

32 Endocrine Disrupting Chemicals, Obesogens, and the Obesity Epidemic

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ABBREVIATIONS

BADGE	Bisphenol-A diglycidyl ether
BPA	Bisphenol A
DDT	Dichloro-diphenyl-trichloroethane
DES	Diethylstilbestrol
EDCs	Endocrine disrupting chemicals
F1–F3	First–third filial generation
FABP4	Fatty acid binding protein-4
LPL	Lipoprotein lipase
MSCs	Mesenchymal stem cells
NAFLD	Nonalcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observable adverse effect levels
PCBs	polychlorinated biphenyls
PPAR γ	Peroxisome proliferator activated receptor gamma
RXR	Retinoid X receptor
TBT	Tributyltin
TPT	Triphenyltin
ZFP423	Zinc finger protein 423

ENDOCRINE DISRUPTING CHEMICALS (EDCs) AND HUMAN HEALTH

In the last 60 years, the number of artificial chemicals introduced in our environment has dramatically increased. There is a growing body of research in laboratory animals and in wildlife showing that some of these chemicals used in industry and agriculture may negatively modulate the endocrine system and, therefore, may be involved in the increasing rates of various health conditions worldwide (Diamanti-Kandarakis et al. 2009). As defined by the Endocrine Society, the term endocrine disrupting chemicals (EDCs) refers to “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action” (Zoeller et al. 2012). This differs from the definitions promulgated by the United States Environmental Protection Agency and the World Health Organization that add the qualifier, “and causes adverse health effects in an intact organism, its progeny or subpopulations” (WHO/UNEP 2013). The difference is one of perspective and training. To an endocrinologist, disrupting the normal function of the endocrine system is *de facto*, adverse, even if the results might be subtle and take years to be manifested. To a regulatory toxicologist, adverse consequences must be demonstrated in a short time frame and subtle changes are typically ignored or deemphasized. These different perspectives have led to much debate in the scientific literature between regulators and industrial toxicologists on one side, and the endocrine/environmental health community on the other side. We adopt the view of the Endocrine Society in the review that follows.

In mammals, the endocrine system consists of a complex network of glands and organs that regulate physiological functions such as appetite, circadian rhythms, or reproduction. The classical glands include but are not limited to the pituitary gland, thyroid gland, pancreas, gonads, and adrenal glands (Melmed et al. 2011). However, other organs such as fat tissue, liver, and intestines also have endocrine functions that are critical for the maintenance of body functions, including metabolic homeostasis (Kershaw and Flier 2004). The link between the classical endocrine glands and other organs with endocrine functions lies in the fact that all of them secrete hormones into the bloodstream in response to certain environmental stimuli and will generate a physiological response in a (usually distant) target tissue. Although the endocrine system has the ability to adapt in response to hormonal fluctuations, if the changes occur at critical windows in life (e.g., embryonic development) or last for long periods (e.g., insulin resistance), they may have permanent detrimental effects on the physiological response of the individual (reviewed by Gore et al. 2015).

The mechanisms through which EDCs act are diverse and include their interactions with nuclear and nonnuclear hormone receptors (e.g., nuclear and membrane estrogen receptors, respectively), nonsteroid receptors (e.g., neurotransmitter receptors), or enzymatic pathways involved in the synthesis and metabolism of hormones (e.g., cytochrome P450s). These interactions may activate or inhibit the pathway they regulate by mimicking or blocking the action of the endogenous molecules (Gore et al. 2015).

THE OBESITY EPIDEMIC

The endocrine system may participate in the regulation of energy homeostasis by modulating neuroendocrine circuits involved in the control of appetite and satiety (Mackay et al. 2013); therefore, agents altering hormone levels and activity may contribute to the development of obesity. The most commonly accepted factors involved in obesity are generally ascribed to positive energy balance (Hall et al. 2012). Other factors such as genetics or gut microbiome may not be directly associated with lifestyle but their effects can be exacerbated by it (McAllister et al. 2009, Turnbaugh et al. 2006). However, the continuous worldwide increase in global obesity rates is difficult to explain by only considering the traditional factors associated with this health condition (Ng et al. 2014, Ogden et al. 2014). These trends open the debate regarding what are all of the major causes contributing to the obesity epidemic. More alarming is the fact that this increased tendency toward obesity has also been shown for children below 5 years of age, who, in 2013, numbered at least 40 million worldwide

