

Endocrine Disrupting Chemicals and Obesity: A Review

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Abstract: Obesity is becoming a worldwide problem with almost half a billion of the world's population now considered to be overweight or obese. The purpose of this review was to summarize that some environmental chemicals called endocrine-disrupting chemicals (EDC's) may be able to interfere in the endocrine regulation of energy metabolism and adipose tissue structure and that there is a relationship between exposure to these chemicals and obesity in humans. This review examined the major sources of EDC's, their routes into the human body, mechanism of action and how they alter metabolism thereby causing obesity. Also, the paper reviewed a few key experiments using animal models that have validated that these chemicals disrupt the endocrine system, thereby resulting in obesity.C

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I. Introduction

The statistics on obesity are alarming, with nearly two billion of the world's population now considered to be overweight or obese¹. The problem does not only affect developed countries, as there is now a significant increase in overweight and obese people throughout the developing world. The prevalence of obesity is increasing and is a serious global public health challenge, and the incidence and prevalence has greatly increased over the past three decades in almost all countries around the world. It is very important to define what obesity is. The World Health Organization² defined obesity as abnormal or excessive fat accumulation that presents a risk to health. A crude population measure of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in meters) and a person with a BMI of 30 or more is generally considered obese. The World Health Organization included excess weight, with a prevalence higher than undernutrition, as one of the top 10 health risks worldwide.

The rise in the incidence in obesity has occurred at the same time with the rise in the use and distribution of industrial chemicals that disrupts the endocrine system, termed endocrine disrupting chemicals. These chemicals are thought to have some roles in development of obesity.

Endocrine-disrupting compounds as defined by the U.S. Environmental Protection Agency (EPA) are agents that interfere with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development and/or behavior³. More simply defined, endocrine disruptors are chemicals, or chemical mixtures, that interfere with normal hormone function.

An accumulating body of evidence suggests that endocrine-disrupting chemicals (EDCs) may be linked to the obesity epidemic. It is suggested that exposure to endocrine-disrupting chemicals (EDCs) also known as obesogens contribute to the increased incidence of obesity. Obesogens can modify the epigenome of multipotent stromal stem cells, biasing them to the adipocyte lineage at the expense of bone. Hence, humans exposed to obesogens during early life might have an altered stem cell compartment, already preprogrammed for an adipogenic outcome.

The purpose of this review is to discuss current evidence that endocrine-disrupting chemicals may be able to interfere in the endocrine regulation of energy metabolism and adipose tissue structure and the relationships between exposure to these chemicals and obesity in humans. Specifically, this review focuses on sources of endocrine disrupting chemicals, their classification, routes of passage into the body, risks of early exposure, some animal models that have shown that endocrine disrupting chemicals could be involved in obesity, mechanism of action and how they alter different systems in the body.

Sources and classification of Endocrine disrupting chemicals

Endocrine disrupting chemicals termed "obesogens" can increase adipogenesis and result in weight gain. Humans are exposed to EDC at differing levels in daily life through their use in pesticides/herbicides,

household products, industrial products, plastics, detergents, flame retardants and ingredients in personal care product.

Endocrine disrupting chemicals are highly heterogeneous and can be classified as follows⁴ (Diamanti-Kandarakesis et al., 2009)

- a. Naturally occurring: Natural chemicals found in human and animal food (e.g. phytoestrogen: genistein and coumestrol), and
- b. Those that are synthesized, these can be further grouped as follows:
Synthetic chemicals used as industrial solvents or lubricants and their byproducts (e.g. polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins)
Plastics (e.g. bisphenol A (BPA)), Plasticizers, Pesticides (e.g. dichlorodiphenyl-trichloroethane (DDT)), Fungicide (e.g. vinclozolin) and some pharmaceutical agents (e.g. diethylstilbestrol (DES)).

Routes of endocrine disrupting chemicals into the body

Endocrine disrupting chemicals can get into the body through a variety of routes, some of these routes include:

