Endocrine disruptors and obesity

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Abstract | The increasing incidence of obesity is a serious global public health challenge. Although the obesity epidemic is largely fueled by poor nutrition and lack of exercise, certain chemicals have been shown to potentially have a role in its aetiology. A substantial body of evidence suggests that a subclass of endocrine-disrupting chemicals (EDCs), which interfere with endocrine signalling, can disrupt hormonally regulated metabolic processes, especially if exposure occurs during early development. These chemicals, so-called 'obesogens' might predispose some individuals to gain weight despite their efforts to limit caloric intake and increase levels of physical activity. This Review discusses the role of EDCs in the obesity epidemic, the latest research on the obesogen concept, epidemiological and experimental findings on obesogens, and their modes of action. The research reviewed here provides knowledge that health scientists can use to inform their research and decision-making processes.

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Introduction

The prevalence of obesity in humans is increasing in both developed and developing countries.[1] Obesity is rapidly becoming a worldwide public health problem despite food shortages in many parts of the world. In 2010, the World Health Organization estimated that >700 million people worldwide have obesity and ~2 billion people are overweight.[2] The prevalence of childhood obesity is also increasing and is a strong risk factor for adult obesity.[3] Furthermore, an overwhelming majority of individuals with obesity have multiple comorbidities that result in poor health. Some of these comorbidities include type 2 diabetes mellitus, gall bladder disease, sleep apnoea, high blood pressure, insulin resistance, inflammation, breathlessness, the metabolic syndrome, nonalcoholic fatty liver disease and gestational diabetes mellitus.[2,4] Individuals with obesity also have an increased risk of coronary heart disease and stroke, osteoarthritis and gout, impaired fertility, cancers, cataracts and back problems.[5] Obesity is, thus, an issue of considerable concern, and the prevention of childhood obesity is an essential step in controlling the development of the disease.

The endocrine system controls body growth, weight and metabolic processes by producing hormones and growth factors that function through a series of tightly integrated signalling pathways. Hormones regulate signalling pathways in the gastrointestinal system, pancreas, muscle, liver, adipose tissue, immune system and brain, which, in turn, regulate the number and content of fat cells, as well as appetite and satiety.[6–10] Adipose tissue functions as an endocrine organ that produces and responds to hormones and adipokines. As hormones regulate the physiology of these systems, their action can be disrupted by chemicals in the environment that mimic or block normal endocrine functions. This Review focuses on developmental exposures to endocrine-disrupting chemicals (EDCs) and their subsequent effects on weight gain. We emphasize long-term weight gain, not *in utero* exposures that result in low birth weight, as this factor is associated with compensatory growth (as stated by the Barker hypothesis[11]).

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EDCs and obesogens

As obesity is a multifactorial and complex endocrine disease, its aetiology involves interactions between genes and the environment. Poor nutrition and lack of exercise are important factors in the burgeoning obesity epidemic, but other factors evidently have important roles,[12] including the built environment, stress, air pollution, and first and secondhand exposure to cigarette smoke.[13] Interestingly, the current increase in obesity and other metabolic diseases correlates with substantial increases in environmental chemical production and exposures over the past few decades.[14,15] EDCs are exogenous chemicals capable of mimicking or blocking the action of hormones by binding to or interfering with their receptors. This interference disrupts signalling processes throughout the body, which can lead to a variety of diseases of the endocrine system.[13,16] EDCs can also function indirectly by disrupting hormone levels or by altering hormonal transport mechanisms.

