

MINIREVIEW

Transgenerational effects of obesogens

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Abstract

Obesity and associated disorders are now a global pandemic. The prevailing clinical model for obesity is overconsumption of calorie-dense food and diminished physical activity (the calories in—calories out model). However, this explanation does not account for numerous recent research findings demonstrating that a variety of environmental factors can be superimposed on diet and exercise to influence the development of obesity. The environmental obesogen model proposes that exposure to chemical obesogens during in utero and/or early life can strongly influence later predisposition to obesity. Obesogens are chemicals that inappropriately stimulate adipogenesis and fat storage, in vivo either directly or indirectly. Numerous obesogens have been identified in recent years and some of these elicit transgenerational effects on obesity as well as a variety of health end-points after exposure of pregnant F0 females. Prenatal exposure to environmental obesogens can produce lasting effects on the exposed animals and their offspring to at least the F4 generation. Recent results show that some of these transgenerational effects of obesogen exposure can be carried across the generations via alterations in chromatin structure and accessibility. That some chemicals can have permanent effects on the offspring of exposed animals suggests increased caution in the debate about whether and to what extent exposure to endocrine-disrupting chemicals and obesogens should be regulated.

1 | INTRODUCTION

The obesity pandemic is an escalating worldwide public health crisis, affecting over 650 million people across all race, age and socio-economic groups. Despite global recognition and endless health campaigns targeting caloric intake and physical activity, the trends in obesity and obesity-related diseases are steadily rising. Worldwide obesity tripled from 1975 to 2016 and obesity in the United States alone more than doubled between 1980 and 2010.^{1,2} These rates continue to rise, with the most recent statistics indicating that the fraction of obese adults in the United States has reached nearly 40%.^{3,4} This burden of obesity falls most heavily on woman and some minority populations with the obesity rate in African American and Hispanic women exceeding 50%.⁴ Alarming, childhood obesity rates have more than tripled in the United States.⁵ Even the percentage of obese

2- to 5-year-olds has more than doubled from 5% to 13.9% and among teens ages 12-19, the rate increased four times, from 5% to 20.6%.⁵ Childhood obesity can be detrimental to physical and emotional health and is closely associated with negative social and health outcomes including poor self-esteem, academic performance and impaired cardiovascular health. Moreover, overweight children are likely to continue being overweight or obese into adulthood and the fraction of obese adults who successfully lose large amounts of weight and then maintain this weight loss is than 17%.^{6,7} Obesity is associated with the development of non-communicable diseases such as type 2 diabetes, cancer and cardiovascular disease which contribute greatly to the medical costs of obesity. These costs were recently estimated at more than \$200 billion annually in the United States,⁸ and the fraction of these costs that could be attributed to but a small number of known obesogens was substantial.^{9,10} The actual cost is likely

to be significantly higher. This magnitude of the medical and human capital costs of obesity underscores the necessity of investigating all relevant factors to the obesity pandemic.

2 | THE ENERGY BALANCE DOGMA

On the surface, the cause of this obesity pandemic seems simple: too much caloric intake and not enough exercise. As a result, health professionals have led the general public to focus on weight management strategies that involve reducing an individual's net caloric balance through portion control and increasing physical exercise. However, this strategy has proven to be wholly inadequate at the population level as the number of obese people continues to rise worldwide. Moreover, the simplistic concept of increased caloric consumption and reduced exercise cannot explain the rapid rise in obesity. A key recent study examined NHANES data between 1988 and 2006 and found that even at the same levels of calorie consumption and energy expenditure via exercise, the average BMI was 2.3 kg/m² higher in 2006 than in 1988.¹¹ In addition, the same NHANES data set refuted the idea of increased sedentary behaviour in the population by demonstrating that leisure time physical activity increased 47% in males and 120% in females between 1988 and 2006. Another series of studies demonstrated that exercise is consistently linked with increased fat mass in the long term.^{12,13} Thus, the energy imbalance model of calories consumed vs calories expended is not sufficient to explain the uphill trend in obesity; other causes and risk factors should be considered. This has recently been recognized by representatives of the World Obesity Federation, World Economic Forum, the World Health Organization and several leading universities who wrote, "The established narrative on obesity relies on a simplistic causal model with language that generally places blame on individuals who bear sole responsibility for their obesity. This approach disregards the complex interplay between factors not within individuals' control (eg, epigenetic, biological, psychosocial) and powerful wider environmental factors and activity by industry (eg, food availability and price, the built environment, manufacturers' marketing, policies, culture) that underpin obesity."¹⁴ We could not agree more.