1. Oral consumption: They can enter the body through the consumption of food and water. Endocrine disruptors such as polychlorinated biphenyls (PCBs), dioxins, perfluorinated compounds, and dichlorodiphenyltrichloroethane (DDT) commonly found in industrial waste or pesticide contaminated soil or ground-water can get entry into human body by oral consumption of food and water. Leaching of chemicals like Bisphenol A (BPA), phthalates from food and beverage containers and pesticide residues in food or beverage can also enter the body by this route⁵.
2. Inhalation or skin contact: The body can come in contact with pesticides commonly used in agriculture, homes, or public disease vector control (DDT, chlorpyrifos, vinclozolin, pyrethroids) through contact with skin and/or by inhalation. Also, brominated flame retardants (BFR), a flame retardant which is commonly used in household furniture can enter the body via inhalation or skin contact. Cosmetics, personal care products, antibacterials, sunscreens, medications (phthalates, triclosan, parabens and insect repellants) applied to the skin is also a common route of exposure.
3. Intravenous route: Phthalates which are commonly used in intravenous tubing use the intravenous route to enter the human body⁵.
4. Biological transfer from placenta and maternal milk: The body can be exposed to endocrine disrupting chemicals without being in contact with them. This may occur by biological transfer of EDC from placenta and mother's milk if the woman has been exposed to EDC⁵.

Risks of early exposure to endocrine disrupting chemicals

A very sensitive time frame for exposure to obesogenic compounds is prior to birth in utero or in the neonatal period. Some experiments using animal models have shown that when pregnant mice were exposed to tributyltin, it resulted in offspring which are heavier than those that were not exposed⁶. Similarly, neonatal mice that were exposed to synthetic oestrogen diethylstilbestrol (DES) have also been reported to have increased body weight⁷. Also, there has been a rise in obesity of children under 2 years of age which potentially could be partly the result of increased exposure to EDC⁸. It is very unlikely that such young children would consume significantly greater amounts of food and exercise less than the previous generation but rather it is evident that it may be because of the altered environment in utero or postnatally which is affecting fat deposition in their early life. This is also corroborated by epidemiological evidence in which studies of babies born to mothers who smoked tobacco during pregnancy have been found to have low birth weight, but paradoxically to then be at increased risk of obesity. Metaanalysis of multiple studies confirms that early-life-exposure to some components of tobacco smoke can lead later to obesity⁹. Other studies have shown that early-life exposures to PCB and bisphenol A are also associated with increased body weight in young children¹⁰. Interestingly, some studies have shown that exposure to some of these endocrine disruptors could be passed on from generation to generation up to the third generation (F3) even with no further exposure⁶.

Mechanism of action of obesity causing endocrine disruptors.

Obesity causing endocrine disruptors cause weight gain by changing or altering lipid homeostasis to promote adipogenesis and lipid accumulation and this may occur through multiple mechanisms as summarized below (Figure 1). Obesity could occur through increasing the number of adipocytes, increasing the size of adipocytes or altering the endocrine pathways responsible for the control of adipose tissue development⁹.

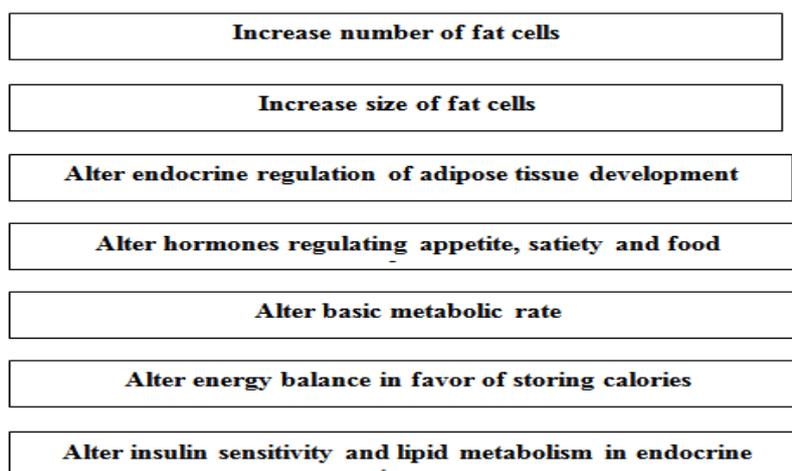


Figure 1. Multiple mechanisms by which endocrine disruptors could cause obesity

In general, early developmental changes (in utero or postnatally) involve an increase in adipocyte numbers, whilst changes later in life during adulthood tend to involve mainly an increase in the size of adipocytes. Current evidence shows that the number of adipocytes are set by the end of childhood and any increase in adipocyte numbers in early life tends to be permanent¹¹.

Other mechanisms of interference by endocrine disrupting chemicals (obesogens) may involve altering hormones that regulate appetite, satiety and food preferences, altering the basal metabolic rate or altering the energy balance to favor storage of calories. Another mechanism may involve altering insulin sensitivity and lipid metabolism in endocrine tissues such as pancreas, adipose tissue, liver gastrointestinal tract, brain or muscle.