A subclass of EDCs have been identified that can disrupt sensitive metabolic processes if exposure occurs during early development, which leads to obesity, type 2 diabetes mellitus and the metabolic syndrome.[13] These chemicals, so-called 'obesogens', are thought to predispose individuals to weight gain owing to changes in metabolic 'set-points', particularly if exposure occurs during sensitive periods of early life.[17–19] For example,

Key points

- Obesity is an increasing global public health problem
- Obesity is a disease of the endocrine system, which involves many tissues and metabolic processes
- The rapid growth of the obesity epidemic over the past few decades suggests that environmental factors might have a role in the aetiology of the disease
- Obesity probably has its origins during development, when susceptibility to weight gain and alterations in metabolism develop
- Obesogens are a subclass of endocrine-disrupting chemicals (EDCs) that might predispose individuals to the development of obesity
- The obesogen hypothesis provides a means for the prevention of obesity by reducing exposure to EDCs during early development

the pharmaceutical diethylstilbestrol is a model EDC that causes obesity in animals when, even low-level, exposure occurs during sensitive periods of development.[20] Some EDCs function by increasing the number of adipocytes and/or the storage of fat in existing adipocytes.[21] EDCs can also indirectly promote obesity by shifting the energy balance in favour of fat storage in adipocytes and by altering the body's basal metabolic rate.[21]

Developmental origins of health and disease

A growing body of research has shown that many adult diseases might originate during fetal and early childhood development. This concept—the developmental origins of health and disease (DOHaD)—proposes that early life exposures to environmental chemicals or poor nutrition can alter developmental pathways in ways that lead to diseases and/or dysfunctions later in life.[22] These early-life periods are particularly vulnerable to environmental chemicals as a consequence of incomplete development or partial functioning of protective mechanisms, such as DNA repair, immunity, xenobiotic metabolism and the blood–brain barrier, in the fetus or neonate. In addition, the developmental period is a 'plastic' phase that is sensitive to altered programming of cell and tissue differentiation by environmental stressors, and which can cause changes in gene expression and protein levels due to alterations in the levels or actions of hormones and growth factors. For example, small changes in nutrient availability at critical time points can result in cascading effects on adipose tissue development and metabolic programming during early periods of growth.[11] Importantly, in epidemiological and animal studies, maternal, paternal and *in utero* nutritional factors have been shown to have important roles in determining birth weight and susceptibility to long-term obesity.[23,24]

The concept of disruption of developmental programming also includes non-nutritional early-life exposures that have been shown to alter the body's physiology.[22] Prenatal exposure to chemicals in the environment can modify normal cellular and tissue development and function, even at the level of stem cell development. For instance, *in utero* exposures to certain obesogens have been shown to cause multipotent stem cells to prematurely differentiate into lipid-filled mature adipocytes.[25] The DOHaD concept, therefore, provides a framework to assess the effects of obesogenic chemicals on long-term health and provides a common mechanism for chemical and nutritional stressors that ultimately leads to obesity.[22]

Obesogen action during development

Almost 90% of individuals who lose a considerable amount of weight regain that weight within 1 year.[26] An improved understanding of the physiological factors that dictate metabolic 'set points' and the propensity for retaining weight is, therefore, critical. One aspect to consider is that the endocrine system, which controls eating behaviour, is extremely sensitive to perturbation by EDCs. Early in life, EDCs can affect fetal adipose tissue by increasing the number and size of adipocytes.[21] Fat cells are generated from mesenchymal stem cells, which are also capable of differentiating into bone cells, cartilage cells and cells of other tissues.[27] Obesogenic chemicals can artificially direct mesenchymal stem cells to differentiate into adipocytes, and promote the accumulation of triglycerides in mature adipocytes (Figure 1).[21] These effects can lead to alterations in the 'set point' for gaining weight and thus contribute both to weight gain and the problems associated with weight loss.

EDCs can also cause changes in the hypothalamus—the region of the brain that has a particularly important role in eating behaviour.[13] Disruptions in hypothalamic programming might result in altered metabolic 'set points' in adolescents and adult individuals. These adjustments might manifest and explain differences between the eating behaviour of lean individuals and those with obesity. Exposure to EDCs can also alter the organization and function of dopaminergic pathways throughout the developing brain, which results in lifelong behavioural effects.[28] For example, early-life exposure to bisphenol A has been shown to alter both presynaptic and postsynaptic dopamine activity in brain regions associated with addictive and impulsive behaviour.[29] Thus, obsessive eating patterns observed in adult individuals with obesity might be, in part, due to chemically-induced alterations in neural programming early in life.