3 | OBESITY LACKS A SINGLE CAUSE

Generally speaking, adult body-weight is stable over time and normal physiological mechanisms balance metabolic control with hedonic inputs from the nervous system.¹⁵ Thus, the brain can sense environmental cues, process metabolic inputs from multiple tissues and integrate these disparate data

to manage body-weight. In the typical situation, a temporary weight loss from illness or weight gain from holiday eating or the first year of university 10-15-pound weight gain is compensated and a "normal" weight is regained when these disturbances are remediated. This has led to the proposal that there is a type of "body weight set point."¹⁵ While this is not an immutable set point such as body temperature, it makes sense that body-weight is managed around such a set point. One factor that argues strongly in favour of such a set point is the observation that obesity is rarely reversible once established. More than 83% of obese individuals who lost substantial amounts of weight through rigorous adherence to a regimen of dietary restriction and exercise gained it back within a few years.^{6,7,16} In the absence of a body-weight set point that these people had to fight (and failed), it is difficult to understand why such a small fraction of people who successfully remodelled their bodies could maintain this new normal. How and when might such a set point be established?

4 | THE DEVELOPMENTAL NATURE OF OBESITY

A number of factors can play into the obesity equation, including diet,¹⁷ genetics,^{18,19} smoking during pregnancy,^{20,21} stress,^{22,23} the microbiome²⁴⁻²⁶ and timing of meal consumption.^{27,28} However, an ever growing body of evidence demonstrates that obesity can be orchestrated before a person is even born. The foetal origins hypothesis, first promulgated by David Barker, proposes that the 9 months in utero has the ability to shape individual health outcomes and future well-being trajectories.^{29,30} Barker showed that infants born small for gestational age (and presumably undernourished as foetuses, in utero) were more likely to become obese adults and suffer unfavourable metabolic and cardiovascular conditions in comparison with infants who were not subjected to a nutritionally poor environment.^{31,32} Barker called this the "thrifty phenotype" and posited that it reflected an imbalance between the nature of the foetal environment and the adult environment; the undernourished foetus adapted itself to a calorie-poor environment but grew up to experience a calorie-sufficient or calorie-rich environment for which it was not prepared.³⁰ This provided a strong link between the prenatal environment and postnatal health outcomes and presumed the existence of "prenatal programming" which became known as the foetal origins model. Since it is also recognized that critical periods in development are not restricted to the in utero period, Gluckman and Hanson proposed the "Developmental Origins of Health and Disease" or DOHaD paradigm to reflect this fact.³³⁻³⁵

A key tenet of the DOHaD and foetal origins models is that foetal and early life programming set the parameters of "normal" adult physiological function. Developmental

disturbances can produce adult physiology that is outwardly normal but which has underlying functional deficits that can increase susceptibility to disease. An extensive set of studies in animals and humans have borne out a connection between poor prenatal nutrition and increased risk of diseases such as obesity throughout the life course and even in subsequent generations.^{29,36} What is currently lacking is an understanding of the molecular details through which such developmental programming occurs. Recent studies have implicated epigenetic mechanisms which will be discussed further below.³⁷⁻³⁹

Economists have expanded on the DOHaD hypothesis, investigating a broader range of fetal shocks and circumstances and have found a wealth of later-life outcomes including test scores, educational attainment, and income, along with health that reflect these exposures. For example, adults with prenatal exposure to maternal fasting during Ramadan were 20% more likely to have mental and learning disabilities compared to adults that were never exposed.⁴⁰ The fact that these effects were observed with a relatively mild fetal shock (episodic periods of fasting) leads one to question how much of an effect other common exposures would produce. The 1918 influenza pandemic was a more severe prenatal stressor, and one-third of babies born in early 1919 had mothers who acquired the infection while pregnant.⁴¹ Despite the short time period of exposure to the fetal stressor, the individuals exposed to the influenza in utero were 20% more likely to be disabled and experienced reduced educational attainment.⁴¹ These are but two among many examples of diverse fetal exposures resulting in significant, persistent and unfavorable health outcomes.

To further support the importance of environmental effects on development, the escalating obesity trend in humans is mirrored in animals living in close proximity to humans. These include our pet cats and dogs but also feral rats living in cities and, crucially, rats, mice and primates living in research colonies where caloric intake is strictly controlled.⁴² This puzzling finding highlights just how little is known about the factors influencing fat accumulation and shines a bright light on the potential role of the environment in addition to lifestyle choices as drivers of the obesity pandemic.