At the molecular level, endocrine disrupting hormones can act by interfering with nuclear transcriptional regulators that control lipid flux and/or adipocyte proliferation/differentiation, such as the peroxisome proliferator-activated receptors (PPAR α , PPAR- δ and PPAR- γ) and steroid hormone receptors⁹.

Endocrine disrupting chemicals acting through interference with peroxisomeproliferator-activated receptors (PPARs)

PPARs can bind a wide range of unsaturated fatty acids and therefore act as lipid sensors to regulate homeostasis. PPAR γ functions in energy storage through its regulatory actions on adipogenesis and has therefore been defined as a master regulator of fat cell development.

PPARs act by heterodimerisation with retinoid X receptors (RXRs), and activation of RXR-PPAR γ favors the differentiation of adipocyte progenitors and preadipocytes in adipose tissue and regulates lipid biosynthesis and storage¹². Several EDCs have now been shown to alter adipogenesis through interfering with PPAR γ actions.

Endocrine disrupting chemicals acting through interference with Steroid receptors

Dietary soy phytoestrogens, such as genistein and daidzein, modulate estrogen receptor signaling and reverse truncal fat accumulation in postmenopausal women, an effect which has been demonstrated also in ovariectomized rodent models¹³. However, fetal or neonatal estrogen exposure can have the opposite effect and lead to obesity later in life, which emphasizes, again, that timing of exposure can be important in the consideration of outcomes.

Rodents treated with phytoestrogens during pregnancy or lactation were observed to develop obesity at puberty, especially in males, which might question the wisdom of the consumption of soy-based products by neonatal males.

Neonatal exposure of female mice to the synthetic estrogen (Diethylstilbestrol (DES)) initially led to depressed body weight, but was followed by long-term weight gain in adulthood although notably not in male mice¹⁴, demonstrating the obesogenic effect of a potent estrogen on adipogenesis which can be gender-specific. Whilst some EDCs may act directly through cellular steroid receptors, other EDCs may act less directly by stimulating estrogen synthesis.

Endocrine disruptors act through Aryl Hydrocarbon receptors

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that senses the presence of foreign compounds such as persistent organic pollutants (POPs) and leads to the activation of cytochrome P450 enzymes needed for their clearance from the body. However, AhR can indirectly influence adipogenesis through altering PPAR γ expression, and some POPs with obesogenic activity, which can be inhibited by AhR antagonists, have been suggested to function through this mechanism of action¹⁵.

Endocrine receptors act by altering recruitment of fat cells

Mature adipocytes are generated from multipotent stromal cells (MSCs) of fetal and adult tissues. These multi stromal cells can differentiate into several different cell types in vitro, including not only adipose tissue but also bone, cartilage and muscle, and regulation of these processes is essential for homeostasis. Kirchner et al. showed that exposure of pregnant mice to Tributyltin (TBT) results in MSCs which differentiate in offspring preferentially into adipocytes rather than bone and, furthermore, which have epigenetic alterations in the methylation status of some adipogenic genes¹⁶. Similar results were obtained by Li et al. following prenatal exposure to the fungicide triflumizole, which demonstrates that some EDCs can act by altering recruitment as well as differentiation of fat cells. A sensitive time for such alterations would be during the development of adipose tissue in early life¹⁷.

Endocrine disrupting chemicals act by altering appetite, satiety and food preferences.

Endocrine disrupting chemicals may act through altering the energy between energy intake and energy expenditure, especially by altering appetite, satiety and food preferences.

Bisphenol A has been shown to induce obesity in experimental studies¹⁸ and is present in over 90% of urine samples in the US population (Calafat et al., 2008). Recently, Bisphenol A levels have been found to correlate in humans with circulating levels of leptin and ghrelin. Alterations to the circulating levels of these hormones suggest that BPA may be able to act by interfering with hormonal control of hunger and satiety²⁰.

II. Conclusion

Endocrine disruptors can have a major role in causing obesity in both young and the adult, there is higher risk when one is exposed to these obesogenic hormones at an early age in utero or neonatally. Also, young children that have exposure to some of these obesogenic compounds or hormones have higher risk of developing obesity later in life.

Endocrine disruptors contributing to the incidence of obesity do not only just have the effect of causing obesity, but rather have also been established to be an underlying risk factor for many diseases including metabolic syndrome, diabetes, cardiovascular diseases and cancer. However, most of the experiments to prove this have been conducted or modelled in animals and very few experiments have been conducted in humans. To further substantiate and have more solid knowledge about how endocrine disrupting chemicals contribute to obesity in humans, there would be need for more studies in humans. Also studies that track subjects from childhood to adulthood will be beneficial and will be a great addition to current knowledge about endocrine disrupting chemicals.

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