Epigenetic changes probably have an important role in the mechanism by which obesogens exert their effects. Epigenetic events (that is, DNA methylation and acetylation, ubiquitination or other histone modifications) lead to heritable patterns of gene expression during development and are, therefore, important in the formation of normal tissue and organs.[30–32] As the epigenome cycles through a series of precisely timed events during gamete development, fertilization and fetal development, the system is particularly vulnerable to interference from EDCs.[33] Exposure to environmental stressors during development can lead to epigenetic changes that persist throughout life. Although a causal link between epigenetic changes and increased susceptibility to obesity has not been established, epigenetic modifications along with other programming changes represent a plausible mechanism that links genes, environmental stressors and susceptibility to obesity (Figure 2).[34–36] Some research suggests that changes to our epigenome can be permanent and inherited by subsequent generations.[25,28,37–41]

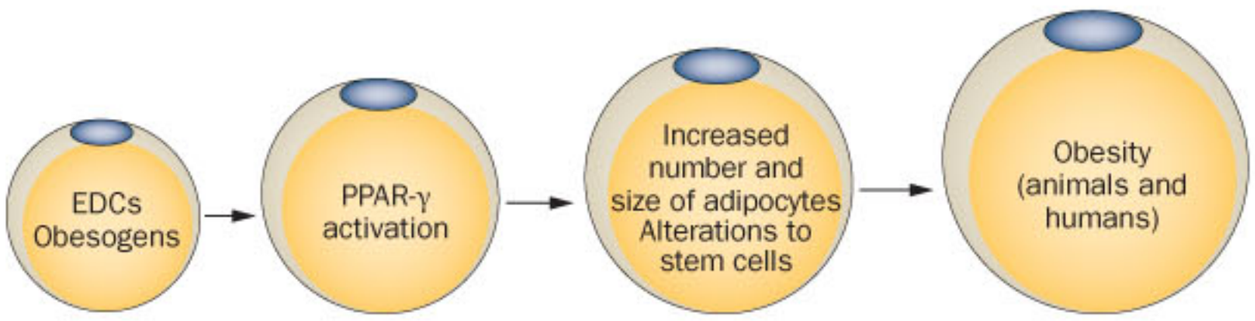

Figure 1 | Potential mechanism by which environmental chemicals cause obesity in animals and in humans. Several EDCs and obesogens such as organotins and the fungicide triflumizole are known to activate PPAR-γ, which leads to weight gain *in vivo* and reprogramming of mesenchymal stem cell fate to favour formation of adipogenic cells at the expense of the osteogenic fate. Triflumizole also functions via PPAR-γ to induce adipogenesis in mesenchymal stem cells and preadipocytes *in vitro* through a PPAR-γ-dependent mechanism and promotes increased white adipose tissue depot size and altered stem cell programming *in vivo*. Abbreviations: EDC, endocrine-disrupting chemical; PPAR-γ, peroxisome proliferator-activated receptor γ.