5 | ENDOCRINE-DISRUPTING CHEMICALS

The endocrine system plays many important roles in energy balance, fat deposition and fat distribution in the body. Insulin and glucagon produced in the pancreas modulate glucose uptake and usage; ghrelin and cholecystokinin affect metabolism in the gastrointestinal tract; glucagon, insulin and fibroblast growth factor 21 (FGF21) act in the liver to control metabolism, hunger and satiety. The brain itself is an endocrine organ that controls hedonic circuits that modulate food intake via reward mechanisms involving peptide

hormones, neurotransmitters and growth factors as well as regulating metabolism.^{15,43-45} Sex hormones such as estradiol and testosterone can affect food intake, body-weight and fat distribution and can alter the balance of glucose and insulin, lipogenesis and lipolysis, all of which affect energy metabolism and, ultimately obesity [reviewed in⁴⁶].

It is now widely accepted that endocrine-active chemicals in the environment can disrupt hormone function to influence health, particularly by altering developmental programming [reviewed in^{47,48}]. The Endocrine Society defines an endocrine-disrupting chemical (EDC) as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action."⁴⁹ This is distinct from the EPA and WHO definitions which add the rather vague requirement that such effects must also be "adverse." Endocrinologists and endocrine scientists recognize disruption of hormonal signalling as adverse, per se.⁴⁹ A general feature of endocrine signalling systems is that the endogenous hormones function at quite low levels (nano- to picomolar); therefore, molecules capable of disrupting them are expected to act at similar doses and not to exhibit threshold effects because endocrine signalling systems are typically already active.⁵⁰

6 | THE OBESOGEN HYPOTHESIS

In 2006, Blumberg and Grün proposed the existence of chemicals, including EDCs, that could influence adipogenesis and obesity and be important, yet unsuspected players in the obesity pandemic. These "obesogens" can be defined by their function as chemicals that promote obesity in humans or animals.⁵¹ The obesogen hypothesis extended the DOHaD paradigm for obesity by proposing that obesogens could act during development to predispose the exposed individual to obesity in adolescence or adulthood. In principle, obesogens can act directly on cells to increase the commitment or differentiation of adipocytes from stem cells or pre-adipocytes, thereby altering adipocyte number. They can also act by inducing adipocytes to increase triglyceride storage and/or by altering adipocyte homeostasis. The average adipocyte lives for 10 years⁵²; therefore, altering the rate of adipocyte birth or death can influence the total number. Obesogens can also act indirectly to increase fat mass by changing basal metabolic rate, by modulating food intake via effects on the brain, pancreas, adipose tissue, liver, gastrointestinal tract, brain and muscle, by shifting energy balance to favour calorie storage, and by altering the composition of the microbiome [reviewed in^{46,53,54}]. Recent studies have established that obesogens can alter metabolic "set points" leading to obesity later in life, particularly when dietary composition or caloric intake is changed.^{55,56} Obesogens do not necessarily induce obesity alone, but they can alter developmental programming, affecting nuclear factors or other endocrine pathways

during development in ways that lead to obesity later in life. It is important to note that not all EDCs are obesogens and not all obesogens are EDCs; there are dietary obesogens such as refined sugars that may not meet the strict definition of an EDC, but which are definitely obesogens. A list of known obesogens and putative mechanisms of action is provided in Table 1.

7 | MECHANISMS OF OBESOGEN ACTION

An important outstanding question is the extent to which exposure to obesogens contributes to the obesity pandemic in humans. To address this important question, one must examine the data that support or refute the obesogen hypothesis and the extent to which these data are consistent with the importance of environmental obesogens in the aetiology of obesity. Moreover, it is critical to have extensive data from longitudinal epidemiological studies in humans, together with accurate and repeated measurements of obesogen levels at least throughout pregnancy (which are largely absent from the literature at the moment). Numerous reviews have been written on this topic based on data from human and animal studies.^{46,53,54,57,58} EDCs have been linked to obesity, and obesogens have been detected in humans^{63,64} and animals.^{68,69} It is important to note that no systematic effort has yet been undertaken to determine the number of potential obesogens that are present in the tens of thousands of chemicals in widespread use. These chemicals are pervasive in the environment; therefore, it is crucial to understand which of them might be obesogens, how they disrupt developmental programming, predisposing individuals to obesity and related disorders. At this writing, about 50 chemicals have been identified that can act as obesogens, *in vivo*.⁴⁶ Unfortunately, we currently know very little about the molecular mechanisms through which most obesogens act but some examples of known obesogens follow together with the mechanisms through which some of them act.

