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Putative Environmental-Endocrine Disruptors and Obesity: A Review

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Abstract

Purpose of the review—There has been a substantial increase in the prevalence of obesity in the last several decades. Recent evidence suggests that endocrine disrupting chemicals, e.g. halogenated aromatic hydrocarbons, may cause perturbations in endogenous hormonal regulation and alter other mechanisms involved in weight homeostasis, which may lead to weight gain by increased volume of adipose tissue. Synthetic chemicals derived from industrial processes are suspected to play a contributory role. Yet of the approximately 70,000 documented synthetic chemicals, few have been examined to determine their effects on the endocrine system.

Recent findings—The present study examines prior laboratory, epidemiological and experimental research findings. Data demonstrate migration of endocrine disruptors in the environment and are beginning to catalogue their effects on adiposity. We present postulated relationships between these chemicals, their mechanisms of action, and the obesity epidemic.

Summary—Endocrine disruptors may adversely impact human and environmental health by altering physiological control mechanism. Obesity, which is known to increase medical costs and reduce quality and length of life, may be increasing as a function of endocrine disruptor exposure. This merits concern among scientists and public health officials and warrants additional vigorous research in this area.

Keywords

Endocrine disruptors; Obesity; bisphenol A; phthalates; butyltins

Introduction

Endocrine-disrupting chemicals (EDCs) are compounds that mimic or interfere with the normal actions of all endocrine hormones including estrogens, androgens, thyroid, hypothalamic and pituitary hormones [1**]. There is particular concern about EDCs that are lipophilic, resistant to metabolism, and/or able to bioconcentrate up the food chain. This is because these substances become stored in body fats and can be transferred to the developing offspring via the placenta or via the egg. In spite of the accumulating substantial evidence for an obesity epidemic, our knowledge about the effect of environmental chemicals on weight gain and the magnitude of human or wildlife exposure to these chemicals is limited.

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Endocrine disruptors and the obesity epidemic

EDCs can be placed into two broad categories: naturally occurring and anthropogenic sources. Natural EDCs such as phytoestrogens present in grains, some fungi, grasses, herbs, legumes, and fruits are weaker than endogenous estrogens. However, the second class of compounds, man-made organic compounds synthesized from carbon and other elements such as hydrogen, nitrogen, and chlorine, are more recalcitrant and pose greater risks to human health. Example of the latter are flame-retardant polybrominated diphenyl ether (PBDE), diethylstilbestrol (the drug DES), the plasticizer bisphenol A (BPA), heavy metals, solvents, pesticides [such as organophosphates, dichloro-diphenyl-trichloroethane (DDT)], phthalates, dioxins, polychlorinated biphenyls (PCBs), and butyltins (Table 1 [2]).

They usually vary in potency and in the level of exposure required to produce a deleterious effect. Individually, in some instances these compounds may pose little risk at the levels at which they are typically found. However, in various combinations, weak compounds may interact synergistically and prove to be more potent than either compound alone.

Humans and animals are exposed to EDCs through direct contact with chemicals such as insecticides, herbicides, fumigants, and fungicides; and they are indirectly exposed through ingestion of contaminated water or food. Endocrine disruptors enter the environment from various sources as a result of many manufacturing processes and when plastics and other materials are burned (Table 1).

Hypothesized modes of action

The hormonal activity of EDCs is thought to occur through a variety of mechanisms. The most commonly proposed mechanism is by direct binding to nuclear receptors such as the estrogen receptor (ER). A second proposed mechanism for endocrine disruptor function is as nuclear receptor antagonists. Endocrine disruptors have also been proposed to function indirectly by inhibiting aromatases such as the P450 family members CYP19 and CYP3A1, which, among their many functions, convert testosterone to estradiol, a third possible mechanism of action. Finally, endocrine disruptors can disrupt hormone levels by activating expression of the P450 enzymes. In addition to these four proposed mechanisms, endocrine disruptors have also been shown to alter neuronal synapse formation [3], which could potentially affect release of brain-produced substances that bind to nuclear receptors and may affect energy regulation.

The Obesity Epidemic

Obesity increased in prevalence to a considerable extent during the last half of the 20th century in both adults and children [4–6]. Obesity has been labeled as a foreboding threat to our population's health by many public and private organizations such as the National Institute of Health (NIH) [7], United States Department of Agriculture (USDA) [8], and World Health Organization (WHO) [9], in both developed and developing countries. Over 50 million persons in the USA are obese. The most recent data show no decreases in prevalence [10]. Obesity is believed to causally contribute to cardiovascular diseases [11–13], type-2 diabetes [14–17], and breast, colon, and renal cancer [18–20]. It is also known to reduce the quality and quantity of human life [21].