(Ng et al. 2014). In parallel to the trends observed in humans, it has been shown that wild and domestic animal populations living in proximity to humans have also undergone significant average increases in body weight in recent years (Klimentidis et al. 2011). An easy explanation for this trend would be to assume that animals living around industrialized areas have easy access to unhealthy food wasted by humans. Interestingly, laboratory animals that are maintained on what are thought to be tightly controlled, optimal diets are also following the same trend (Klimentidis et al. 2011), suggesting the existence of additional, unidentified factors that are contributing to the increasing rates in overweight in different species.

In 2006, our laboratory introduced the “obesogen hypothesis” that proposes the existence of a subset of EDCs that alter lipid metabolism to inappropriately stimulate an increase in the number of adipocytes or the amount of fat stored within these cells, which may contribute to disturbances in metabolic homeostasis (Janesick and Blumberg 2011). This alteration in energy balance may ultimately lead to the development of obesity.

OBESOGENS, ADIPOGENESIS, AND OBESITY

Since the introduction of the obesogen hypothesis, the effects of a growing list of obesogens have been characterized using both *in vitro* and *in vivo* approaches.

Although not all obesogens act through the same pathways, a subset of obesogens act through the peroxisome proliferator activated receptor gamma (PPAR γ), which is considered to be the “master regulator of adipogenesis” (Tontonoz and Spiegelman 2008). PPAR γ is highly expressed in fat tissue and functions as an obligate heterodimer with the retinoid X receptor (RXR) (Kliwer et al. 1992). Upon ligand binding, this heterodimer transcriptionally activates downstream genes involved in lipid synthesis and metabolism such as fatty acid binding protein-4 (FABP4), lipoprotein lipase (LPL), and leptin.

IN VITRO EXPOSURE TO OBESOGENS AND ADIPOGENESIS

The organotins tributyltin (TBT) and triphenyltin (TPT) were the first obesogens described and they both activate PPAR γ (Grun et al. 2006, Janesick et al. 2015, Kanayama et al. 2005). More recently, the pesticides triflumizole, quinoxifen, spirodiclofen, and zoxamide have been shown to activate PPAR γ and to increase lipid accumulation using *in vitro* models such as the murine pre-adipocyte 3T3-L1 cell line and mouse and human mesenchymal stem cells (MSCs) (Janesick et al. 2015, Li et al. 2012). In the same study, we found that the fungicide fludioxonil is not a PPAR γ activator, but it activates RXR and increases lipid accumulation in 3T3-L1 MSCs (Janesick et al. 2015). MSCs are able to differentiate into a variety of cell types including adipocytes, osteoblasts, chondrocytes, and myocytes, depending upon the stimuli they receive (Cristancho and Lazar 2011). By exposing 3T3-L1 cells or MSCs to obesogen candidates in the presence of an adipogenic cocktail, it is possible to assess the adipogenic capabilities of individual chemicals by analyzing lipid accumulation and mRNA expression levels of adipogenic marker genes such as those described earlier (Chamorro-Garcia et al. 2012, Grun et al. 2006, Janesick et al. 2015, Kirchner et al. 2010). There is a subset of candidate obesogens whose mechanisms of action remain unknown. One example is bisphenol-A diglycidyl ether (BADGE), which is used in the manufacture of epoxy resins, paints, and as a coating in food cans. BADGE induces lipid accumulation in 3T3-L1 pre-adipocytes and MSCs, but the inhibition of PPAR γ with the specific antagonists T0070907 or GW9663 does not interfere with BADGE-induced accumulation of lipids (Chamorro-Garcia et al. 2012). Other potential obesogens whose mechanisms of action remain unknown are imazalil, tebupirimfos, florchlorfenuron, flusilazole, acetamiprid, and pymetrozine, which are not PPAR γ or RXR activators but induce adipogenesis in 3T3-L1 cells (Janesick et al. 2015). These studies indicate that further analyses are needed to more fully understand the mechanisms through which obesogens act.