8 | OBESOGENS REPROGRAM STEM CELL FATE

One of the first *bona fide*, *in vivo* obesogens to be identified was the antifouling agent, tributyltin (TBT). Organotin compounds are widely used in industry, and the related chemical, triphenyltin (TPT), is used in agriculture, primarily as a miticide. Although there are no biomonitoring efforts to monitor organotin exposure in humans, exposure likely occurs through dietary sources such as seafood and shellfish contaminated by TBT used in marine shipping applications or as fungicides for paper mills and industrial water systems. TPT use as a

fungicide on high value food crops presents more opportunities for human exposure. TBT is present in vinyl plastics as a contaminant (non-intentionally added substance) of the heat stabilizer dibutyltin (DBT) and has been found at appreciable levels in house dust in the United States.^{72,73} TBT binds directly to the “master regulator” of adipogenesis, peroxisome proliferator-activated receptor gamma (PPAR γ) and its heterodimeric partner, 9-cis retinoic acid receptor (RXR) at nanomolar (parts per billion) levels.^{70,74,75} Several studies have shown that pre-adipocytes as well as mouse and human multipotent mesenchymal stromal cells (aka mesenchymal stem cells, MSCs) can be induced to differentiate into adipocytes by organotins such as TBT and TPT^{70,75} as well as the highly prevalent DBT.^{76,77} These results are largely dependent on the ability of these chemicals to activate PPAR γ .^{78,79} Adult mice exposed to TBT *in utero* displayed increased lipid accumulation in adipose depots, livers and testis^{70,81} and treatment of adolescent or adult mice, rats, goldfish and zebrafish led to increased fat deposition and hepatic steatosis.^{82,83} Very few epidemiological studies of TBT levels exist, yet TBT continues to be found in house dust⁷³ and in seafood,⁸⁶ and at least one study shows increased ponderal index in human infants with the highest prenatal TBT exposure.⁸⁷

Several other chemicals have been identified as obesogens, *in vivo*. These include the fungicides triflumizole,⁷⁹ tolylfluanid⁸⁸ and the plasticizer diethylhexyl phthalate.⁸⁹ Tolylfluanid was shown to act via the glucocorticoid receptor⁸⁸ whereas triflumizole acts through PPAR γ .⁷⁹ Which receptor diethylhexyl phthalate acts through is unknown but the action may be via its metabolite monoethylhexylphthalate on PPAR γ .

A variety of other potential obesogens have been identified that are known to act on pre-adipocytes or MSCs to promote adipogenic differentiation.^{90,91} It was recently shown that TBT and other chemicals that activate RXR commit MSCs to the adipose lineage by activating RXR, but not PPAR γ . TBT and pharmacological RXR agonists derepress genes important for adipogenic commitment by decreasing deposition of the repressive chromatin mark, histone 3 lysine 27 trimethyl (H3K27^{me3}) in the promoters and regulatory regions of these genes, leading to increased expression of their mRNAs.⁹² Therefore, it is likely that other RXR activators (these are collectively called “rexinoids”) such as the fungicide fludioxonil or the surfactant SPAN-80 will produce similar effects. Intriguingly, a variety of other fungicides with widely divergent structures, including flusilazole, zoxamide and quinoxifen, are candidate obesogens, *in vitro*.⁹⁰ Other agrochemicals such as tebuirimfos, forchlorfenuron, acetamiprid and pymetrozine induce 3T3-L1 pre-adipocytes to differentiate into adipocytes in culture by mechanisms other than activating PPAR γ .⁹⁰ Flame retardants, phthalates, plasticizers, parabens, alkylphenols and bisphenols can all differentiate 3T3-L1 cells to adipocytes *in vitro* [reviewed in⁴⁶].

Which of these candidate obesogens lead to increased fat accumulation in vivo remains unknown. However, the next chemical shown to induce the differentiation of fat cells, in vitro, that does not cause fat accumulation in vivo, will be the first.

9 | OBESOGEN EXPOSURE CAN PRODUCE UNHEALTHY ADIPOCYTES

Considering how many chemicals increase the commitment or differentiation of adipocytes, it is reasonable to ask whether the adipocytes produced are normal and fully functional.⁹³ Such studies were prompted by the studies of Sargis and colleagues who investigated the effects of TBT vs the pharmaceutical PPAR γ activator, troglitazone on the differentiation and function of 3T3-L1 pre-adipocytes, in vitro.⁹⁴ TBT-induced adipocytes produced lower levels of adiponectin and CEBP α mRNA and protein than did troglitazone-induced adipocytes. The TBT-induced adipocytes displayed reduced GLUT4 expression but normal glucose uptake and they inferred that TBT had produced “unhealthy” adipocytes.⁹⁴ White adipocytes play an important role in metabolic health by removing glucose from the circulation when stimulated by insulin.⁹⁵ White adipose tissue (WAT) also releases important adipokines such as adiponectin.⁹⁶ Adiponectin expression is inversely correlated with risk of type 2 diabetes largely by suppressing gluconeogenesis and stimulating β -oxidation of fatty acids in the liver.⁹⁷ Pharmaceutical PPAR γ activators are thought to promote the development of “healthy” adipocytes which are characterized by their production of healthy adipokines such as adiponectin, their sensitivity to glucose, their anti-inflammatory and non-fibrotic local microenvironment and by being normoxic and not hypertrophic.^{98,99}