The rapid increase of the environmental burden of chemical toxins coincides with the rising epidemic of obesity during the past 40 years [22]. Since the "second industrial revolution" the world population has been apparently exposed to an exponential rise in the production of these chemicals [23]. Furthermore, scientific evidence suggests that developmental exposure to environmental hormone-mimetic may affect many health problems. Recently, exposure to EDCs has been suggested as contributing to obesity in both humans and animals, possibly by

the mechanisms described above [1**,24,25**,26,27]. The purpose of this study is to provide a *brief* review that highlights some of the emerging evidence related to the putative effects of environmental-endocrine disruptors on adiposity or obesity.

Recent findings

We present recent findings below in three major categories: evidence from laboratory studies (including both in-vivo and in-vitro work), evidence from observational epidemiologic studies, and evidence from human experimental research.

Laboratory studies

Bisphenol A—In-vitro studies showed that BPA triggers 3T3-L1 cells (mouse fibroblasts that can differentiate into adipocytes) to differentiate into adipocytes [28], and also in combination with insulin, BPA accelerates adipocyte formation [29–30]. Important questions that have arisen from in-vivo research concern the nature of the dose-response relation between BPA and adiposity and the potentially differential effects of exposure during different developmental periods. In-utero exposure of mice to low doses of BPA was associated with weight gain and postnatal increase in weight was observed on maternal exposure of mice to 2.4–500 μg/Kg per day of BPA [31–35]. In another study [36], perinatal and postnatal mice were exposed to 1 μg/ml (low dose) or 10 μg/ml (high dose) of BPA in their drinking water. A 13% increase in females mean body weight in the low-dose group and 11% increase in the high-dose group were observed. In males, the mean body weight increased by 22% in the high-dose group, with a mean adipose tissue increase of 22 % as compared with the control. These findings agree with other study [37] that pups born to BPA-exposed females have increased weight as compared with control rats. Furthermore, depending on the age and sex of the rats, there was a significant difference in body weights exists between low-dose and high-dose exposures [37].

Contrary to the aforementioned, exposure of ovariectomized adult female rats to different doses of BPA resulted in the significant *reduction* of body weight gain with no reduction in food intake [38]. In a related study [39], the effect of BPA on body weights of ovariectomized rats was negligible. Moreover, BPA stimulated a decrease in maternal body weight and body weight gain during pregnancy [40–42]. Nevertheless, BPA did not have an effect in body weight gain during lactation [40].

Accelerated maturation of fat pads and a significant increase in the number of adipocytes in mammary glands were observed after exposure of female mice fetuses' mice to 250 ng BPA/Kg bidy weight per day [43]. In addition, the study described an increase in fat vacuoles per cell in animals exposed to BPA in contrast with the control. Their results suggest that BPA may speed lipid uptake, explaining the advanced maturation of fat pads. These results are supported by several in-vivo and in-vitro studies [44,45].

Tributyltin—Tributytin (TBT) has been shown to disrupt normal development and homeostatic controls over adipogenesis and energy balance [27,46]. Several studies showed organotin disruption of signaling genes such as retinoid X receptor (RXR) and peroxisome proliferator-activated receptor gamma (PPARγ), which play a key role in adipocyte differentiation and energy storage resulting in mammalian adipogenesis [27,47–49]. Although, several studies[50–52], suggested an inhibition of adipogenesis in the 3T3-L1 cells, it had been demonstrated that TBT stimulates adipocytes differentiation *in vitro*, and increases adipose mass *in vivo* in the 3T3-L1 cells [53 *]. Similarly, TBT-induced lipid droplets accumulation in 3T3-L1 cells after a 2-day incubation [54]. Also, prolonged in-vivo exposure to TBT in the environment may increase body fat mass and be involved in obesity development. In-utero studies, showed TBT to accumulate lipids in adipose, testis, and liver tissues in neonate mice

and increasing epididymal adipose mass in adult mice [53]. In addition, the authors described an increase of fat tissue in and around the gonads after exposure to TBT in amphibians.

Other chemicals—The effect of 4-nonylphenol on cell proliferation showed the ability to stimulate the propagation and to inhibit adipocyte formation in cultures of fully differentiated 3T3-L1 cells [55]. Additionally, daily exposure of rats to 14 mg/Kg body weight of PBDE has no effect on animal or adipocyte size [56*]. Some studies indicated that benzo[a]pyrene can favor obesity in mice by impairing β-adrenergic stimulation of adipose tissue lipolysis [57]. The level of LD50 for dioxins was found to be inversely correlated with the body fat mass of animals, meaning that the acute toxicity of dioxins correlates positively with the total quantity of adipose tissue [58]. In animal studies, it has been shown that high-dose DES exposures during pregnancy produce small to normal-size offspring that tend to stay small as adults, whereas low-dose exposures produce normal-size offspring that tend to fatten as they age [59].

Epidemiological studies

Epidemiologic studies have shown that exposure to putative EDCs is near ubiquitous among modern humans. For example, phthalates are esters mainly used as plasticizers to make polyvinyl chloride more flexible. Furthermore, phthalates metabolites have been detected in 98% of the urine samples, indicating a ubiquitous exposure throughout the last 20 years in a German sample [60*]. In a similar study [61], BPA was detected in 95% of the 394 adults sample; however, 4-Nonylphenol was detected in only 51% of the urine samples. A number of workers have shown that organochlorine concentrations were in plasma and in abdominal and femoral subcutaneous adipose tissue among men in a weight loss programme [62–63]. The results of a recent national biomonitoring project found industrial chemicals - that have been implicated in the genesis of obesity - with variable high concentrations in all the 35 diverse people tested [64**].