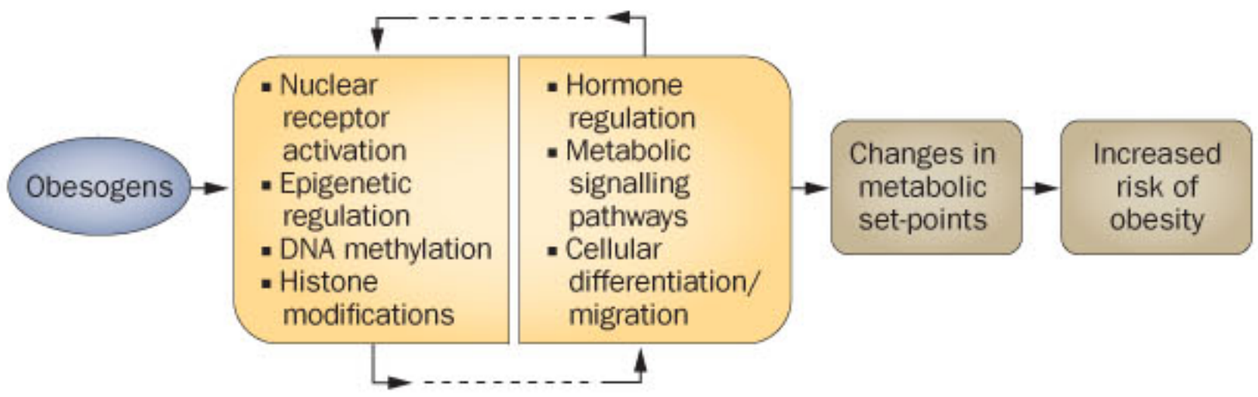

Figure 2 | Potential mechanisms of obesogen action that alter metabolic set-points and increase the risk of obesity. If these programming events occur early in embryonic development, they can lead to persistent changes in hormone signalling. Numerous obesogens have been shown to act through activation of fat-regulating nuclear receptors or other receptors that regulate key metabolic signalling processes. Other obesogens act via unidentified pathways such as those that result in various epigenetic changes, and which can have transgenerational effects on a variety of health endpoints, including obesity in offspring.

Obesogenic chemicals

A variety of prescription drugs have adverse effects that result in weight gain, such as thiazolinediones (anti-diabetic drugs), tricyclic antidepressants, selective 5-hydroxytryptamine uptake inhibitors and atypical antipsychotic drugs,[42–44] which provides a proof-of-principle that chemicals with similar structures and modes of action might have a role in the obesity epidemic. Animal studies indicate that EDCs such as tributyltin, estrogenic chemicals such as bisphenol A, and chemicals acting via other mechanisms such as lead, perfluoroctanoic acid, phthalates, polychlorinated biphenyls, some pesticides, dichlorodiphenyltrichloroethane (DDT) and tobacco smoke, can lead to weight gain later in life (Table 1).[25,37,41,45]

Importantly, weight gain can be a poor proxy for increased fat content as infiltrating adipose tissue can replace bone, muscle or other tissues without a significant gain in weight. Studies that measure the size of fat depots or assess adipocyte number and size more effectively reflect the percentage of fat in an individual than those that just measure weight gain. Exposure to environmental chemicals during development probably increases susceptibility to weight gain; however, the full spectrum of symptoms associated with obesity might not be apparent unless a secondary challenge occurs later in life, such as a high-fat diet or other stressors.

Cigarette smoke

Epidemiological data strongly support a positive and probable causal association between maternal smoking and increased risk of obesity or overweight in offspring. This conclusion is based on the very consistent pattern of overweight and/or obesity observed in children whose mother smoked during pregnancy along with findings of obese offspring from laboratory animals exposed to nicotine during pregnancy.[41] Approximately 20 epidemiological studies have examined the effects of maternal smoking during pregnancy on body weight of offspring during childhood or adulthood. These studies show a consistent association between maternal smoking during pregnancy, low birth weight, and increased risk of overweight and/or obesity in offspring. This literature was evaluated in two meta-analyses which indicated a 50–64% increase in obesity due to smoking during pregnancy.[46,47]

Polycyclic aromatic hydrocarbons and air pollution

Polycyclic aromatic hydrocarbons (PAHs) are a family of environmental chemicals that occur in oil, coal and tar deposits, and are produced as byproducts of fuel burning (both fossil fuel and biomass), including cigarette smoke and diesel exhaust. Benzo(a)pyrene is a PAH that has been shown to inhibit lipolysis and cause increased fat accumulation in adult mice.[48] Air pollution can result in low birth weight and preterm birth, factors that can lead to weight gain later in life.[49,50] For example, in a study of pregnant women who wore personal air monitors during the second trimester, prenatal exposure to PAHs was associated with increased body size of their children at age 5 and 7 years.[51] Additionally, air pollution near roads can contribute to obesity late in life if the exposure occurs during fetal development or childhood.[52,53] Longitudinal epidemiological studies that encompass the prenatal period through to adulthood are needed to determine the lifelong effects of exposure to PAHs.

