDE-153 and the polybrominated biphenyl PBB-153 showed an inverted U-shaped association with type 2 diabetes and metabolic syndrome (51). Clearly, more studies are needed to clarify the possible extent of BFR-related damage.

2.4.3. Alkylphenols. Alkylphenols such as 4-*n*-nonylphenol and 4-*n*-octylphenol are surfactants widely used in detergents, emulsifiers, antistatic agents, demulsifiers, and solubilizers and are found commonly in wastewater (52). They are also used as additives to plastics such as PVC and polystyrene, from which they can leach. Alkylphenols are capable of initiating proliferation in breast tumor cells in the laboratory (53), consistent with their capacities for estrogenic and antiandrogenic activity (54, 55, and references therein). However, given the low environmental concentrations and the current regulation of alkylphenol use in the European

Union [Directive 2003/53/EC (2003)], some authors argue that alkylphenols do not pose a health risk. Human exposure was recently evaluated in a population of women in southern Spain; nonylphenol was detected in 100% of the adipose tissue samples tested. In this study, body mass index was associated with nonylphenol levels and emerged as a determinant of exposure (56). More studies with larger study populations are thus required to evaluate the risks still posed by these chemicals.

2.4.4. Bisphenol A. Bisphenol A (BPA) is a high-volume-production monomer ($>2.5 \times 10^6$ kg year^{-1}) used in polycarbonated plastic, in polystyrene resins, and as dental sealants. It is also used as an additive to other plastics such as PVC, and halogenated derivatives of BPA are widely used as flame retardants (55). Because unbound monomers remain after BPA polymerization, BPA molecules can be released from beverage and food containers, for example, from plastic baby bottles or from tin can liners. Human exposure to BPA is thus widespread, and unconjugated BPA molecules are detected in human blood, tissues, and milk. In a reference study in the United States, as many as 95% of human urine samples contained detectable levels of BPA in a range that is predicted to be biologically active (38, 57). Estrogenic properties of BPA were first described in 1936 (58). Since then, experiments performed in rodents have confirmed its hormonal activity, although the models and the high doses reported do not allow direct transposition to human risks. Thus, the potential human health risks caused by BPA exposure remain fiercely debated. Experimental data have been used to evaluate long-term exposure of mammalian model organisms during development and in adulthood to low doses of BPA [levels that fall below the regulatory safety standard (59)]. In short, these studies point to a number of adverse effects in mammals that include abnormal penile/urethra development, decreased sperm count, early sexual maturation in females, and brain and behavioral abnormalities. As such, the potential impact of BPA on human health is not easily dismissed.

Bisphenol A (BPA): a high-volume-production plasticizer that is an estrogen mimic and is detected in 95% of human urine samples

A few epidemiological and preliminary studies, based on small populations, have uncovered associations between BPA blood levels in women and various ailments, including obesity, recurrent miscarriages, and sterility (60–62). Additionally, higher urinary concentrations of BPA are associated with an increased prevalence of cardiovascular disease, diabetes, and liver enzyme abnormalities (60). This last study highlighted the need for regulatory action regarding BPA exposure, and Canada was the first country to ban the use of BPA in baby bottles.

2.4.5. Phthalates. Phthalate esters have been used worldwide as softeners to impart flexibility, pliability, and elasticity to otherwise rigid polymers such as PVC. Produced in large quantities since the 1930s, nearly all groups of industrial consumer products contain phthalates or traces of phthalates. These molecules are found mostly in industrial paints and solvents but also in toys, personal-care products, and medical devices such as intravenous tubing and blood transfusion bags. In such devices, they can make up 80% of the product's weight (32). Unlike BPA, phthalates are not covalently bound to the polymer matrix, making them highly susceptible to leaching. As a result, phthalates contaminate food, particularly meat and milk products, and are found nearly everywhere in interior environments. In addition, important routes of human exposure include dermal uptake from personal-care products and from plastic medical devices that come into direct contact with biological fluids. Exposure to phthalates can occur in the developing fetus through the placenta-blood barrier and in postnatal stages during breast feeding or from mouthing toys and baby-care products. Once incorporated into the human body, phthalates are short-lived and are rapidly metabolized in a two-phase process (63). In phase I, diester phthalates are hydrolyzed into monoester phthalates, whose dosage is used for biomonitoring human exposure. The conjugation process in phase II

Diethylhexyl phthalate (DEHP): the most-used phthalate; its metabolite, MEHP [mono(2-ethylhexyl)phthalate], interferes with several types of nuclear receptors

leads to the urinary excretion of the conjugated metabolites.

Among all the phthalates, diethylhexyl phthalate (DEHP) elicits the most concern, with more than two million tons produced annually. This compound is widely used in medical devices and in a variety of food products. DEHP causes animal toxicity in many physiological systems; however, many of the abnormalities that have been characterized since the 1940s have occurred at high DEHP doses (32). In addition, DEHP promotes liver tumor development in rodent models through severe peroxisomal proliferation. However, peroxisome proliferation has not been observed in humans, and according to a decision of the International Agency for Research on Cancer, DEHP cannot be classified as a human carcinogen.

Experimental studies at low doses of DEHP exposure, which appear to be most pertinent to human health, have demonstrated subtle reproductive toxicity in male rodents (64, 65). Other reproductive outcomes include testicular dysgenesis together with permanent feminization and demasculinization, resulting in a reduced anogenital distance (66).

Some epidemiological studies reported an association between cord blood levels of mono(2-ethylhexyl)phthalate (MEHP), a DEHP metabolite, and shorter gestational age of delivery. Indirect evidence also suggests that diethyl phthalate and dibutyl phthalate may impart antiandrogenic effects in the perinatal period (reviewed in Reference 67). Maternal urine levels of metabolites of DEHP (benzylbutyl phthalate, diethyl phthalate, and dibutyl phthalate) are associated with a higher risk of incomplete testicular descent for male human infants and are inversely correlated with the anogenital distance (68, 69). Other developmental effects of phthalate exposure may cause damage to the pulmonary system and may result in asthma (70).

