Chapter

Environmental Obesogens and Human Health

Archisman Mahapatra, Priya Gupta, Anjali Suman and Rahul Kumar Singh

Abstract

Obesity is an alarming public health concern that contributes to a substantially increased risk of multiple chronic disorders, including diabetes. As per WHO data, in 2016, almost 39% adult population of the world is overweight, 13% of them were obese. There is prominent evidence on the involvement of environmental endocrine-disrupting chemicals, termed obesogens, in the prevalence of this growing worldwide pandemic, obesity. The exaggerated effect of obesogens on endocrine disruption, lipid metabolism and homeostasis, adipocyte functioning, impaired thermogenesis, inflammation, epigenetics, and overall human health will be covered in this chapter. This chapter will discuss the environmental obesogen hypothesis, the epidemiological and experimental evidence of obesogens, its chemical characteristics, and possible mechanism of actions. It will also focus on some recent indications of obesogens and their correlation in COVID-19 disease pathogenesis. This chapter will try to conclude with strategies for identifying the underlying mechanisms of obesogens within model systems and the human body, including future directions.

Keywords: endocrine disrupting chemicals, obesogens, obesity, gut microbiota, peroxisome proliferator-activated receptor γ, lipid metabolism, energy homeostasis

1. Introduction

1.1 Endocrine-disrupting chemicals

As defined by the US Environmental Protection Agency (EPA) [1], an endocrine-disrupting chemical (EDCs) is "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process." Diamanti-Kandarakis et al. [2] among thousands of human-made chemicals, almost 1000 chemicals may have endocrine-disrupting properties [3]. Initially, it was thought that EDCs deploy their actions mainly through various nuclear hormone receptors like estrogen receptors (ERs), progesterone receptors (PRs), androgen receptors (ARs) and thyroid receptors. However, as research progressed on EDCs and their mechanism of actions, it is now known that they can also act on non-nuclear receptors, nonsteroid receptors, orphan receptors and other enzymatic pathways related to metabolism, cancer and other physiological processes [2].

As the compounds classified under EDCs are from dispersed heterogeneous sources, they can be divided into two major classes, synthetic and natural. Synthetic EDCs include industrial solvents and their byproducts [dioxins, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), alkylphenols etc.], agricultural pesticides [methoxychlor (MTX), chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)], fungicides, herbicides, insecticides, plasticizers [phthalates, bisphenol A (BPA)] and pharmaceuticals [diethylstilbestrol (DES)] whereas, phytoestrogens (genistein, coumestrol etc.) are grouped under natural sources of EDCs. Humans are exposed to the broad range of EDCs mainly through the dietary intake (fish, meat, dairy and poultry products) and to some extent by inhalation and dermal uptake [2, 4]. Mostly EDCs are highly lipophilic, and they tend to get accumulated in the adipose tissues [5, 6]. They can accumulate in human and other large mammals' fatty tissues through biomagnification and bioaccumulation as they are the top predators in the food chain [7]. Due to their long half-life, they remain stored in the adipose tissues for years. Persistent Organic Pollutants (POPs) are the best example of long term accumulations in human tissues [8]. However, plasticizers like BPA have a very short estimated half-life of about four hours. Instead of bioaccumulation, they generally get excreted via urine [9]. Still, BPA has a very adverse effect on the human endocrine system due to their continuous exposure throughout the days [10].

Among the vast range of chemicals under EDCs, some are referred to as "obesogens" as they promote or induce weight gain in individuals by altering endocrine pathways involved in metabolism, energy homeostasis and appetite. The phthalates, perfluorinated compounds, BPA, dioxins, and some pesticides showed obesogenic potentials [11, 12]. Though their mechanism of action is not very well understood, some report indicated that these chemicals might act through Peroxisome proliferator-activated receptor gamma γ (PPAR-γ), a ligand-activated transcription factor, has a role in various cellular functions as well as glucose homeostasis, lipid metabolism, and prevention of oxidative stress [13, 14]. Some suggest they may act via the thyroid axis, as the thyroid hormone is a crucial regulator of metabolism [15, 16]. Hence, this field is relatively new and emerging in EDC's research and needs further studies.

2. Environmental obesogen hypothesis

The prevalence of obesity and associated diseases like type 2 diabetes, cardiovascular diseases, metabolic syndromes and cancers are progressively increasing at an alarming rate in recent years. Globally the cases of obesity have nearly tripled since 1975. As per a WHO report, in 2016, 13% of adults aged 18 or more are obese worldwide. A more recent report stated that approximately thirty-eight million children (under five years) are obese. In simple language, obesity can be defined as an "abnormal or excessive fat accumulation that may impair health" [17]. The measure of obesity is generally done by body mass index (BMI), defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m^2). A BMI of 30 or greater falls within the obese range; the limit changes to 25 or more in Asian populations [18, 19]. It is a widely accepted fact that the primary cause of obesity is the imbalance between calory intake and energy expenditure. However, obesity is a complex disease caused mainly by endocrine disruption, which also involves interaction between genetic and environmental factors.