Population-based epidemiologic studies evaluating associations between various endocrine disruptors and obesity are modest in number and scope. Studies on the association between high serum PCBs and serum lipids in Native American population showed that individuals with higher levels of PCBs tend to have higher levels of total serum lipids, showing a significant association among PCBs, lipids, age, and BMI [65]. On the contrary, another study [66] found no association between total plasma organochlorine concentration and BMI in 53 individuals ranging from lean to obese. On a similar study [67] analyzing serum samples, BPA was detected to be higher in both non-obese and obese women with polycystic ovary syndrome compared with BPA levels in non-obese normal women. Plasma organochlorine concentrations were positively associated with higher BMI and fat mass in humans [68].

Recent studies showed the association between persistent organic pollutants [polychlorinated dibenzo-*p*-dioxins (PCDDs), nondioxin-like PCBs, and organochlorine pesticides] and diabetes to be stronger among obese individuals compared to lean individuals in a National Health and Nutrition Examination Survey (NHANES) population [69]. Additional studies showed non-dioxin PCBs to be inversely associated with BMI and organochlorines pesticides to be positively associated with BMI [70]. Furthermore, in a cross sectional study [71**] urine concentrations of four phthalate metabolites were positively and significantly correlated with abdominal obesity among adult U.S. males.

Some authors have observed a lower birth weight on exposure of rats to PCBs measured in maternal serum [72]. In contrast, no association between birth weight and maternal serum polybrominated biphenyls at conception or enrollment PCBs in 444 mothers and their infants were observed in another study [73].

Experimental Human Studies

We know of no randomized experiments evaluating the effects of putative endocrine disruptors on adiposity in humans. The closest reports are case studies in which olestra is introduced into humans in an attempt to evaluate its impact on reducing the body burden of one or more putative endocrine-disrupting substances and, in turn, on body weight or fat. Olestra is a dietary fat resistant to digestion by mammalian lipases and therefore non-absorbable in mammals. As it passes through the gastrointestinal track, it tends to pull lipophilic substances with it. The addition of olestra to an obese patient's diet decreased Arochlor 1254 contamination in his adipose tissue from 3200 to 56 mg/Kg in 2 years, and facilitated weight loss in an obese diabetic man [74]. Similar case reports exist.

Conclusion

The role of environmental chemicals role in the obesity and overweight epidemic is a new emerging area of interest that requires more understanding and research, especially in identifying these chemicals and their mechanisms of action. In spite of that, the weight of evidence is enough to suggest the vital need for further studies as well as to prompt a precautionary attitude towards EDCs.

Exposure to low levels of EDCs may be of concern. This is seemingly ubiquitous in today's environment, and consequently the effects of EDCs may manifest primarily in populations (i.e., changes over time) and less with respect to interindividual variation within populations. EDCs are detectable in nearly all human blood samples, and even some of the shorter-lived potential endocrine disruptors are frequently detected in general population surveys of residues in blood or urine. The near omnipresence of the exposures combined with the nontrivial potential health effects justifies further research, education and consideration of preventive action to reduce human exposures to endocrine disruptors.

Studies of potential adverse effects in humans, wildlife, and laboratory studies have focused mainly on reproductive and sexual development, nervous system function, and hormone disorders. The potential hazardous effects that estrogen-like and androgen-like chemicals may have both on wildlife and human health have attracted much attention from the scientific community. The fact that different species have ddifferent responsiveness to EDCs may be taken as a sign of multiple mechanisms of action. Limited evidence from laboratory studies suggests that synthetic chemicals may affect obesity-related pathways by changing hormone levels or altering gene expression, but virtually no experimental human studies have been conducted. Presently, the evidence for effects in wildlife is better documented than in humans.

Public health officials should think of the obesity epidemic as a function of a multifactorial complex of events, including environmental-endocrine disruptors, in addition to more commonly perceived and discussed putative contributors to obesity.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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** Of outstanding interest

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Table 1

Sources, Types, and Examples of Chemicals Identified as Potential Endocrine Disruptors (Adapted [2])

Sources	Types	Examples of Chemicals
Incineration	Industrial by-products	PCBs, dioxins
Atmospheric transport	Organochlorine pesticides	DDT, lindane, dieldrin
Agricultural runoff	Pesticides currently in use	Atrazine
Harbors	Antifoulants from paint applied to hulls of ships	TBT
Industrial/municipal effluents	Alkylphenols, natural estrogens	Nonylphenol, estradiol
Pulp mill effluents	Plant estrogens	Genistein
Consumer products	Flame Retardants	PBDEs
Consumer products	Plasticizers	Dibutyl phthalate