More recently, several studies have demonstrated a correlation between phthalates and metabolic disorders. In short- and long-term rodent studies, dose-related deregulation of levels of serum insulin, blood glucose, liver glycogen, T3, T4, thyroid-stimulating hormone, and cortisol was observed (71, 72). In humans, the log-transformed concentrations of several phthalate metabolites positively correlated with abdominal obesity and insulin resistance in adult males (73). These analyses support the concept of environmental obesogens but await further confirmation by longitudinal studies.

At first glance, this presentation of so many types of chemicals suspected of generating metabolic disruptors may seem alarming (see **Tables 1** and **2**). However, because many studies discussed here are cross-sectional, a definitive causal link between metabolic disorders and EDC exposure is still hypothetical. For that reason, parallel studies aimed at identifying the molecular mechanisms of EDC activity with regard to metabolism should provide greater insights into the real health risks posed by these compounds.

3. METABOLIC DISRUPTION: MECHANISTIC APPROACHES

In the context of endocrine disruption, metabolic disruption may result from three main types of activity. First, hormones in general and sex steroid hormones in particular contribute to general body homeostasis through diverse metabolic regulations. Thus, a certain number of metabolic perturbations are simply the result of hormonal disruption. Second, direct EDC activity through receptors responding to xenobiotics and regulating xenobiotic metabolism may also contribute to a metabolic phenotype. Third, EDC interactions with specialized metabolic receptors may serve as a primary mechanism for metabolic disruption. This article presents and discusses experimental observations linking EDCs with metabolic disruption along these three types of activity (see **Figure 1**).

3.1. Metabolic Disruption Through Hormone Receptors

Hormone receptors belong to a class of classic hormone receptors that recognize only one or a few molecules with high affinity. Thyroid hormone (TH), mineralocorticoid, glucocorticoid, retinoic acid, estrogen, vitamin D, progesterone, and androgen receptors belong to this class. Initial studies identified ER and AR as the targets of many EDCs, which resulted in developmental and reproductive effects, as well as metabolic alterations.

3.1.1. Metabolic disruption mediated by inappropriate activation of the estrogen receptor. ERα and ERβ are the main mediators of the biological effects of estrogens. Upon estrogen binding, they form homodimers that bind to the promoters of estrogen-responsive genes. These molecules share a similar structure and bind to the same response element but have varying relative binding affinities for some steroid hormones. In addition to their well-established roles in reproduction, ERα and ERβ are involved in brain development and function of many other organs, such as skin, bone, and liver.

Several lines of evidence link ERs to metabolism. For example, in postmenopausal women and ovarectomized rodents in which estrogen is low, one observes an increase in white adipose tissue; estrogen replacement therapy reverses these effects. ERα but not ERβ appears to mediate these effects, as inferred from studies using mice in which ERα is knocked out: Both male and female mutant mice show increased insulin resistance and impaired glucose tolerance (74, 75). Although the underlying mechanisms remain unclear for these observed results, it seems likely that ERα activation modulates neural networks controlling food intake as well as acts directly in adipose tissue (reviewed in Reference 76). At a cellular level, preadipocytes also express ERα and ERβ, and during development, estrogens contribute to an increase in adipocyte number, with subsequent effects on adipocyte function (77). At the molecular level, ERs and estrogens regulate many aspects of metabolism, including glucose transport, glycolysis, mitochondrial structure and activity, and fatty acid oxidation (reviewed in Reference 8).

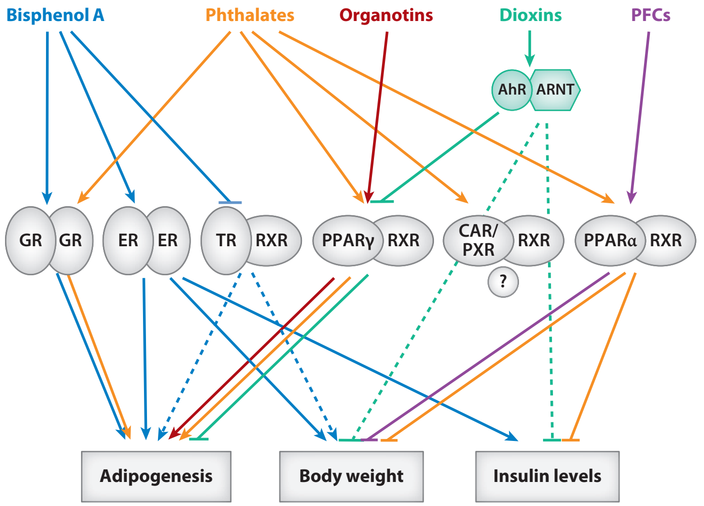

Figure 1

Endocrine-disrupting chemicals (EDCs) interact with aryl hydrocarbon receptor (AhR) and with diverse members of the nuclear receptor (NR) superfamily, which convey EDC-mediated metabolic disruption. Sensor receptors like peroxisome proliferator–activated receptors (PPARs) play a prominent role: PPARγ activated by phthalates or organotins induces adipogenesis in vitro, and this effect is inhibited by dioxins through AhR activation. PPARα, which has a major role in fatty acid oxidation, limits adipogenic activity and is activated in vivo by phthalates and polyfluoroalkyl compounds (PFCs). Estrogenic EDCs such as bisphenol A have also been involved in metabolic disruption through complex interaction with hormone receptors such as the estrogen receptors (ERs), thyroid hormone receptor (TR), and glucocorticoid receptor (GR). These receptors are important for the control of adipogenesis, weight gain, and insulin levels, although the underlying mechanisms are not yet well understood (*dashed lines*). Finally, even though the mechanisms have yet to be described (*dashed lines* and *question mark*), the xenosensors pregnane X receptor (PXR), constitutive androstane receptor (CAR), and AhR also play a crucial role in regulating metabolic homeostasis via direct or indirect interaction with the metabolic pathways. Other abbreviations used: ARNT, aryl hydrocarbon receptor nuclear translocator; RXR, retinoid X receptor.