Shoucri and colleagues confirmed and extended these results to a stem cell model and addressed the mechanistic underpinnings of the obesogenic phenotype. They treated differentiating MSCs with the PPAR γ activator rosiglitazone (ROSI), the RXR activator IRX4204 or the dual RXR/PPAR γ agonist TBT and investigated the transcriptome and function of the adipocytes produced in this way. They showed that TBT- and 4204-treated cells accumulated essentially the same amount of fat as did ROSI-treated cells but that TBT- and 4204-induced adipocytes differed in a number of ways from ROSI-induced adipocytes.⁹³ TBT- or 4204-induced adipocytes expressed reduced levels of GLUT4 accompanied by lower glucose uptake. They produced lower levels of adiponectin mRNA and protein and showed elevated levels of molecular markers of inflammation and fibrosis.⁹³ The TBT- or 4204-treated cells were impaired in their respiratory function, measured in vitro and, as might be expected,

contained fewer mitochondria.⁹³ Intriguingly, the TBT- or rexinoid-induced adipocytes were less able to produce thermogenic beige/brite fat. Taken together, these data show that while ROSI-, TBT- or rexinoid-differentiated adipocytes all accumulated fat to similar levels, in vitro, the TBT- or rexinoid-differentiated cells did not respond to normal signalling processes. This may be highly relevant to the observations that animals treated with these chemicals accumulate excess fat. To what extent other environmental obesogens produce normal or dysfunctional WAT and the mechanisms through which they accomplish this is an open and exciting question to address in the future.

10 | OBESOGENS EXPOSURE CAN IMPAIR THERMOGENESIS

An important recent advance in understanding adipocyte function was the discovery that thermogenic brown adipose tissue (BAT) is found in adult human beings, albeit dispersed, rather than concentrated in discrete depots as in human infants.¹⁰⁰ Another key discovery was that white adipose tissue (WAT) can be induced to produce thermogenic fat, which has been termed beige or brite fat.^{101,102} Both the differentiation of *bona fide* brown adipocytes and the beiging of white adipocytes are characterized by the increased production of mitochondria. Thermogenesis relies on the presence of Uncoupling Protein 1 (UCP1) which uncouples cellular respiration from ATP synthesis to generate heat instead of ATP. There is some recent evidence that at least a few obesogens exert some of their functions by impeding the production or function of thermogenic adipocytes. La Merrill and colleagues showed that perinatal exposure to the insecticide dichlorodiphenyltrichloroethane (DDT) produces an interesting phenotype: adult female animals are intolerant to cold and have reduced core temperature accompanied by lower energy expenditure.¹⁰³ The authors ascribed much of this reduced BAT function to diminished expression of peroxisome proliferator-activated receptor γ coactivator 1 α (Ppargc1 α or PGC-1 α) and iodothyronine deiodinase 2 (Dio2, which converts thyroxine, T4, to the more thermogenic triiodothyronine, T3). Secondly, as noted above, Shoucri and colleagues recently found that production of beige/brite fat cells from MSCs was inhibited by TBT or rexinoids.⁹³ These examples indicate that obesogens can influence obesity by impairing thermogenesis, in vitro and in vivo. This is an intriguing area for future study. The European Union has recently funded several large grants through their Horizon 2020 programme that aim to develop sensitive new assays to assess the effects of EDCs on metabolic end-points. Among these are assays that will identify chemicals that affect thermogenesis which may allow the identification of more such chemicals.

11 | CAN OBESOGENS MODULATE METABOLIC SET POINTS?

Despite abundant evidence from animal models showing that obesogen exposure can elicit increased fat depot weight, adipocyte size and number, the human situation will undoubtedly be more complex. Humans have a number of contributing factors to obesity such as diet composition and caloric input, composition of the gut microbiome, circadian rhythms, type and amount of exercise, environmental stressors such as air pollution, noise and light pollution and some input from genetics. Moreover, these multiple influences interact with each other and with confounding factors such as prescription drugs, dietary supplements and individual variation. The common human lament of weight being easy to gain yet hard to lose, together with abundant evidence showing that sustained weight loss in obese individuals is rare, and that adding exercise to one's lifestyle without modifying caloric input results in increased body fat all support the existence of some sort of body-weight set point. In this view, the combination of physical activity and caloric intake is a key factor in weight control and the effects of obesogen exposure are superimposed onto these other factors. That is, obesogen exposure alone may be insufficient to produce obesity, interactions with other factors such as diet may be critical.