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IN VIVO EXPOSURE TO OBESOGENS DURING ADULTHOOD AND OBESITY

Epidemiological studies showed a positive association between the presence of some EDCs in blood and an increase in fat storage. Multiple independent epidemiological studies have linked high plasma levels of polychlorinated biphenyls (PCBs) with obesity (Dhooge et al. 2010, Donat-Vargas et al. 2014, Lee et al. 2011). Cross-sectional analyses showed that increased urine levels of phenols (e.g., bisphenol A; BPA), whose use is widespread in industry, and phthalates, used as plasticizers and in personal care products, are associated with an increase in fat content in the adult human (Carwile and Michels 2011, Song et al. 2014). In many cases, the increase in fat storage is accompanied by other metabolic conditions such as insulin resistance, type 2 diabetes, and cardiovascular disease (James-Todd et al. 2012, Lind, Zethelius, and Lind 2012, Shankar and Teppala 2011).

Likewise, studies performed using laboratory animals have also demonstrated a positive association between obesogen exposure during adolescence and adulthood, and obesity and related diseases. Adult exposure to PCB-153 in mice led to increased fat storage, liver steatosis, and abnormal levels of adipokines in plasma when animals were fed with a high-fat diet (Wahlang et al. 2013). Mice chronically exposed to a mixture of different PCB congeners and dichloro-diphenyl-trichloro-ethane (DDT) developed insulin resistance, glucose intolerance, and visceral adiposity (Ibrahim et al. 2011). Adult mice exposed to BPA had a significant increase in body weight, hyperglycemia, and insulin resistance (Alonso-Magdalena et al. 2006, Marmugi et al. 2014). Female mice exposed to phthalates showed increased body weight, visceral adiposity, and food intake (Schmidt et al. 2012). Juvenile exposure to organotins such as TBT induces fat storage, fatty liver, and insulin resistance in rodents (Penza et al. 2011, Zuo et al. 2011). Taken together, both human epidemiological studies and studies performed in animal models show the positive association between the presence of obesogens in the body in adult individuals and an increase in fat storage and obesity.

DEVELOPMENTAL ORIGINS OF OBESITY

ENERGY BALANCE DURING DEVELOPMENT

There is a growing body of evidence showing that obesity during adulthood may have a developmental origin (Janesick and Blumberg 2011). The developing organism possesses plasticity to adapt to environmental stimuli and this plasticity may be detrimental for the organism later in life, since it may promote the development of a variety of health conditions. Thus, environmental insults such as under- or overnutrition or the presence of artificial chemicals during embryogenesis may lead to detrimental effects later in life.

Epidemiological studies found a correlation between maternal overweight during pregnancy and increased body weight at birth (Surkan et al. 2004). Experiments performed in rodents showed that high-fat diets during pregnancy and lactation lead to obesity, hypertension, and insulin resistance in the offspring even if they were maintained on a normal diet after weaning (Armitage et al. 2005, Khan et al. 2003, Taylor et al. 2005). Experiments performed with cross-fostering approaches between control dams and dams exposed to a high-fat diet showed that both *in utero* and lactational exposure to a high-fat diet are critical factors in the development of metabolic syndrome later in life and that these effects can be transmitted to subsequent generations (Hoile et al. 2015, Khan et al. 2005). More strikingly, rats exposed to cafeteria-style “junk-food” during *in utero* development showed a biased preference toward palatable high-fat diets compared to animals exposed to control rat diet, which indicates that high-fat and high-sugar exposure during critical windows of development cause an alteration on the central reward pathways that will condition diet choices and food intake later in life (Ong and Muhlhauser 2011).