Experimental evidence showing the effects of estrogen-mimicking EDCs such as BPA on metabolism remains scarce and has been restricted to cultured cell line models. Studies using 3T3-L1 cells suggested that early BPA exposure may enhance adipocyte differentiation in a dose-dependent manner and may permanently disrupt adipocyte-specific gene expression and leptin synthesis (78, 79). For instance, the estrogenic surfactant octylphenol elevates adipocyte production of resistin through activation of the ER and extracellular signal–regulated kinase pathways in 3T3-L1

Thyroid hormone receptor (TR): TRα and TRβ are nuclear receptors that are activated by the thyroid hormones and play an important role in development and metabolism regulation

cells (80). Resistin is secreted by adipocytes and may cause insulin resistance and predisposition to type 2 diabetes (81). These limited in vitro studies suggest that octylphenol-induced secretion of resistin may contribute to metabolic disorders. Finally, BPA may affect ERα activity in the pancreas and increase insulin secretion (82). According to this report, short exposure to BPA provokes chronic hyperinsulinemia, with perturbations of glucose and insulin tolerance tests. This activity has been related to ERα expression in the pancreas, with 17β-estradiol shown to increase β-cell insulin content, insulin gene expression, and insulin release (82).

There are two important aspects to consider with respect to estrogen-like activity and metabolic changes. The first aspect concerns nongenomic responses to estrogen mediated by the nonclassical transmembrane receptor GPR30. GPR30 deletion in mice revealed its major role in many facets of estrogen metabolic activity (83), with phenotypes including impaired glucose tolerance and reduction of bone growth. This membrane receptor can also be activated by BPA and nonylphenol, as assessed in an in vitro cell culture model (84). Further studies are thus needed to evaluate the in vivo relevance of this activation.

The second major question concerns exposure to estrogenic EDCs during the critical period of development. Indeed, embryos and fetuses are likely to be much more sensitive to perturbation by endocrine-like activities. Protective mechanisms available in adult animals, such as DNA repair mechanisms or liver detoxification and metabolism, are not fully functional in the fetus or neonate. Thus, exposure to EDCs during this period can cause adverse effects, some of which are not apparent until much later in life. This point is best illustrated by prenatal exposure to the estrogen derivative diethylstilbestrol (DES), which was widely used until the 1970s as an antimiscarriage medication; this early exposure impaired reproduction later in life (85). Mice exposed to low DES doses during pregnancy produced normal-sized offspring but later showed an age-dependent increased body weight gain and altered obesity-related gene expression. Prenatal exposure to DES also led to elevated serum levels of leptin, adiponectin, interleukin (IL)-6, and triglycerides in mice prior to their becoming overweight and obese (86). With regard to EDCs, the effects of prenatal exposure to BPA are well documented. In contrast to the reduced body weight associated with BPA exposure in adult rodents, exposure to BPA during fetal life resulted in an increase in adult body weight (87). In rats, perinatal exposure to low BPA doses increased adipogenesis and body weight in adult females, which exhibited adipocyte hypertrophy and overexpression of lipogenic genes (88). Accordingly, high- or low-dose exposure to BPA during gestation to puberty leads to hyperlipidemia with increased body and adipose tissue weight in both sexes (89).

An epigenetic mechanism has been proposed to explain these transgenerational effects. Epigenetic changes are inherited changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence. Epigenetic effects involve modifications in the activation of certain genes. It is thus hypothesized that EDCs impact obesity via estrogen-driven epigenetic reprogramming of gene activity during development (90) (see **Figure 1**).

3.1.2. Metabolic disruption through inappropriate activation of thyroid hormone receptor and glucocorticoid receptor. EDCs may also modulate other hormone nuclear receptors, particularly thyroid hormone receptor (TR) and glucocorticoid receptor (GR). Most TH activity is mediated by the TRs TRα and TRβ, which form heterodimers with RXR to bind the promoter sequences of target genes. TR agonists relieve the repression that unliganded TRs may exert on some target genes, thus further inducing gene expression. In addition to an important role in brain development, THs are tightly associated with metabolism. Elevated TH levels accelerate metabolism, increase lipolysis as well as hepatic cholesterol biosynthesis and excretion, and provoke weight loss. The exact opposite results are observed with low TH levels.

In contrast to TR, GR forms homodimers and resides in the cytosol, forming complexes with molecular chaperones. Ligand binding releases the chaperones, triggers GR nuclear translocation, and influences gene expression. Glucocorticoids acting through GRs allow an organism to adequately respond to physical or emotional stresses by promoting gluconeogenesis, increasing blood glucose levels, and mobilizing the oxidation of fatty acids. The pharmacological uses of glucocorticoids, chiefly in the context of controlling chronic inflammation, have serious metabolic side effects such as diabetes, muscle wasting, and growth retardation in children.