The Obesogen Hypothesis suggests that environmental chemicals, characterized as "obesogens," induce obesity by enhancing the engagement, differentiation and size of adipocytes, by altering metabolic setpoints or modifying the hormonal

control of appetite and satiety [20]. Many EDCs are obesogens in nature and found abundantly in our environment, which may induce adipogenesis and lipid accumulation in the tissues. About 50 of such compounds have been identified to date [20]. Various mechanisms of action of the obesogens are discussed later in this chapter.

3. Chemical characteristics of obesogens

Obesogens have peculiar characteristics which make them potential to interfere with various endocrine and metabolic pathways. They are believed to be xenohormones as they imitate or partially resemble natural hormones and have unwanted physiological effects. They can bind to endocrine receptors present on the cell membrane, cytosol, or nucleus, thereby altering their natural functions [21]. Along with the structural similarities with native hormones, their ability to do this also relies on its lipophilicity and small molecular weight. Partition coefficient, half-life and molecular weight are the three main components of xenohormones. A partition coefficient (P) is "the ratio of the concentration of a substance in one medium or phase (C1) to the concentration in a second phase (C2) when the two concentrations are at equilibrium; that is, partition coefficient = (C1/C2)equal." [22]. This is how the distribution efficiency of a chemical is measured between two mediums. Here in obesogen's case, it is between the tissue and blood. A compound's octanol–water partition coefficient expresses that (K_{OW}), referred to the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system [23]. It is an essential measure of its lipophilicity of a chemical. The bioaccumulation and toxicity of a chemical largely depend upon

Source	Obesogens	Chemical characteristics		
		Log K_{OW}	**Biological Half-life**	**Mol. weight**
Industrial	BPA	3.32	21.3 +/− 7.4 h [26]	228.29 g/mol
	Bisphenol S (BPS)	1.65	6.8 ± 0.7 h [27]	250.27 g/mol
	BDE-47	6.76 [28]	664 days [29]	485.79 g/mol
	3,3′,4,4′-Tetrachlorobiphenyl (PCB-77)	6.72	1.2 Months [30]	292 g/mol
	bis(2-ethylhexyl) phthalate (DEHP)	7.6	12 hours [31]	390.6 g/mol
	Dioxin	6.8	5.8 years [32]	322 g/mol
	Perfluorooctanoic acid	4.81	12.6 days	414.07 g/mol
Pesticides/ insecticides	Dichlorodiphenyl-trichloroethane (DDT)	6.91	7 years [33]	354.5 g/mol
	Tributyltin (TBT)	3.1–4.1 [34]	23–30 days [35]	290.1 g/mol
	Atrazine	2.61	10.8–11.2 hours [36]	215.68 g/mol
Pharmaceuticals	Diethylstilbestrol (DES)	5.07	2–3 days [37]	268.3 g/mol
	Nicotine	1.17	2 h [38]	162.23 g/mol

Note: All values are acquired from the PubChem database otherwise mentioned.

Table 1.
Chemical characteristics of some obesogens.

K_{OW}. As being organic, obesogens are naturally lipophilic compound, which means they have a higher K_{OW} value. More the value of the K_{OW} of a compound, the more will be its tendency to accumulate in the adipose tissues [24].

Now, coming to the half-life, the biological half-life of a chemical is the time it takes to break down or eliminate half of the chemical's quantity from the body. In the body, a longer biological half-life implies longer endurance. Ideally, obesogens have longer biological half-lives means a short exposure can have life-long consequences [25]. The last of the three properties, molecular weight, refers to the size of a compound molecule. Small molecules can diffuse more readily through adipocytes. However, many large molecules having high molecular weight can give rise to smaller metabolites which may have a similar effect to obesogens [24]. The bioaccumulation and the binding affinity for the receptors largely depend upon these three criteria. Many obesogens perfectly fit into these criteria. Moreover, some of them are also resistant to degradation [e.g. 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47)] [21]. A summary of some well-known obesogens with their characteristics is listed in **Table 1**.

4. Mechanisms of action of obesogens

Though the mechanism of obesogens' actions in inducing obesity is not very clear, some studies suggest few mechanisms by which obesogen could act. This disruption of lipid homeostasis by obesogen may involve several mechanisms, some of which are as follows (**Figure 1**):