Research in multiple laboratories has supported the existence of a body-weight setpoint that can be altered by obesogen exposure. Perinatal exposure to the oestrogen, diethylstilbestrol led to weight gain at adulthood despite no detectable increase in food intake.¹⁰⁴ Prenatal nicotine exposure in rats produced adults that required less high-fat food to gain weight.¹⁰⁵ Exposure of F0 female mice to TBT throughout pregnancy and lactation led to males of the unexposed F4 generation gaining weight very rapidly when dietary fat was increased; they retained much of this extra fat even after their chow was returned to the previous low-fat diet.⁵⁵ The animals also overexpressed leptin, and the authors inferred they were leptin-resistant.⁵⁵ A very important recent study in humans showed that caloric restriction in a clinical setting led to weight loss, irrespective of the type of diet but that individuals regained weight at different rates when dieting was ceased.⁵⁶ Intriguingly, those individuals who regained weight the most quickly had lower resting metabolic rates than those who regained weight more slowly and the rapid weight gainers had the highest levels of perfluoroalkyl chemicals in their blood.⁵⁶ This provided the first link between metabolic rate in humans and chemical contaminants in blood. Resting metabolic rate is the biggest consumer of calories in human physiology; therefore, small alterations in this rate can have large consequences on body-weight. In sum, these data

support the concept of a metabolic set point that might be malleable by exposure to chemical obesogens.

12 | THE EFFECTS OF EDCS AND OBESOGENS CAN BE HERITABLE

One of the most startling results in the EDC field came in 2005 when Michael Skinner and colleagues showed that prenatal exposure to the anti-androgenic fungicide vinclozolin, or the oestrogenic pesticide methoxychlor led to disease in various organs in the F4 generation.¹⁰⁶ More recently, when pregnant mice were treated with environmentally relevant (nM) doses of TBT via their drinking water, effects were detected in the F1-F3 descendants of F0 mice exposed during pregnancy⁸¹ or the F1-F4 descendants of animals treated during pregnancy and lactation.⁵⁵ Notably, unlike TBT, the pharmacological obesogen, ROSI which activates PPAR γ , could not produce such transgenerational effects on obesity, suggesting that despite its action through PPAR γ in cell culture, additional or different targets of TBT were required to generate transgenerational effects.^{55,81} TBT exposure led to a transgenerational "thrifty phenotype" in F4 male (but not female) mice. This thrifty phenotype was manifested as males being resistant to fat loss during fasting and showing an increased propensity to gain weight when dietary fat was increased. Since this phenotype was not observed until diet challenge, it is clear that it does not result from the trivial explanation of fat animals producing fat offspring. The authors inferred that the thrifty phenotype was associated with changes in chromatin structure that led to subsequent alterations in DNA methylation and overexpression of leptin and important metabolic genes in white adipose tissue (WAT).⁵⁵ In addition to these effects of TBT on obesity, Skinner and colleagues have shown that plastic components BPA, diethylhexyl and dibutyl phthalates,¹⁰⁷ the pesticide methoxychlor,¹⁰⁸ a mixed hydrocarbon mixture (jet fuel JP-8)¹⁰⁹ and the pesticide, DDT,¹¹⁰ can all cause transgenerational obesity in the rat model.

It is currently controversial which molecular mechanisms underlie transgenerational inheritance of any trait, including obesity. While most investigators in the EDC field believe that these effects are transmitted in an epigenetic manner, this idea has met with strong resistance in the genetics community.¹¹¹ However, it is clear that the normal development of mammalian germline cells depends on hormonally regulated functions of somatic cells supporting their survival and differentiation; thus, it is reasonable to hypothesize that EDCs could affect epigenetic reprogramming of germline cells. Perhaps the strongest argument raised against the transmission of epigenetic marks such as DNA methylation is that genome-wide epigenetic reprogramming in mammalian germline cells should erase epimutations from the preceding

TABLE 1 List of known obesogens and potential obesogens with selected end-points and references. The reader should also consult references in previous review articles ^{46,121}