Animals exposed to diesel exhaust *in utero* and a high-fat diet as an adult showed increased susceptibility to diet-induced weight gain and neuroinflammation later in life.[54] Similarly, early-life exposure to air pollution particulates (particulate matter [PM] 2.5 for 3–10 weeks) in mice led to increased visceral obesity, insulin resistance and inflammation.[55] Also, mice fed a high-fat diet for 10 weeks who were then exposed to PM 2.5 as adults for 24 weeks had increased visceral obesity, insulin resistance and inflammation.[56] These results indicate an interaction between air pollution, diet and metabolic programming, particularly during periods of development. Although these select studies indicate that exposure to various components of air pollution might have a role in susceptibility to obesity, additional research is needed in both animals models and in humans to accurately define the levels of air pollutants that cause obesity.

Table 1 | Environmental chemicals associated with obesogenic properties

Chemical	Source/commercial use	Potential mechanism
Cigarette smoke	First-hand and second-hand smoke	Prenatal nicotine exposure alters neurological development and exposures ↑ rates of preterm and low-weight births[41,46,47]
Air pollution Polycyclic aromatic hydrocarbons	Incomplete combustion of fossil fuels	↑ Accumulation of visceral fat[55] Inflammation[56]
Tributyltin	Fungicide in paints and components of polyvinyl chlorides	Activation of peroxisome proliferator-activated receptor γ[37,58,59] and increased fat cell differentiation[60–63]
Bisphenol A	Plastics and epoxy resins	Estrogenic[82,83] Inhibition of proliferation of neural progenitor cells[86]
Flame retardants	Chemicals applied to furniture and electronics	↑ Rate of adipogenesis[105] ↑ Glucose intolerance[106]
Polychlorinated biphenyls	Coolants, plasticizers and flame retardants	Altered thyroid function[96,101] Altered metabolism[112] Bioaccumulation in fat cells[109]
Phthalates	Plasticizers, adhesives and personal care products	↑ Rate of adipocyte differentiation[117,120–122]
Perfluorooctanoic acid Perfluorooctanoate sulphonate	Components of lubricants, nonstick coatings and stain-resistant compounds	↑ Serum levels of insulin[126] ↑ Serum levels of leptin[126]

Tributyltin

Tributyltin is an organotin that is used as a fungicide and as a heat stabilizer in polyvinyl chloride. This obesogenic chemical has been found in house dust and in human liver and blood, although data on human exposures are limited.[57] Tribuyltin functions as an agonist of retinoic acid X receptor and peroxisome proliferator-activated receptor γ (PPAR-γ) owing to its ability to bind and induce transcriptional activation of these receptors.[37] Several laboratories have shown that tributyltin stimulates adipogenesis in 3T3 L-1 preadipocytes at nanomolar concentrations,[37,58,59] and drives adipogenesis in human and mouse mesenchymal stem cells.[60–62] Mesenchymal stem cells from tributyltin-treated animals have an increased propensity to develop into adipose tissue and a decreased commitment to develop into bone.[63] Prenatal exposure to tributyltin results in increased lipid accumulation in adipose tissue and liver and reduced muscle mass in neonatal mice, effects that persists into adulthood and even into future generations.[64,65] Tributyltin has also been shown to enhance weight gain in mice exposed during puberty and early adulthood.[66]

Bisphenol A

Bisphenol A is a high production chemical that is widely used in polycarbonate plastics, can linings and cash register receipts. The chemical structure of bisphenol A enables it to fit into the binding site of the estrogen receptor, which enables the compound to activate both nuclear and cell membrane-localized estrogen receptors.[67]

Studies in rodents and humans have yielded conflicting results with regard to *in utero* and/or neonatal bisphenol A exposure and increased weight gain in young and adult mice.[68–70] In a systematic review of cross-sectional studies limited associations were found between adult exposure to bisphenol A and obesity.[68,71] Investigators in other studies have reported mixed associations between concurrent bisphenol A exposure (as measured by spot urine samples) and weight gain in children.[72–74] Although not examining weight gain, in one study increased placental levels of bisphenol A were associated with low birth weight;[75] results from another study showed that maternal exposure to bisphenol A correlated with reductions in the birth weight of offspring.[76]

