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Review Article

Obesogens – new global health problem?

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Abbreviations:
BPA – bisphenol A
DDT – dichlorodiphenyltrichloroethane
DEHP – di(2-ethylhexyl) phthalate
DES – diethylstilbestrol
EDCs – endocrine disrupting compounds
PBDE – polybrominated diphenyl
PCB – polychlorinated biphenyl
PPAR – peroxisome proliferator activated receptor
PVC – polyvinyl chloride
RXR – 9-cis retinoic acid receptor
TBT – tributyltin

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Abstract

Obesity is a serious global public health problem. It is a complex disease caused by a combination of several factors including overeating and a sedentary lifestyle, genetic susceptibility, and environmental factors. Substantial scientific evidence indicates that increase in obesity prevalence correlates with increase in production and human exposure to environmental chemicals, suggesting that a long list of chemical compounds that can be found all around us may play a role in the etiology of obesity.

Endocrine disrupting compounds (EDCs) are chemicals that can interfere with the function of endocrine system. A subclass of EDCs that can disrupt a great number of metabolic processes including normal development of adipose tissue and balance of lipid metabolism thus leading to obesity are called obesogens. They can be found in electronics, plastics, furniture, clothes, cosmetics and also in the air, water and food that people consume. Persistent organophosphate pesticides, flame retardants, nicotine and plastics have all been linked to obesity particularly if exposure occurs during early life (in utero, *newborns*). *Early development is the most vulnerable period for obesogen exposure leading to epigenetic changes that persist throughout life.*

Current knowledge on obesogens is probably just "the tip of the iceberg" and future research is needed as well as increasing public awareness of this problem and its implications to human health. It is important to establish control over obesogens and try to prevent or at least limit the exposure of people, especially children and pregnant women, to these dangerous and harmful chemical compounds.

INTRODUCTION

Obesity represents a major global health problem that is associated with an increased risk of morbidity and mortality. Although it has a long historical background, current standard definition was endorsed at the beginning of this century. World Health Organization (WHO) has defined overweight and obesity as *"the disease in which excess body fat has accumulated to such an extent that health may be adversely affected"* (*1*).

Over the last few decades, obesity has been transformed from relatively minor public health issue that primarily affected the most affluent societies to a major threat to public health that is being increasingly seen worldwide (*2*). Obesity has an important contribution to the global incidence of cardiovascular disease, type 2 diabetes mellitus, cancer, gall bladder disease, sleep apnea, reproductive problems, and osteoarthritis (*3*). Currently at the global level, it has been estimated that about 2 billion people are overweight and one third of them are obese (*4*). If secular trends continue, an estimated 38% of the world's adult population will be overweight and another 20% will be obese by 2030. In the USA, the

direst projections based on earlier secular trends point to over 85% of adults being overweight or obese by 2030 (*5*).

There is scientific consensus that obesity is caused by an energy imbalance when the intake of energy is greater than the consumption. In addition, complex interactions between genetic and environmental factors are known to have a role in the etiology of obesity. Commonly recognised causes of obesity are overeating and a sedentary lifestyle which is imposed on a background of genetic pre-disposition for the disease. However, according to the present knowledge, the epidemic of obesity cannot be explained by diet and reduced physical activity alone. The historical global increase in the production of synthetic organic and inorganic chemicals parallels with the worldwide increase in obesity prevalence. Evidence from animal and human studies indicates that exposure to some chemical compounds is associated with an increase in body weight. These chemicals, called obesogens, are a subclass of endocrine disrupting compounds (EDCs), that can interrupt the function of endocrine system (*6*). The role of environmental chemicals in the development of obesity is an emerging area of research as scientists are just beginning to uncover the role chemical compounds have in the regulation of human fat metabolism and obesity. The aim of this review is to summarise current evidence on obesogens and its role in the development of obesity.

ENDOCRINE DISRUPTORS AND OBESOGENS AS ETIOLOGICAL FACTOR OF OBESITY DEVELOPMENT

Endocrine disrupting compounds were defined by the U.S. Environmental Protection Agency as "*exogenous agents that interfere with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process*" (*7*). Given the current knowledge adverse developmental, reproductive, neurological, and immune effects on human body and metabolism could be attributed to EDCs. Therefore, exposure to EDCs may result in lowered fertility, increased incidence of endometriosis and abnormalities that may lead to the development of cancer. Also, EDCs can cause neurological or thyroid disorders and metabolic syndrome (*8*).

Research shows that exposure to EDCs represent the greatest risk for human health during prenatal or early postnatal period when organ and neural systems are forming. It has become clear that these compounds can fully or partly mimic functions of naturally occurring hormones in the body, including estrogens, androgens, and thyroid hormones which play a very important role in brain development early in life and regulate various processes in adults (*9*).