EDCs also interact with these TR and GR receptors. For instance, in differentiating 3T3-L1 cells, BPA and dicyclohexyl phthalate stimulate GR-mediated lipid accumulation and synergize with a weak GR agonist to increase expression of adipocyte-specific markers (91). BPA may also act as an antagonist of the TR pathway by enhancing recruitment of the corepressor NCoR to TR (92). In parallel, perinatal exposure of BPA increases levels of thyroxine (T4) (93). Given the important role of TH in energy homeostasis, BPA effects on TR during development may be important in long-term body weight increase. BFRs also disrupt the TH pathway, and daily exposure of rats to PBDE over four weeks resulted in a significant increase in lipolysis and a significant decrease in glucose oxidation, characteristics associated with obesity, insulin resistance, and type 2 diabetes, although such exposure had no effect on body weight and adipocyte size. Although the underlying molecular mechanisms remain to be experimentally addressed, these physiological effects are consistent with a change in ER and TR pathways (94, 95).

3.2. Metabolic Disruption Through Xenosensors

The body is protected from the accumulation of toxic chemicals by a complex strategy that in part takes place in the liver, regulating the expression of drug-metabolizing enzymes and transporters. This adaptive response incorporates at least three xenosensors: pregnane X receptor (PXR), constitutive androstane receptor (CAR), and aryl hydrocarbon receptor (AhR), as well as xenobiotic metabolism and transporter systems.

3.2.1. Pregnane X receptor and constitutive androstane receptor. PXR and CAR are members of the NR superfamily of sensor receptors, and although they were originally defined as xenosensors involved in regulating the metabolism of xenobiotics, their contribution to fatty acid, lipid, and glucose metabolism has been only recently appreciated (96, 97).

PXR and CAR regulate gene expression by forming heterodimers with RXR that bind to xenobiotic response sequences present in the promoters of their target genes. However, their mechanisms of activation differ. PXR is located primarily in the nucleus and is strongly activated upon ligand binding. In contrast, in the absence of ligand, CAR is retained in the cytoplasm through association with the cytoplasmic CAR-retention protein (CCRP) and heat-shock protein 90 (HSP90). In the presence of activators, CAR dissociates from its two chaperones and translocates into the nucleus, where it forms heterodimers with RXR (reviewed in Reference 98).

PXR and CAR are highly expressed in the liver, where they act as master regulators of detoxification pathways through induction of phase I to phase III enzymes. In the first phase, a polar group is added to hydrophobic substrates by hydroxylation and oxidation via the cytochrome P450 (CYP) mono-oxygenase system. CYP3A is responsible for the metabolism of up to 60% of the drugs presently on the market (reviewed in Reference 94) and is a major target gene of PXR, whereas phenobarbital-induced activation of CAR triggers the expression of CYP2B. Phase II enzymes increase hydrophilicity of the compounds through various conjugation reactions, and phase III involves transporters that allow

Pregnane X receptor (PXR): a nuclear receptor known as a xenosensor and master regulator of detoxification pathways; known as steroid X receptor in humans

Constitutive androstane receptor (CAR): a nuclear receptor known as a xenosensor and master regulator of detoxification pathways

AhR: aryl hydrocarbon receptor

Cytochrome P450 (CYP) family: a large and diverse group of enzymes playing an important role in the detoxification pathways. Their substrates include metabolic intermediates and xenobiotic substances

Peroxisome proliferator–activated receptor (PPAR): PPARα, -β/δ, and -γ are nuclear receptors that play a prominent role as lipid sensors

for removal of these compounds through secretion. Along these three phases, PXR and CAR have common target genes such as those encoding glutathione-*S*-transferase and multidrug resistance protein (MRP)2 and -3; these receptors also have distinct targets such as multidrug resistance gene (MDR1) and MRP1, respectively. Thus, the combined activities of PXR and CAR modify and eliminate nearly all toxicants encountered by the living organism.

With the above in mind, ligands and activators of PXR and CAR come from two main sources. First, endogenous ligands for human PXR include some bile acid derivatives, pregnanes formed from cholesterol as immediate precursors of progesterone, and other metabolic products of steroids. The ligands of CAR are less promiscuous than those of PXR, perhaps due to the smaller size of the CAR ligand-binding pocket. Examples of CAR ligands include the androstane metabolites and steroid metabolites. This situation supports the hypothesis that PXR and CAR play an important role in endocrine system regulation. The activity of PXR is, however, defined primarily by its interaction with exogenous compounds, including herbal medicines and pharmaceutical drugs (such as rifampicin), synthetic glucocorticoids (such as dexamethasone), or steroid hormones (DES, 17β-estradiol). CAR also responds to exogenous compounds such as phenobarbital, which induces CAR nuclear translocation, or the well-characterized ligand TCPOBOP. A number of EDCs activate PXR and CAR; both may be activated by nonylphenol, DEHP, and MEHP. BPA and some PCBs activate human PXR, whereas PFOA, PFOS, and the organochlorine methoxychlor can activate CAR (99–102).

As mentioned above, PXR and CAR were identified chiefly as xenobiotic-metabolizing regulators; however, clinical observations revealed that many CAR and PXR activators affect lipid and glucose metabolism in patients. For instance, the known PXR activator rifampicin induced liver steatosis in tuberculosis patients (103), and long-term treatment with phenobarbital provoked significant changes in hepatic and plasma metabolite profiles (104, 105). Furthermore, laboratory animal and in vitro studies show a similar trend: PXR activation induced a steatogenic effect in rat and mouse liver (106–108), and CAR and PXR activators repressed hepatic gluconeogenic enzymes and genes (109–111). CAR was recently described as an antiobesity NR that ameliorates diabetes and fatty liver (112, 113). In addition to direct effects of PXR and CAR on lipid and glucose metabolism, PXR and/or CAR indirectly affect these pathways by interfering with other regulatory pathways and NRs (114) (see **Figure 2**). CAR and PXR bind other transcription factors like forkhead boxes A2 and O1, inhibiting their DNA binding (96). PXR and CAR may also compete for the DR1-binding site recognized by the NR hepatocyte nuclear factor 4α (HNF4α) and peroxisome proliferator–activated receptor (PPAR)α. Finally, PXR and CAR can also exert an inhibitory effect by targeting common coactivators like PPARγ coactivator 1α (PGC1α), which interacts with many transcription factors to regulate metabolic homeostasis (96).