Paradoxically, as reviewed in Chapter 28 of this book, undernutrition during critical windows of development also leads to obesity later in life. Epidemiological observations performed in men and women born during the “Dutch famine winter” at the end of World War II in the Netherlands showed that malnutrition during early stages of development led to increased body mass index and

waist circumference in women but not men later in life (Ravelli et al. 1999). Analyses of the same cohort showed that, when the famine period occurred at later stages of development, both men and women had lower glucose tolerance, suggesting that undernutrition during development led to permanent changes in metabolic homeostasis (Ravelli et al. 1998). In line with these findings, studies of a British cohort in Hertfordshire showed that poor nutrition during perinatal development was positively associated with cardiovascular disease and type 2 diabetes during adulthood (Hales and Barker 1992). These observations led David Barker to propose the “Barker hypothesis” also known as the “thrifty phenotype hypothesis.” The fundamental tenet of this hypothesis is that nutritional deprivation during a very energy demanding period of life, such as *in utero* development, will lead to metabolic adaptations in the fetus that favor energy storage; thus, the metabolism “learns” to be thrifty with calories. This enables some degree of adaptation to poor nutrition throughout life. However, if instead this “thrifty phenotype” individual encounters adequate or excess nutrition, the metabolic adaptations made during fetal life will lead to inappropriate storage of ingested calories, altering glucose homeostasis and ultimately leading to obesity and related disorders (Hales and Barker 2001). Thus, the “thrifty adaptations” become detrimental only when the postnatal environment differs from the prenatal setting.

OBESOGENS AND THE DEVELOPMENTAL ORIGINS OF OBESITY

The “obesogen hypothesis” introduces another level of complexity to the developmental origins of obesity. There is a growing body of research showing that exposure to obesogens during critical windows of development such as *in utero* development and during lactation lead to obesity later in life (Heindel, Newbold, and Schug 2015).

The organotin TBT belongs to the group of obesogens whose *in utero* effect has been more deeply characterized (Janesick, Shioda, and Blumberg 2014). In rodents, TBT causes masculinization of females and infertility in mollusks and fish (Bryan et al. 1986, McAllister and Kime 2003) as well as toxicity in liver, nervous system, and immune system (Boyer 1989). More recently, it was shown that exposure to low doses of TBT during tadpole stages in *Xenopus laevis* and larvae stages in *Danio rerio* (zebrafish) increases fat storage (Grun et al. 2006, Tingaud-Sequeira, Ouadah, and Babin 2011). Human studies have shown that the presence of TBT in placenta is positively associated with weight gain in the first months of life (Rantakokko et al. 2014). Experiments performed in mice demonstrated that prenatal exposure to TBT increases adiposity, nonalcoholic fatty liver disease (NAFLD), and the reprogramming of the MSCs compartment favoring their differentiation into adipocytes at the expense of the bone in the offspring (Chamorro-Garcia et al. 2013, Grun and Blumberg 2006, Kirchner et al. 2010).

There are other EDCs with shorter half-lives that are in widespread industrial use, such as BPA. BPA is used in the manufacture of polycarbonate plastics, epoxy resins, and thermal papers; therefore, it can be found in a variety of products the public encounters on a daily basis, including plastic containers, food packaging, thermal papers, medical devices, dental sealants, and so on (Vandenberg et al. 2010). Despite its ephemeral existence, the widespread use of BPA makes it ubiquitously present. BPA has been detected in human samples including urine, serum, breast milk, and fat and is associated with increased body weight, breast and prostate cancer, and alterations in the reproductive system (reviewed by Rubin 2011). Data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional study with over 2500 participants ≥ 6 years of age, revealed that BPA was present in 92.6% of the samples at an average level in urine of 2.6 ng/mL (Calafat et al. 2008). Interestingly, participants between 6 and 11 years of age showed an average BPA level of 4.5 ng/mL. These data raise concern about the impact of obesogens during childhood, when metabolic setpoints are being programmed and are, therefore, more susceptible to environmental insults. Although BPA is an estrogen, its mechanism of action in promoting obesity is not known but it is notable that perinatal estrogen exposure can predispose animals to obesity later in life (Newbold et al. 2007). Experiments performed using animal models showed that *in utero* exposure to low doses of BPA leads to increased body weight and abdominal fat and the disruption of lipid

homeostasis later in life (Alonso-Magdalena et al. 2010, Howdeshell et al. 1999, Somm et al. 2009). Similar results regarding increased body weight during adulthood were found in rodents exposed to the estrogen diethylstilbestrol (DES) during *in utero* development (Newbold et al. 2004).