Major use category	Chemical	In vitro	In vivo	Human	End-points	Reference
Plastics	BADGE	+			Induce adipogenic differentiation in MSC's and in pre-adipocytes	122
	MEHP	+	+		Increased adipogenesis, stimulates 3T3-L1 cells, increased lipid accumulation	63,64,123
	DEHP	+	+		Increased adipocytes, lipid accumulation	63,64,89,123,124
	BBP	+			Increased LA in 3T3-L1 cells	123,125
	BPA	+	+	+	Increased obesity in adults; increased LA in 3T3-L1 cells	Reviewed in ¹²⁶
Flame retardant	Hexabromocyclododecane		+		Impaired Lipid and Glucose Homeostasis	127
	BDE-47	+	+	+	Disruption of glucose homeostasis; up-regulation of denovo lipogenesis genes	128,129
	TBBPA	+	+		Increased lipid accumulation and adipocyte number	131,132
	Triphenyl Phosphate	+	+		Lipid accumulation; increased body-weight and fat mass in mice	134,135
	FM-550	+	+		Lipid accumulation; weight gain	134,135,137,138
	Chlorpyrifos		+		Weight gain and hyperinsulinemia in rats	141,142
	Quinoxifen	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
Pesticide	Forchlorfenuron	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
	Flusilazole	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
	Fludioxonil	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells and MSCs	90
	Acetamiprid	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
	Tebupirimifos	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
	Triflumizole	+	+		Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells, MSCs and in mice	79,90
	Spirodiclofen	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
	Pymetrozine	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	90
	DDE	+	+	+	Adipogenesis in 3T3-L1 cells, increased weight gain in vivo	143,144
	DDT	+	+	*	Adipogenesis in 3T3-L1 cells, increased weight gain, in vivo, transgenerational obesity	110,143,144
	Diazinon	+			Induces adipogenesis in 3T3-L1 cells	reviewed in ¹⁴⁷
	Halosulfuron-methyl	+			Induces adipogenesis in human adipose—derived stromal cells	148
	Diclofop-methyl	+			Induces adipogenesis in human adipose—derived stromal cells	91
Zoxamide	+			Induces adipogenesis in 3T3-L1 cells	91	
Fentin hydroxide	+			Stimulates 3T3-L1 adipogenesis, lipid accumulation	90	
Lactofen	+			Induces adipogenesis in human adipose—derived stromal cells	73,91	
Tolyfluanid	+	+		Induce adipogenesis in 3T3-L1 cells, increases fat mass in mice	91	
					88,149	

(Continues)

TABLE 1 (Continued)

Major use category	Chemical	In vitro	In vivo	Human	End-points	Reference
Drugs	Rosiglitazone, pioglitazone	+	+	+	Induces adipogenesis in 3T3-L1 pre-adipocytes, MSCs, rodents and humans	Reviewed in ⁴⁶ 150,151
	Indomethacin	+			Increased adipogenesis in C3H10T1/2 cells, MSCs, rodents and humans	152
	Triamcinolone				Induces adipogenesis in human adipose—derived stromal cells	152
	Dexamethasone	+			Induces adipogenesis in human adipose—derived stromal cells	152
	Corticosterone	+			Induces adipogenesis in human adipose—derived stromal cells	152
	Prednisone	+			Induces adipogenesis in human adipose—derived stromal cells	152
	Melengestrol acetate	+			Induces adipogenesis in human adipose—derived stromal cells	104,153
	Diethylstilbestrol	+	+		Increased fat mass in mice and rats	105,154
	Nicotine		+	+	Increased body-weight; reduced leptin; impaired glucose homeostasis	155,156
	Cadmium		+	+	Increased BMI in humans, increased lipid accumulation in zebrafish	155,157
Metals	Lead		+	+	Increased BMI in humans, increased adiposity in rats	158
	Mercury			+	Increased BMI in humans	
Food/packaging	Acrylamide	+	+		Increased lipid accumulation in 3T3-L1 cells, increased fat mass in mice	159
	Fructose	+	+	+	Induces adipogenesis in 3T3-L1 cells, Increased body-weight in humans and animals	160 reviewed in 161
	Perfluoroalkyl substances	+	+	+	Induces/potentiates adipogenesis in 3T3-L1, increased adiposity in rodents and humans	71,162,163
	Monosodium glutamate		+	+	Increased obesity in rodents	166,167
Personal care products	Alkylphenols	+	+	+	Increased adipogenesis in 3T3-L1 cells, increased fat depot size in rodents, found in obese patients	123,168,169
	Parabens		+	+	Increased adipogenesis in 3T3-L1 cells	168,170,171
	Dibutyltin (DBT)	+	+		Increased adipogenesis in 3T3-L1 cells and MSCs, obesity in mice	76,77
organotins	Tributyltin (TBT)	+	+		Increased adipogenesis in 3T3-L1 cells and MSCs, transgenerational obesity in mice	55,70,75,80,81
	Triphenyltin, fentin (TPT)	+	+		Lipid accumulation	75,91,173
Persistent organic pollutants	Alpha naphthoflavone	+			Increases lipid accumulation in mature adipocytes	174
	Tetrachlorodibenzodioxin (TCDD)		+	+	Increased adipogenesis in 3T3-L1 cells; diabetes in adults	175
	Polychlorinated biphenyls PCB-77, PCB-138, PCB-180		+	+	Increase in body mass	176,177
Surfactant/emulsifiers	Diethyl sodium sulfosuccinate (DOSS)	+			Increased adipogenesis in 3T3-L1 cells	179
	SPAN-80	+			Increased adipogenesis in 3T3-L1 cells	180
	Alkylphenol ethoxylates	+			Increased adipogenesis in 3T3-L1 cells	181