Considerable limitations exist in the epidemiological studies conducted, so far, on bisphenol A exposure and metabolic outcomes. Most of these human studies have been cross-sectional in design, which provide only suggestive results and cannot address the temporality of exposure and disease.[71] The potential exists for misclassifying exposure to chemicals such as bisphenol A, as they do not persist long-term *in vivo*. Owing to the short biological half-life of bisphenol A, urinary concentrations usually reflect exposures over the past 6–12 h. Therefore, a single spot urine sample will not accurately measure long-term or episodic exposure over weeks, months or years.[77] Additional large prospective cohort studies are needed to confirm and validate findings from cross-sectional human studies.

Several animal studies have demonstrated that exposure to bisphenol A can disrupt multiple metabolic pathways and sites of action, which suggests that exposure to environmentally relevant doses of this compound can increase body weight.[78–81] Although many of these effects are thought to be mediated through estrogen receptors,[82,83] evidence also suggests that bisphenol A and its derivatives act as obesogens by inducing adipocyte differentiation and the expression of genes involved in adipogenesis via various mechanisms.[84,85]

Laboratory studies in bisphenol A-exposed animals have focused attention on the neurological effects of weight gain. Bisphenol A-exposed female mice fed a high-fat diet consumed more food and gained more weight than control animals on the same diet.[81] The

results from this study suggest that early-life exposure to bisphenol A might lead to sexually dimorphic alterations in hypothalamic energy balance circuitry, which results in increased susceptibility to developing diet-induced obesity and metabolic impairment.[81] Similarly, *in vitro* exposure to bisphenol A increased proliferation of neural progenitor cells and altered neurogenesis; some of the changes in gene expression were similar to those occurring in the offspring of obese dams, which have been related to hyperphagia.[86] However, several other studies in both animals and humans have failed to find direct associations between bisphenol A exposure and weight gain, which suggests a need for additional research to delineate the effects of bisphenol A on metabolic systems.[87–89] Interestingly, bisphenol A glucuronide, the major metabolite of bisphenol A, and commonly thought to be inactive, induces adipogenesis but has no estrogenic activity.[90] However, additional research is needed to define the metabolic properties of bisphenol A in both humans and animal models.

The costs associated with obesity due to bisphenol A exposure have been estimated.[91,92] Bisphenol A exposure has been predicted to contribute to 12,404 cases of childhood obesity and 33,863 cases of coronary heart disease with an estimated societal cost of $2.98 billion in 2008.[91] A separate expert panel used a weight-of-evidence approach applied by the Intergovernmental Panel on Climate Change[93] to estimate bisphenol A exposures and calculated that prenatal exposure to bisphenol A had a 20–60% probability of causing 42,400 cases of childhood obesity in the European Union, with associated lifetime costs of 1.54 billion euros.[92]

Flame retardants

Flame retardants are chemicals applied to a variety of materials, including furniture, electronics and construction materials, to reduce their flammability or delay their combustion. Polybrominated biphenyls and polybrominated diphenylethers are widely used as flame retardants and, although a subset are banned according to the Stockholm Convention, some have been detected at biologically active levels in blood in children and in the majority of the population of the USA.[94,95] Flame retardants have been associated with a variety of adverse health outcomes, including obesity and altered or inappropriate thyroid function.[96–99] In several studies, prenatal and/or childhood exposure to polybrominated diphenylethers is associated with low birth weight and altered thyroid function in offspring.[100–102] In a longitudinal birth cohort study of children of Hispanic origin in California, USA, *in utero* and childhood exposure to polybrominated diphenylethers was associated with increased BMI in boys at 7 years of age but not in girls.[103] This finding suggests that time after exposure and sex might have a role in development of the disease. The congener BDE-47 stimulated adipogenesis in a 3T3-L1 adipogenic screen[104] and increased weight gain in rats exposed *in utero*.[105]