The activation of PXR and CAR by EDCs may account for the metabolic responses noted after exposure to these chemicals. For example, DEHP induces CAR-dependent activation of the nuclear receptor Rev-erbα pathway, which in turn helps to control the cellular clock and functions in energy metabolism (101). Because PXR and CAR regulate several CYP family members involved mainly in the metabolism of steroids and other endogenous compounds like sex steroid hormones, their EDC-mediated activation may alter metabolism indirectly by changing the effective concentrations of these hormones (see Section 3.1.1) (98). Although these hypotheses are appealing, to date no studies have established a clear link between EDCs and metabolic disorders via PXR and CAR.

3.2.2. Aryl hydrocarbon receptor.

AhR is a ligand-activated transcription factor that belongs to the basic helix-loop-helix Per-ARNT-SIM (bHLH-PAS—where Per denotes the *Drosophila melanogaster* clock gene *Period*;

ARNT denotes aryl hydrocarbon receptor nuclear translocator; and SIM denotes a neurodevelopmental regulator in flies, *single-minded*) family of proteins. AhR is a xenosensor that mediates the biological response to a wide spectrum of xenobiotics; in particular, AhR is the major factor sensing and mediating the toxic effects of the dioxin TCDD.

The nonactivated AhR protein resides in the cytosol and, upon ligand-mediated activation, translocates into the nucleus, where it heterodimerizes with the ubiquitously expressed ARNT, a member of the same protein family. The AhR/ARNT complex binds to specific regulatory DNA sequences to regulate gene expression. AhR activity may also be mediated by alternative ligands and by an ARNT-independent mechanism, although details of these mechanisms remain poorly understood (116).

Among the targets involved in detoxification, AhR target genes include the phase I enzyme CYP1A1 and the phase II enzymes UGT1A1 and UGT1A6. In addition, AhR may contribute to the coordinated regulation of human drug-metabolizing enzymes and conjugate transporters by inducing PXR and CAR expression (117). Endogenous molecules that bind AhR and benefit from detoxification activity are lipoxin 4 and leukotriene derivatives, as well as the heme metabolites biliverdin and bilirubin. Xenobiotics that activate AhR include various dietary phytochemicals, some PCBs, and TCDD. Because it is very poorly metabolized, TCDD triggers sustained activation of AhR, contributing to the toxic effects of dioxin. These toxic effects thereby highlight the undesired events that may occur through inappropriate AhR activation and reveal a subset of AhR target genes unrelated to detoxification. These targets include the CDK inhibitors $p21^{CIP1}$ and $p27^{Kip1}$ (118), which may explain the broad role of AhR in organogenesis, embryonic development, the cell cycle, immunosuppression, and carcinogenicity.

Recently, AhR has been implicated as a regulator of energy metabolism. Epidemiological studies show an association between dioxin exposure and type 2 diabetes (25). Other studies also demonstrate that high and low doses of dioxins affect genes in an AhR-dependent manner linked with hepatic circadian rhythm, cholesterol biosynthesis, fatty acid synthesis, glucose metabolism, and adipocyte differentiation (119, 120). The mechanisms by which AhR regulates energy metabolism are not yet well described, but various direct and indirect mechanisms including cross-talk with ER may be involved. AhR may disrupt the ER signaling pathways through increased ER proteasomal degradation, modulating estrogen levels via

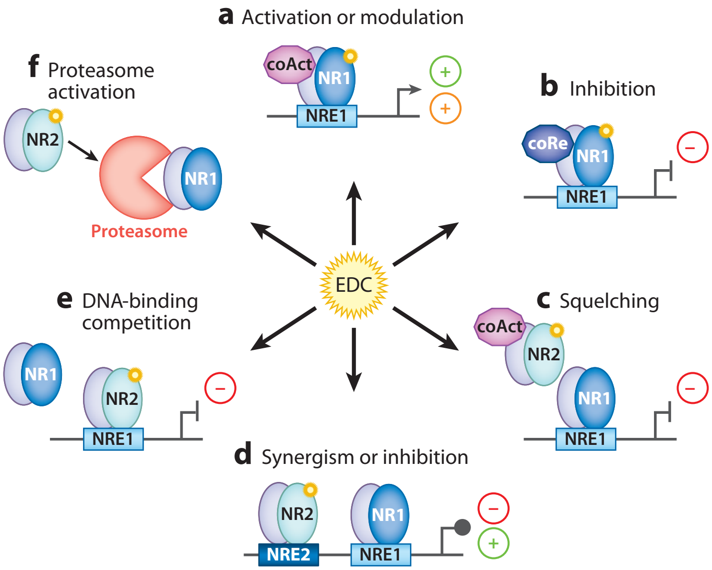

Figure 2

Endocrine-disrupting chemicals (EDCs) interfere with nuclear receptor (NR) signaling via multiple mechanisms. In this figure, NR1 and NR2 are generic names for the NRs discussed in the text. EDCs can act as direct agonists or antagonists of NR1, taking the place of the endogenous ligand. They can direct the recruitment of coactivators (coAct) by the NR and trigger target gene transcription, although some EDCs act as modulators rather than as full agonists by inducing the recruitment of only some of the coactivators. EDCs that act as antagonists favor conformational changes that allow for the recruitment of corepressors (coRe) or inhibit DNA binding and target gene expression (*a*,*b*). Moreover, EDCs can interfere by indirect mechanisms: EDC binding to NR2 leads to disturbances of NR1 signaling via molecular cross-talk such as competition for coactivators (*c*) or for DNA-binding sites (*e*). Other indirect mechanisms are the binding of NR1 and NR2 to neighboring sequences, which may lead to either synergism or inhibition of the regulatory activity (*d*) or to the EDC-mediated activation of NR2, which results in NR1 degradation through proteasome activation (*f*). NRE1/NRE2, nuclear receptor response element 1 and 2.