Based on previously published data it could be proposed that they may interfere with the function of hormones in various different ways, i.e., directly by binding to a receptor within a cell thereby blocking the binding of the endogenous hormone; and indirectly by altering the physiological hormonal transport mechanisms (*6*). Thus, EDCs may disrupt signalling processes throughout the body, which can lead to a variety of diseases of the endocrine system.

Obesogens as a subclass of EDCs can disrupt a great number of metabolic processes particularly if exposure occurs during early life, the most sensitive period of human body development. It was shown by Newbold et al. that even low-level exposure of EDC diethylstilbestrol during early period of development causes obesity in adulthood (*10*). Obesogens may also be defined as exogenous chemicals that inappropriately alter lipid homeostasis and fat storage, change metabolic set-points, disrupt energy balance, or modify the regulation of appetite and satiety which eventually promote accumulation of triglycerides in adipose tissue and thus contribute to the development of obesity.

The term obesogen was coined in 2006 by Felix Grün and Bruce Blumberg from the University of California at Irvine (*11*). They formed environmental obesogen hypothesis and defined obesogens as „*xenobiotic chemicals that can disrupt the normal developmental and homeostatic control over adipogenesis and/or energy balance*." Taking into consideration that regulation of energy balance is a basic concept in the etiology of obesity, Paula Baillie-Hamilton hypothesized that obesogens are responsible for disrupting energy balance making it difficult to lose weight (*12*).

Since obesogens are a large group of chemicals, exposure can occur in a variety of ways: through eating, drinking, or breathing or by absorption through skin. They can be found in the environment and in many products – plastic bottles, metal food cans, detergents, furniture, flame retardants, food, toys, cosmetics, and pesticides. Until now, ~20 chemicals from the environment are found to be potentially implicated in the regulation of metabolic processes in obesity. Some potential obesogens are bisphenol A (BPA) – found in some polycarbonate plastic products and carbonless copy paper; perfluoroalkyl compounds – used in nonstick cookware; organotins – used in agriculture and industry; nonylphenol – found in cosmetics and household cleaners; organophosphate pesticides – used for pest control; dichlorodiphenyltrichloroethane (DDT) – used as pesticide; polychlorinated biphenyl (PCB) and polybrominated diphenyl (PBDE)– used as flame retardants; dioxins and furans – found in plastics; maternal smoking during pregnancy; phthalates – found in some plastics; phytoestrogens, diethylstilbestrol (DES), tributyltin (TBT) and di(2-ethylhexyl) phthalate (DEHP) – used in the manufacture of a wide variety of consumer food packaging, some children's products, and some polyvinyl chloride (PVC) medical devices (*13*).

As previously mentioned, early development (*in utero* and newborns) is the most vulnerable period for obesogen exposure which can occur through maternal diet, by in-

teraction with products that can cross the placental barrier or are transmitted through breast milk. Exposure to certain EDCs during prenatal or early-life probably increases susceptibility to weight gain and thus predisposes some individuals to develop obesity later in life. However, it needs to be emphasized that secondary challenges, like high-fat diet or other stressors, are necessary for the development of full spectrum of symptoms associated with obesity. Experimental animal studies showed that early-life exposure to air pollution led to increased visceral obesity, insulin resistance and inflammation (*14*). In addition, it was shown that mice fed with a high-fat diet for 10 weeks and subsequently exposed to pollution particles as adults for 24 weeks had increased visceral obesity, insulin resistance and inflammation (*15*).

Recent research has also indicated that early-life exposure to EDCs may have different effects than exposure in adulthood because of incomplete development of protective mechanisms, such as DNA repair, xenobiotic metabolism and the blood-brain barrier resulting in more profound long-lasting effects (*16*).

In the past decade, a considerable body of evidence has shown that chemical exposure occurring during certain periods of fetal development can generate phenotypes that persist through multiple generations (transgenerational effect). These phenotypic changes probably do not have a genetic origin as low-dose exposure to obesogens, typically, does not damage DNA but, rather causes epigenetic alterations (DNA methylation and acetylation, histone modifacation) that can be passed on to subsequent generations (*9*).