The Firemaster® 550 flame retardant (Chemtura, USA) mixture came to market as the use of polybrominated diphenylethers was being phased out. This mixture is now the second most commonly *in vivo*-detected flame retardant sold in the USA. Evaluation of the toxicity of Firemaster® 550 in pregnant rats found elevated expression of phenotypic biomarkers associated with the metabolic syndrome in offspring.[106] Effects noted included early female puberty, weight gain (which became evident before puberty and continued into adulthood), male cardiac hypertrophy, glucose intolerance, and increased serum levels of thyroxine, as well as reduced hepatic carboxylesterase activity in the dams.[106] Subsequent studies reported that the obesogenic effects of Firemaster® 550 might be mediated by binding to and activation of PPAR-γ, similar to those of organotins.[107,108]

Polychlorinated biphenyls

Polychlorinated biphenyls are a major component of the highly persistent organic pollutants found in our environment. These agents are man-made synthetic chemical mixtures, which were widely used in industry until the late 1970s, after which time they were banned in the USA and many other developed countries. Exposure to polychlorinated biphenyls remains ubiquitous because of improper disposal and bioaccumulation in the environment. In some studies, these lipophilic pollutants have been shown to accumulate at high levels in adipose tissue and might be a contributing factor in the obesity epidemic.[41,109] The NHANES 1999–2002 survey[110] showed an association between waist circumference and BMI in individuals with detectable levels of persistent organic pollutants, which suggests a contribution to the ongoing obesity epidemic. Data supporting the association between polychlorinated biphenyls and metabolic disease continues to be reported, with two studies in the past few years reporting that early-life exposure to polychlorinated biphenyls is closely associated with childhood obesity.[111,112]

Phthalates

Phthalates are diesters of phthalic acid and are a class of chemicals that are commonly used to impart flexibility in plastic products (plasticizers) including polyvinyl chloride, and as a carrier for fragrances in cosmetics. These compounds are also found in a variety of household and personal care products, including food packaging and medical devices.[113,114] Phthalates easily leach from these products and, thus, are found in indoor air and house dust; human exposure to phthalates has been well documented.[115]

Diethylhexylphthalate, or its metabolite monohexylphthalate, has been linked with obesity in animal models.[116,117] Prenatal and neonatal exposure to diethylhexylphthalate in pregnant mice led to increased body weight, numbers and size of adipocytes, and activation of PPAR-γ in male offspring, which suggests a sexually dimorphic effect.[117] Using a different mouse strain, exposure to diethylhexylphthalate *in utero* and throughout lactation led to increased weight gain, which persisted into adulthood.[118] Both of these studies

reported nonmonotonic dose responses, with lower doses (0.05 and 0.5 mg/kg/day) resulting in weight gain, but no effect at the higher dose of 500 mg/kg/day. These *in vivo* results were confirmed in the 3T3-L1 preadipocyte cell line.[119] Monohexylphthalate or diethylhexylphthalate induced the expression of PPAR-γ, expression of its target genes and the differentiation of these cells into adipocytes.[117,120–122] When diethylhexylphthalate was administered to adult mice for 8 weeks, all doses (0.5, 5 and 500 mg/kg/day) resulted in increased food intake, increased plasma levels of leptin, decreased adiponectin expression in adipose tissue, weight gain and adipocyte hypertrophy.[118] These data indicate that phthalates have the ability to increase adipose tissue mass both during development and in adulthood, although the mechanism and sensitivity in these periods are probably different.