CYP expression, altering ER transcriptional activity via coactivator squelching, or promoting DNA-binding competition (121, 122) (see **Figure 2**). In addition, AhR also indirectly affects adipogenesis through inhibition of PPARγ expression (123).

Additional experimental and epidemiological studies are still required to assess whether AhR-mediated responses affect metabolism in addition to the well-known roles of Ahr in immunity, development, and cancer.

3.3. Metabolic Disruption Through Peroxisome Proliferator–Activated Receptors

Metabolic homeostasis requires a controlled balance between energy storage and consumption; several NRs and their coregulators are instrumental in these processes. Among these, the PPARs act as lipid sensors that cooperate in different organs to adapt gene expression to a given metabolic status. PPARs are sensor receptors with a rather large ligand-binding domain, which can accommodate a variety of ligands, primarily lipid derivatives. In the presence of ligand, PPARs heterodimerize with RXR and bind to the PPAR response elements localized in the promoter regions of their target genes (124).

The PPAR family is composed of three isotypes: PPARα, -β/δ, and -γ. PPARα is expressed predominantly in tissues characterized by a high rate of fatty acid catabolism such as liver, kidney, heart, and muscle. PPARα was first identified as the protein responsible for the induction of peroxisome proliferation in rodents exposed to a variety of compounds collectively termed peroxisome proliferators. However, humans do not undergo peroxisome proliferation and are thereby protected from the consequent liver tumors observed in sensitive species. PPARα plays a major role in fatty acid oxidation in all species, controlling lipoprotein metabolism and limiting inflammation. PPARβ is ubiquitously expressed, shares partially overlapping functions with PPARα, and also plays a role in cell differentiation and survival (125, 126). Finally, PPARγ functions in adipogenesis, lipid storage, and the control of insulin sensitivity; it also participates in inflammatory responses (127).

Plasticizers, surfactants, pesticides, and dioxins can modulate PPAR activity, although fairly little is known about the molecular mechanisms and the physiological outputs involved. The specificity of this PPAR-mediated response is highlighted in a study in which 200 pesticides were systematically screened for their peroxisome proliferation activity. Only three compounds were identified as having PPARα transcriptional activity, and none possessed PPARγ transcriptional activity (127). Among these pesticides, diclofop-methyl and pyrethrins induced PPARα target gene expression at levels similar to those induced by classic agonists in mice (128, 129).

The phthalates are another group of well-characterized peroxisome proliferators (130). In vitro transactivation assays and intact cellular systems were used to reveal that phthalates and their metabolites bind and activate the three PPARs, among other NRs (131–134). These studies also determined the range of potency and efficacy of phthalate monoesters, showing differences between isotypes and species. Modeling the DEHP metabolite MEHP in the PPARγ ligand-binding pocket indicates that MEHP may contact residues similar to those defined for the classic PPARγ agonist rosiglitazone (135). MEHP induces adipogenesis in a PPARγ-dependent manner, albeit with lower efficiency than rosiglitazone in 3T3-L1 cells (134). Accordingly, gene expression microarray analyses indicate that 70% of the genes are regulated by either ligand, some of them to differing degrees. However, 30% of the genes are exclusively regulated by rosiglitazone and not by MEHP, suggesting that MEHP acts as a selective modulator of PPARγ rather than as a full agonist. This differential activity results from the different abilities of MEHP and rosiglitazone to induce the release of corepressors such as NCoR and the recruitment of coactivators such as p300 or PGC1α (133). Taken together, these in vitro data demonstrate that MEHP is proadipogenic in a cell culture model, suggesting that it may act as a metabolic disruptor and may promote obesity in vivo.

Paradoxically, in vivo experiments partially contradict these results (136). Adult mice treated with high or low doses of DEHP are protected from weight gain, gaining 30% less weight than controls. These mice possess a reduced fat mass and a metabolic improvement, with lower levels of triglycerides in the liver and the blood, smaller adipocytes, and enhanced glucose tolerance. These effects were not observed in PPARα-null mice, confirming that in vivo DEHP activity is mediated primarily by PPARα in the liver, leading to increased fatty acid catabolism and induced expression of PPARα target genes such as that encoding fibroblast growth factor 21 (FGF21) (137) or genes controlling fatty acid β-oxidation. Surprisingly, this phenotype is also completely abolished in PPARα-humanized mice (mice in which the mouse PPARα alleles are replaced by the human PPARα gene). These mice, when exposed to a DEHP-containing diet, tend to be more sensitive to diet-induced obesity than are untreated controls (136). These observations point to the possibility of species-specific EDC activity, due at least in part to evolutionary differences in the receptors interacting with them.

Studies of phthalate exposure in utero have yielded dissimilar results. Male and female offspring of rats exposed to diisobutyl phthalate and butylparaben exhibit reduced plasma leptin and insulin levels, similar to the modifications observed upon in utero exposure to rosiglitazone (138). In contrast, a study evaluating the impact of in utero exposure to DEHP could not identify parameters indicating adult metabolic disorders (6). These differences may be attributable to the compounds tested as well as the specific experimental protocols. In any case, these studies highlight the necessity to investigate the risks engendered by fetal exposure to phthalates.