OBE SOG E N S A N D T H E T R A N S G E N E R A T I O N A L T R A N S M I S S I O N O F O B E S I T Y

Recent studies performed in animal models have revealed that ancestral perinatal exposure to obesogens leads to obesity in subsequent generations (Chamorro-Garcia et al. 2013, Manikkam et al. 2013). The transgenerational transmission of diseases implies that the germ line genome has been modified in nucleotide sequence (mutations) in epigenomic marks (epimutations) or both. As discussed more extensively in Chapter 28, the mechanisms involved in the modification of the epigenomic profile include covalent modifications of the DNA (e.g., methylation and hydroxymethylation of cytosines) and histones (e.g., methylation of lysines), and the presence of noncoding RNAs (Xin, Susiarjo, and Bartolomei 2015). By modifying the epigenomic profile of the cell, it is possible to modulate the functional output of the information stored in the genome sequence. During early stages of the development, the primordial germ cells go through a genome-wide demethylation/remethylation cycle before implantation. At this stage, the genome is extremely sensitive to the exposure of agents that may permanently change the original methylation pattern (Heard and Martienssen 2014). Thus, any changes in the epigenomic profile in the germ line at these developmental stages and the biological traits associated with them may be transmitted to subsequent generations, although, the precise mechanisms remain to be elucidated.

Experiments performed in our laboratory showed that *in utero* exposure to environmentally relevant doses of TBT (5.42, 54.2, and 542 nM) of the first generation (F1) led to the development of obesity in subsequent generations with a sexually dimorphic penetrance (Chamorro-Garcia et al. 2013). F1 female mice exposed to TBT exhibited increased adiposity in a dose-dependent manner, whereas in F1 male mice this effect was not as strong as in subsequent generations. Both males and females developed nonalcoholic fatty liver with the phenotype stronger in females. F2 females and F2 and F3 males derived from TBT-exposed animals showed a dramatic increase in adiposity, whereas F3 females did not show significant changes. Gene expression analyses in the MSCs showed a significant increase in the gene expression levels of adipogenic markers such as ZFP423, FABP4, LPL, and PPAR γ in both genders. These effects were stronger in the F3 males than in previous generations, suggesting the existence of an epigenetic mechanism involved in the regulation of this phenotype (Chamorro-Garcia and Blumberg 2014, Chamorro-Garcia et al. 2013). It is worth noting that two of the TBT concentrations used in this experiment (5.42 and 54.2 nM) were lower than the established no observable adverse effect levels (NOAEL) (Vos et al. 1990). Other obesogens involved in the transgenerational inheritance of obesity include BPA, phthalates, hydrocarbons, and DDT. In all cases, the exposure to obesogens led to sperm epimutations in regions associated to obesity (Manikkam et al. 2013, Skinner et al. 2013, Tracey et al. 2013).

A recent study showed that surgery-induced weight loss in obese men led to a significant change in the DNA methylation profile of genes involved in central control of appetite in the sperm (Donkin et al. 2015). Studies performed in a different cohort of obese men showed that noncoding RNA expression levels and DNA methylation profiles in sperm were significantly different when compared to the profiles in lean men (Donkin et al. 2015). These data indicate that the epigenome of the male germ line is susceptible to environmental changes.

OBE SOG E N S A N D C A R D I O V A S C U L A R D I S E A S E

Obesity, NAFLD, and type 2 diabetes are just a few examples of risk factors for future cardiovascular diseases such as heart failure, coronary heart disease, or atrial fibrillation (Mozaffarian et al. 2016). Therefore, it should come as no surprise that factors that are contributing to obesity, NAFLD, and type 2 diabetes also contribute to cardiovascular comorbidities.