Perfluorinated chemicals

The perfluorinated chemicals, perfluorooctanoic acid and perfluorooctane sulphonate, which persist in the environment, are used to repel grease and oil, are found in Teflon™ (DuPont, USA), Scotchguard™ (3M Company, USA) and in carpets and clothing to repel staining, and have been linked to obesity.[123] Human and animal studies on the metabolic effects of these compounds are inconclusive. In one study in humans, perfluorooctanoic acid concentrations over the first 3 years of life were compared with BMI in adulthood; no risk of becoming overweight was demonstrated.[124] A separate study in a Danish cohort measured perfluorooctanoic acid concentrations at gestational week 30 and showed a positive association with BMI and waist circumference at 20 years of age in female individuals but not in male individuals.[125] Differences in study design probably account for the different results. Young adult mice exposed *in utero* to perfluorooctanoic acid were overweight and had increased serum levels of insulin and leptin.[126] However, in a different mouse model bred for intestinal neoplasia, neither perfluorooctanoic acid nor perfluorooctane sulphonate (0.01, 0.1 or 3 mg/kg/day given on gestational day 17) led to weight gain in offspring at 10 weeks and 20 weeks of age.[127] Currently, insufficient data exists to determine if perfluorooctanoic acid and/or perfluorooctane sulphonate should be classified as obesogens.

Transgenerational obesogenic transmission

In the past decade, a considerable body of evidence has shown that chemical exposures occurring during certain periods of fetal development can generate phenotypes that persist through multiple generations.[128] These phenotypic changes probably do not have a genetic origin as low-dose exposure to EDCs typically does not damage DNA but, rather, causes alterations in the epigenetic profile that can be passed on to subsequent generations.[31,45,129] For example, exposure to pesticides, fungicides, jet fuel, plastics and air pollution have been linked to reproductive diseases in the F3 generation of mice.[130] Maternal exposure to bisphenol A has been linked to behavioural changes in offspring through four generations, which is probably due to epigenetic modification of imprinted genes.[131]

A preponderance of data supporting the concept of transgenerational inheritance of obesity is beginning to emerge in the literature. For instance, mice prenatally exposed to tributyltin have increased adipose depots and adipocyte size, as well as fatty liver through three generations.[45] Transgenerational inheritance of obesity resulting from exposure to DDT,[132] a mixture of bisphenol A and di-(2-ethylhexyl)-phthalate, and a hydrocarbon mixture (jet propellant 8; commonly known as JP-8) has also been demonstrated.[133,134] However, in other studies no transgenerational transmission of obesity after exposure to dioxin, vinclozolin or a mixture of permethrin and *N*,*N*-diethyl-meta-toluamide that indicates chemical selectivity of effects on metabolic processes[135] and specificity of chemical-induced transgenerational effects has been found. Although the mechanism of transgenerational inheritance is far from understood, transmission of epigenetic information is probably involved.[136–138] Indeed, the global demethylation that is required to maintain the germline epigenetic programme and thus reset the gamete epigenome for pluripotency is incomplete during this period of development.[139] Some loci in the germline of humans and mice are resistant to DNA demethylation, thereby providing the potential for transgenerational epigenetic inheritance.[140] In summary, early-life exposure to at least some obesogens might exert permanent and transgenerational effects.

Ideal conditions for obesity

We propose that the convergence of early nutrition and exposure to obesogens during development (*in utero* and in first few years of life) in association with overnutrition and decreased physical activity later in life, creates ideal conditions that drive the worldwide obesity epidemic.[141] Continued exposure to obesogens throughout life exacerbates the problem by interfering with the endocrine system, which controls metabolism. This problem burgeons as infants born to parents with obesity also have an increased risk of being obese. Dealing with the obesity epidemic will require additional research in the understanding of how nutritional and environmental chemical exposures affect the basic mechanisms underlying the development and function of adipose tissue, as well as eating behaviours. The implications of the obesity epidemic are vast, and new research into the metabolic effects of chemical exposures during development offers a window on prevention and/or intervention.

Conclusions

Although the obesogen hypothesis is less than 10 years old, the obesogenic properties of ~20 environmental chemicals are already known. Given the difficulty in treating obesity, the obesogen hypothesis opens the door to reducing the incidence of this global health problem by focusing on its prevention through reducing early-life chemical exposures.

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Author contributions

J.J.H., R.N. and T.T.S. researched data for the article, provided substantial contributions to discussions of content, wrote the article and reviewed and/or edited the manuscript before submission.