The PFCs, particularly PFOA and PFOS, can also activate mouse and human PPARs in transactivation assays (139), although the in vivo consequences of such activity remain quite controversial. Adult mice exposed to high doses of PFOA exhibit weight loss, which is abrogated in PPARα-null mice (140). The proposed mechanism involves PPARα-dependent anorexigenic activity in the hypothalamus of adult rodents (141). In contrast, Hines et al. (142) reported that PFOA has no effect on body weight gain when exposure occurs at the adult stage. However, developmental exposure to low PFC levels results in increased body weight and increased serum insulin and leptin levels at midlife (142). Again, species-specific PPARα activity was proposed because low doses of PFOA significantly activate the function of PPARα in wild-type mice but not in PPARα-humanized mice. Human PPARα may therefore be less responsive to PFOA, increasing the possibility of species-specific EDC activity. More specifically, the extent to which these PPAR activators influence metabolic homeostasis in humans deserves more study (143).

Several EDCs also specifically target PPARγ. Using a high-throughput method, Kanayama et al. (31) showed that among 40 EDCs, organotins such as TBT and TPTO are activators of human PPARγ and RXR. TBT binds to and activates the three human subtypes of RXR as well as many permissive heterodimeric partners such as liver X receptor (LXR), nuclear receptor–related 1 protein (NURR1), PPARβ, and PPARγ, but not PPARα. Organotins bind and activate, primarily through RXR and not through PPARγ, the PPARγ:RXR heterodimer at nanomolar concentrations. The crystal structure of the RXRα ligand-binding domain bound to TBT indicates that TBT binds with high affinity to RXR, even though TBT is structurally distinct from above-described ligands and only partly occupies the RXRα ligand-binding pocket (144). Consistent with the critical role played by PPARγ:RXR signaling in mammalian adipogenesis, TBT promotes adipogenesis in 3T3-L1 cells by direct transcriptional effects on the PPARγ target genes. In utero exposure to TBT in rodents led to alterations in fat structure and metabolism, with a disorganization of hepatic and gonadal architecture, steatosis in the liver, and an increase in lipid accumulation and mature adipocytes. The fat mass—but not the total body weight—of in utero TBT-treated mice significantly increases in adulthood, supporting the conclusion that embryonic and chronic lifetime organotin exposure may contribute to the incidence of obesity through disruption of the PPARγ:RXR pathway (28).

Altogether, these many examples of EDC interaction with receptors highlight the fact that a given compound can interfere with different NRs and different pathways (see **Table 1**). For example, depending on the compound, BFRs interface with AR, ER, and progesterone receptor to elicit both agonist- and antagonist-like effects (94). PBDEs bind but do not activate AhR (145); in contrast, they induce the expression of various CYP enzymes, in part through the activation of PXR (146, 147). PBDEs are also active in TH regulation by disrupting peripheral TH transport and metabolism/deactivation or by binding and activating TRs (148, 149). The final consequences of EDCs exposure are thus due to cross-talk between these pathways, rather than to a linear causation chain (96, 114, 122, 123, 150), and are much more complex to decipher in vivo.

4. METABOLIC DISRUPTORS: TOWARD MANY CHALLENGES

This review emphasizes the remarkable emergence of EDC-related research, which has shifted focus from endocrine disruption to metabolic disruption. Epidemiological studies that underscore the parallels between EDC exposure and obesity incidence, as well as animal laboratory studies that demonstrate the ability of EDCs to act on metabolic transcription factors, are lines of investigation that cannot be casually discounted. However, there are many difficulties to overcome before one can fairly assess the risks that past, present, and future environmental chemicals engender on human and wildlife health. In this last section, we highlight some of the important questions that remain for researchers and regulators.

4.1. Monitoring Exposure Levels

Ambient monitoring is performed by sampling air, dust, water, etc., and by measuring the levels of the pollutants of interest in these samples. This method is often reasonably easy and reliable. However, ambient monitoring provides a value valid only at the time of sampling, which may not reflect levels of chronic exposure; it also does not take into account the efficiency with which living organisms breathe, ingest, or absorb these compounds. In that respect, biomonitoring is a more appropriate evaluation of the presence of compounds or their metabolites in biological samples, particularly in blood and urine, and ideally in tissue samples. Biomonitoring does not identify the source of the contamination but provides the individual exposure level at a given time point. Biomonitoring assays also reflect past exposure to persistent pollutants. However, biomonitoring is invasive and costly and cannot be proposed as a standard routine evaluation, except for occupational exposure. Alternatively, biomonitoring of wildlife samples can be more easily performed and may serve as a good indicator of exposure to some pollutants widely found in the environment.

4.2. Identifying the Metabolic Effective Dose

One current issue in identifying the metabolic effective dose concerns the so-called U-shaped or inverted U-shaped dose-response curve. A dose-response curve of this form is reported for BPA: Effects are observed at very low doses (from 10^{-12} M) and at high doses (10^{-8} M), but no effects are observed at intermediate doses (10^{-9} M). These U-shaped curves suggest the existence of two independent mechanisms for low doses and high doses (151, 152). However, mechanistic studies are still lacking, and evidence for low-dose activity is not available in epidemiological studies.

A second complication is exposure to a mixture of EDCs rather than to a single EDC. Humans and wildlife are exposed daily to a variety of compounds, and it is thus likely that even if none of the compounds reach an effective level, the combination or mixture of chemicals may become effective. This scenario is supported by the observation that various EDCs share receptors, and thus additive effects should be observed (see **Figure 1**; **Tables 1** and **2**). Few experimental studies addressing this issue exist, and given the vast number of EDCs, it is unclear how to monitor exposure and how to use or develop assays that capture the effects of these mixtures. At a practical level it is also unclear how regulatory decisions will be amended to account for exposure to mixtures rather than to single compounds.