In the last two decades, there is increasing evidence showing an association between obesogen exposure and cardiovascular disease. Independent cross-sectional and longitudinal epidemiological studies revealed that urine BPA levels in adults is associated with an increasing risk for future coronary artery disease and high blood pressure (Bae et al. 2012, Lang et al. 2008, Melzer et al. 2010, 2012). *Ex vivo* analyses of rat cardiomyocytes showed that exposure to low doses of BPA alters electrical conduction causing arrhythmias in females; moreover, this effect was exacerbated when other conditions such as stress and previous heart damage were also present (Posnack et al. 2014, Yan et al. 2011, 2013). Two independent experiments showed that chronic BPA exposure in adult mice caused increased blood pressure and atherosclerosis (Saura et al. 2014, Sui et al. 2014), whereas perinatal chronic exposure to low doses of BPA modified the epigenetic profile of cardiac cells, leading to remodeling of cardiac structure and function (Patel et al. 2013). Although the mechanism underlying this phenotype remains unclear, alterations in the activity of the estrogen receptor and the pregnane X receptor are two hypotheses under investigation (Sui et al. 2014, Yan et al. 2013).

As mentioned earlier, our lab showed that *in utero* exposure to TBT causes increased fat storage and NAFLD in mice and that this phenotype is transmitted to future generations (Chamorro-Garcia et al. 2013). It has been reported that TBT alters cardiac function by increasing coronary perfusion pressure and cardiac hypertrophy in adult Wistar rats exposed to TBT for 15 days via gavage feeding (dos Santos et al. 2012). There is a notable lack of epidemiological studies associating TBT with cardiovascular disease, but these experiments performed in rodents suggest the potential contribution of TBT to the development of these health conditions.

Other EDCs that have been shown to alter cardiac function are dioxins, whose presence in blood in humans has been associated with artery disease when combined with other risk factors such as obesity (Min et al. 2011).

CONCLUSION AND FUTURE DIRECTIONS

Evidence is mounting regarding the existence of factors relevant to the obesity epidemic other than nutrition and exercise, which have been typically considered to be the most important factors in obesity. However, understanding the potential interactions between nutrition and other factors such as stress, exercise, genetics, and so on has become an important challenge.

The obesogen hypothesis introduces another level of complexity to the current understanding of obesity and related disorders and offers a different perspective. One key point is that there is now abundant evidence showing that obesogens are ubiquitously present in industrialized societies, occurring in water pipes, personal care products, food packaging, and agriculture. As a result, it makes sense to devote resources to understanding how obesogens act in biological systems in order that their effects on human, animal, and wildlife health be better assessed.

Experiments performed using *in vitro* models such as cell lines and primary cultures are contributing to the detection of new EDCs with obesogenic properties. Although such experiments have obvious limitations, they can contribute to a deeper, mechanistic understanding of how obesogens act. *In vivo* experiments performed in animal models will be required to definitively prove that chemicals are *bona fide* obesogens. Moreover, transgenerational studies in animal models are changing the genetic determinism dogma that the inheritance of certain phenotypes results solely from genomic mutations by providing evidence that epigenomic changes in DNA and histone methylation also play an important role in phenotypic inheritance. These new approaches demonstrate that, despite efforts to reduce or ban the use of certain artificial chemicals, the effects of such chemicals could last for generations not only as residues in nature but even more alarming, in our epigenome.

Further studies are needed to determine what interactions exist between obesogens and traditional factors involved in obesity such as diet. We currently know very little about the effects of exercise in fat mobilization and thermogenesis after obesogen exposure, the interactions of obesogens with diet composition, or the potential effects of obesogens on the balance of bacterial strains present in the gut microbiome.

Obesity is a multifactorial disease that is difficult to treat once it has developed. Obesity affects a significant fraction of the world population irrespective of the country, average income, age, gender, or lifestyle (Ng et al. 2014). The prevalence of other conditions associated with obesity (e.g., type 2 diabetes, hypertension, and cardiovascular disease) continues to increase in parallel with the obesity epidemic. Since obesity is largely refractory to treatment, new approaches are needed to prevent obesity from developing. The obesogen hypothesis offers a new perspective for understanding this global problem and proposes that the reduction of chemical exposure during critical windows of development may offer an additional approach for prevention.

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Author Queries

- [AQ1] Please check if “quinoxifen” should be changed to “quinoxyfen.”
- [AQ2] Please provide volume number and page range for Donkin et al. (2015), Heindel et al. (2015).
- [AQ3] Please update Janesick et al. (2015).
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