MECHANISMS OF OBESOGEN ACTION

Current data suggest that obesity is the result of a prolonged disturbance in the homeostatic regulation of energy metabolism that favours triglyceride storage and adipocyte hypertrophy. There are a number of mechanisms through which obesogens can disrupt the activity of adipose tissue. Considering that obese individuals exhibit increased number and volume of adipocytes and that early-life exposure to EDCs exerts the same effect on fetal adipose tissue, it has been suggested that obesogens could act on metabolic sensors that control adipocyte differentiation and function (*17*). They can disrupt metabolic sensors by mimicing metabolic ligands, blocking or upregulating hormone receptors. Also, they dysregulate sex steroid synthesis by altering the ratio of sex hormones leading to changes in their control of lipid balance and they can change central integration of energy balance including the regulation of appetite and satiety in the brain. Obesogens can also artificially direct mesenchymal stem cells to differentiate into adipocytes and promote the accumulation of triglycerides in mature adipocytes (*18*, *19*).

There are two most important pathways of obesogen disruption. First is the disruption of metabolic sensors and second is the disruption of central energy balance (*20*).

Metabolic sensors

Obesogens have been shown to target a number of transcription regulators found in gene networks whose function is to control intracellular lipid homeostasis, adipocyte proliferation and differentiation. The major group of targeted regulators is a group of nuclear hormone receptors known as peroxisome proliferator activated receptors (PPAR) α, δ, and γ. These hormone receptors serve as metabolic sensors for a variety of metabolic ligands, including lipophilic hormones, dietary fatty acids and their metabolites, but also control transcription of genes involved in lipid metabolism (*21*). In order to become active and function as proper metabolic sensors and transcription regulators, the PPAR receptors have to bind to another receptor known as the 9-*cis* retinoic acid receptor (RXR), thus forming a heterodimer required for its proper function. The PPARγ receptor, when complexed with RXR and activated by the binding of fatty acids or their derivatives, stimulates lipid biosynthesis resulting in storage of lipids rather than fatty acid oxidation. What also needs to be taken into consideration is that agonists may activate multiple isoforms of PPAR. The issue is important since it was shown that lipid mobilization developed as a result of PPARγ activation requires continuous obesogens exposure. But, single or episodic exposure to obesogens results in lipid mobilization caused by activation of PPARγ, so it is indispensable to establish its effect in adipose tissue (*22*). In addition, PPAR activation promotes differentiation of preadipocytes and the conversion of mesenchymal progenitor cells to preadipocytes in adipose tissues (*23*). Obesogens that target the PPARγ/RXR complex mimic the metabolic ligands and activate signalling pathways leading to upregulation of lipid accumulation which explains their obesogenic effects (*24*).

Central integration of energy balance

The hypothalamic-pituitary-adrenal axis is involved in the control of appetite and satiety in order to maintain energy homeostasis. Regulation of appetite and satiety are mediated by a large number of monoaminoergic, peptidergic and endocannabinoid signals that originate from the digestive tract, adipose tissues and brain. It is these types of signals that provide a likely target for obesogens that have shown to have weight altering effects (*25*). Several peptidergic pathways controlling appetite and energy balance by hormones like ghrelin, neuropeptide Y and agouti-related peptide are particularly sensitive to changes in nuclear receptor signalling pathways and can therefore be easily altered by the introduction of obesogens (*26*). Such alteration can lead to induced feeling of hunger and decreased feeling of fullness causing an increase in food intake and inability to feel sated, both characteristics of obesity.

FUTURE DIRECTIONS

Dealing with obesity epidemic will require more research into understanding how nutritional and environ-

mental chemical exposures affect the basic mechanisms underlying adipose tissue development and function as well as eating behaviour. The combination of early overnutrition and exposure to obesogens during development *(in utero* and in the first few years of life) along with overnutrition, decreased physical activity and additional environmental exposures to obesogens throughout life generate ideal conditions for obesity development (*27*). It is not important just to identify obesogens, but also to specify their possible molecular targets and describe potential cellular mechanisms through which they might act. The most important question yet to be resolved is how the exposure to obesogens can be maximally reduced given their occurrence and distribution in the environment. It is of particular importance to prevent or at least limit the exposure of young people, especially children and pregnant women, to these dangerous compounds in order to establish control over their adverse effects. However, the concept of obesogens has not spread into the public awareness yet. So, more efforts should be made to garner greater attention in academic and policy spheres regarding the role of environmental chemicals in obesity epidemic (*28*).

CONCLUSION

Although current knowledge on obesogens is comparable with the „top of the iceberg", this subclass of endocrine disruptors are considered to play important role in the etiology of obesity. Dealing with obesity epidemic will require more research into understanding how nutritional and environmental chemical exposures affect the basic mechanisms underlying adipose tissue development and lipid metabolism. It is important to establish control over obesogens and try to prevent or at least limit the exposure of young people, especially children and pregnant women, to these dangerous and harmful chemical compounds.

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