generation.^{111,112} Some investigators report stable transgenerational changes in DNA methylation^{110,114,115}; others found that the same chemicals induced epimutations and alterations in gene expression in the F1 generation, but that these were not conserved in F2 prospermatogonia.¹¹⁶ Other factors such as histone retention and small non-coding RNA inheritance have been invoked as being involved in transgenerational inheritance,¹¹⁷ but the mechanisms underlying the transfer of these factors across generations remain elusive. One possible model comes from the work of Chamorro-García and colleagues who proposed that changes in chromatin accessibility and large scale organization are transmitted across generations. In their model, altered accessibility of the chromatin to DNA and histone modifying enzymes can lead to secondary changes in DNA and/or histone methylation that can ultimately result in differential gene expression.⁵⁵ It remains to be seen just what changes in chromatin structure can be transmitted across generations and whether different chemical obesogens produce overlapping changes in chromatin structure.

13 | FUTURE DIRECTIONS

Obesity adds at least \$200 billion to US healthcare costs annually,⁸ and the number of obese individuals continues to increase.⁴ Thus, studies aimed at discovering the many mechanisms underlying the predisposition to obesity and related disorders are timely and important. Recent estimates of the impact of three obesogens on the cost of obesity to the EU inferred an annual cost of €18 billion.¹⁰ A similar study was performed for the US population and estimated an annual cost of \$5.9 billion.⁹ These are likely to be gross underestimates since they only considered exposure to 3 obesogens. The number was limited to 3 because the number of prospective cohorts with suitable measurements of chemical levels to infer exposure was quite limited. Thus, we need appropriate studies to estimate the cost of the other ~50 known obesogens to world society and to what degree obesogen exposure influences obesity in humans. There are important knowledge gaps regarding the effects of multiple simultaneous or serial obesogen exposures as well as the interactions between obesogen exposure and established risk factors in obesity. Such factors include inflammation, disrupted circadian rhythms, oxidative stress, mitochondrial dysfunction, dietary composition, timing of eating and the regulation of appetite and satiety. These interactions could be critical in understanding the effects of obesogens on humans. We know very little about how to determine who has been exposed to obesogens during their development, or in their ancestry. Identifying biomarkers of exposure is a “Holy Grail” of obesogen research and will allow the establishment of strong links between obesogen exposure, other risk factors and the eventual development of

obesity and related disorders. Effects of obesogen and EDC exposure are at least in part epigenetic, yet we know relatively little about the underlying mechanisms and how the effects are transmitted across the generations. For example, how does exposure of pregnant F0 female mice lead to obesity in unexposed F3 and F4 males?⁵⁵ Is there a causal link between perfluoroalkyl chemicals and reduced resting metabolic rate?⁵⁶ Which molecular targets mediate the effects of obesogens on metabolic programming in vivo? Relatively little is known about the extent to which obesogen exposure programs dysfunctional adipose tissue that may readily store, but not mobilize fat. There is an extreme paucity of data on the effects of multiple or continuing exposures over the life course and across generations.

The obesogen field is only about 15 years old. Much has been learned about the potential effects of EDCs and obesogens in obesity. Perhaps the strongest evidence for the existence of chemical obesogens are the observations that a variety of pharmaceuticals have the side effects of making patients fat [reviewed in^{46,118}]. Drugs are nothing more than chemicals that have been tested and validated to be effective against a particular condition; it is obvious that chemicals targeting the same molecular pathways should elicit similar effects. Several international workshops have been held to discuss the potential role of EDCs in obesity and metabolic disease.^{10,46,119,120} There is wide agreement that obesogens exist and have the potential to influence obesity in humans. Thus, it would be prudent to consider policies and strategies aimed at reducing obesogen exposure in the population in addition to other preventive factors.

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CONFLICT OF INTEREST

BB is a named inventor on US patents related to PPAR γ and other nuclear receptors, some of which have been licensed to for profit entities. None of these present any conflict on interest. MKL has no conflicts to declare.

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