4.3. Establishing the Link Between Exposure and Metabolic Effects

Metabolic alterations such as metabolic syndrome and type 2 diabetes are complex and multifactorial. Elevated body mass index and obesity are not diseases but rather contribute to various alterations that lead to the diseased state. EDC exposure is one more factor that increases an already long list of predisposing factors that act in combination to increase the risk of obesity or other metabolic alterations. Such contributions can be revealed only by comprehensive studies of large and well-characterized cohorts, such as the cohort used for the NHANES project (see sidebar entitled NHANES). However, these studies are cross-sectional (see sidebar entitled Observational Studies), due to the difficulties inherent in the evaluation of exposure, and may be subject to unidentified confounding factors. At best, these studies can demonstrate correlations but not causal links between exposure and effects.

4.4. Experimental Exploration of the Metabolic Disruption Properties of Endocrine-Disrupting Chemicals

How can we reach the most appropriate understanding of EDC biology that will help to define appropriate actions? Although cellular models are flexible and allow large numbers of conditions and doses to be tested, they are limited and unable to factor in bioavailability of the compounds and their metabolites or the route of exposure. Reductionist molecular and cellular studies may not take into account the knowledge that several EDCs interfere with a variety of NRs, not all of which are expressed in the same tissue or at the same time. Additionally, EDCs can affect several organs in the body with different intensities, leading to a global response that may be opposite of that observed in cell cultures. Experimentation in animals is therefore unavoidable, as animals are threatened by environmental contaminants and provide a reasonable approximation of human metabolism for most compounds. However, two main issues must be considered. First, EDC-interacting receptors display species-specific activity that is well described for PPARα, PXR, and CAR (98, 136). The development of humanized mice, in which the gene of the receptor of interest is exchanged for the human allele, provides new tools for this type of investigation (136, 143). Second, issues of dose and exposure time complicate experimental design (see **Table 2**). Mice may live for two years, and a three-month exposure can be considered chronic. Does this experimental setup accurately reflect the decades over which humans might be exposed?

4.5. Exposure During Critical Periods of Development

The dramatic effect of DES exposure on female babies illustrates the critical issue of exposure during development (see Section 3.1.1). Consistent with the well-known functions of classic hormones in developing reproductive organs, the effects are easily understood when these hormones are disrupted or mimicked. Even disregarding transgenerational effects, the metabolic consequences of prenatal exposure that manifest in adulthood are difficult to assess and to understand. As discussed above (see Section 3.1.1), controversy surrounds many of these consequences, and only systematic animal studies may lead to a fair risk evaluation. Future efforts should be aimed at elucidating whether and how epigenetic imprinting is involved in these pathologies (153).

4.6. How Should New Chemicals Be Regulated?

As described in **Table 1**, several chemical products are either totally banned or authorized for use under strict conditions. Banning a persistent organic pollutant will immediately limit exposure, but a number of years will pass before the chemical is entirely suppressed, and such suppression will occur only if large transnational territories ban the chemical of interest (see **Table 2**). Inevitably, banned products are replaced by others that bring other unwanted effects. How do we establish the most pertinent and effective modes of risk evaluation not only for the present but also for any future compound released to consumers?

From the research point of view, recent years have witnessed many efforts to set up new technologies for EDC detection in human tissues, including scenarios of low doses, nonpersistent EDCs, and the developmental period (27, 56, 67). New integrative approaches combining genomics, proteomics, metabolomics, systems biology, and computational modeling should help to understand the complexity of the cocktail effect and its consequences when exposure occurs at various life stages (101, 150, 154). In addition, these approaches should help to evaluate the global effects of EDC interference with different NRs and the activation of a complex biological network. Before reaching this level of understanding, these integrative strategies may help define a signature: a composite signal of no explanatory value but reflecting exposure to metabolic disruptors. Such a signature may help in experimentally establishing a predictive value to new compounds.

From the regulatory point of view, governments face the challenge of making appropriate decisions by balancing potential risks against demonstrated advantages. Help for future decisions will come from two complementary processes. The first process is illustrated by the European Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) program, aimed at protection of human health and the environment through systematic registration, assessment, and annotation of an exhaustive list of industry compounds. The second process encourages research through grant subsidiaries, as illustrated by the recent financing of BPA research by the National Institutes of Health (NIH). These initiatives include incentives for transparency and collaboration, both at the level of government and between scientists. Metabolic perturbations are only one small aspect of the EDC-related problems to be solved, but what we know now may be only the tip of the iceberg. In the present context of endemic metabolic disorders, with severe economic, social, and professional consequences, every action first to understand and then to control risk factors is beneficial on all counts.

SUMMARY POINTS

1. Increasing human exposure to endocrine-disrupting chemicals (EDCs) has been associated with the development of some of the main ailments of the industrialized world, particularly metabolic disorders like obesity, diabetes, and metabolic syndrome.
2. Among different mechanisms of action, lipophilic EDCs compounds can bind specifically to nuclear receptors and can displace the corresponding endogenous ligands to modulate hormone-responsive pathways.
3. Persistent organic pollutants such as organochlorine pesticides, dioxins, and polyfluoroalkyl compounds and nonpersistent pollutants such as bisphenol A and several phthalates are suspected of metabolic disruption activity.

4. A major mechanism of EDC-mediated metabolic disruption is through EDC interaction with nuclear receptors, including (*a*) sex steroid hormone receptors, (*b*) receptors acting as xenobiotic sensors, and (*c*) receptors specialized in metabolic regulations.
5. This field is littered by controversies, in part due to the difficulties in proving or disproving EDC activity. The major issues are the monitoring of exposure levels, the identification of the metabolic effective dose, and the establishment of a link between (*a*) either exposure during critical periods of development or chronic exposure at very low doses and (*b*) metabolic effects. Finally, this area of research would benefit tremendously if common methodologies of experimental EDC exposure were established. All these issues need further work to create a common and effective regulatory policy for environmental chemical pollutants.

DISCLOSURE STATEMENT

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