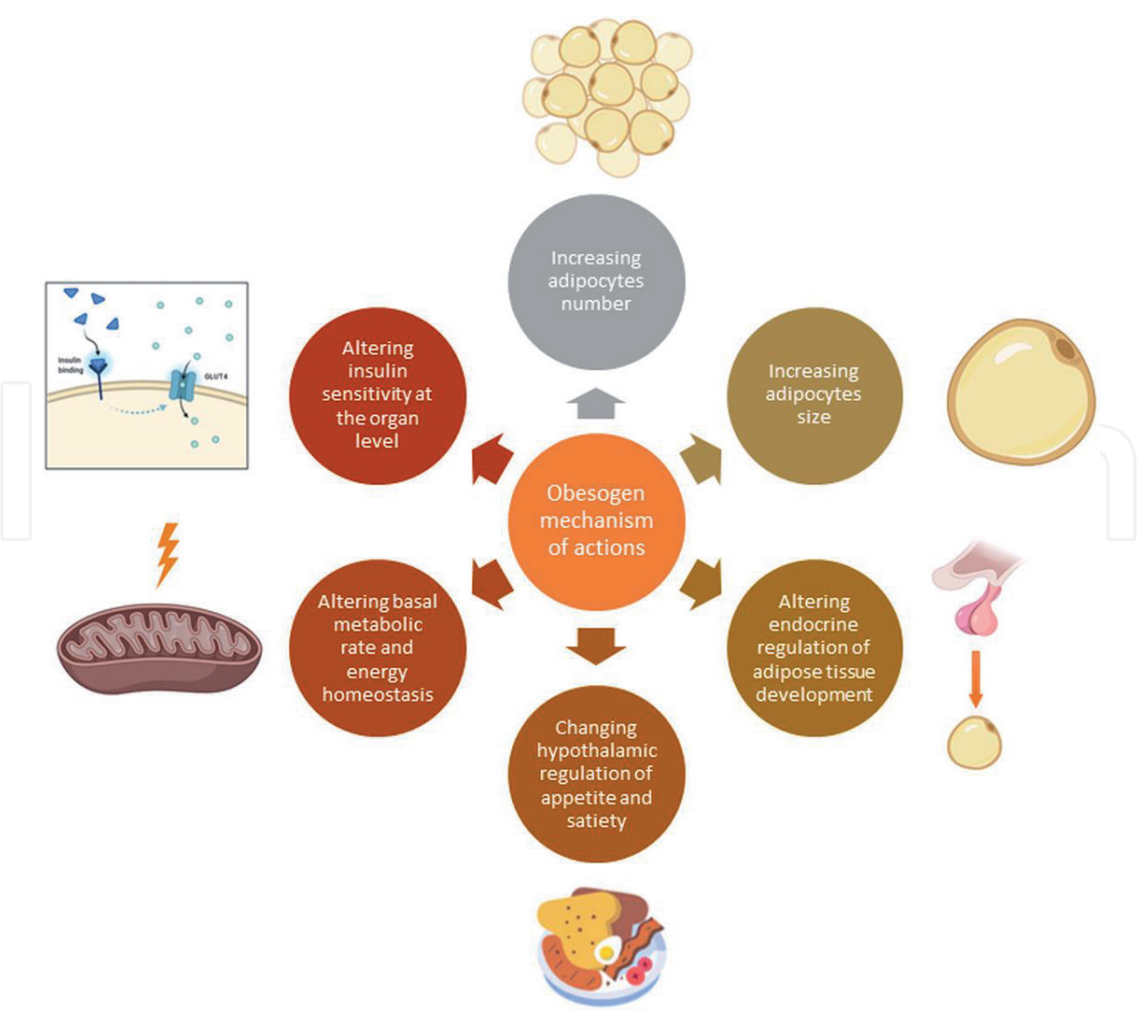

Figure 1.
Mechanisms of obesogen actions.

1. increasing the adipocytes number,

2. increasing the size of the adipocytes,

3. altering endocrine regulation of adipose tissue development,

4. changing hypothalamic regulation of appetite and satiety

5. altering basal metabolic rate and energy homeostasis

6. altering insulin sensitivity at the organ level

4.1 PPARγ-RXR mediated

Obesogens generally disturb the endocrine system by interfering with PPARγ and other hormone receptors like estrogen receptor, androgen receptors and glucocorticoid receptors. PPARγ is one of the primary regulators of adipogenesis. It is highly expressed in adipose tissues and induce differentiation of adipocytes by promoting lipogenic enzymes. Along with adipogenesis, it activates genes involved in maintaining energy balance. Upon activation, PPARγ forms a heterodimer complex with nuclear receptor 9-cis retinoic acid receptor (RXR) an act as promoters for the genes required for storage of fatty acid and repression of lipolysis. That is why this PPARγ:RXR heterodimer is called the "master regulator of adipogenesis" [39]. Obesogen tributyltin (TBT) acts as a ligand and show high binding affinity with PPARγ and nuclear receptor RXR. By activating PPARγ and RXR, it might promote adipogenesis and lipid dysbiosis [40, 41]. Obesogens like spirodiclofen and quinoxyfen activate PPARγ while others like fludioxonil activate RXR [13]. Phthalates are also known activators of PPARγ, as they are shown to promote 3 T3-L1 cells to adipocytes differentiation [42]. Obesogen can increase the amount of adipose tissue by increasing the size as well as numbers of adipocytes. They can induce the Mesenchymal Stem Cells (MSCs) to differentiate into preadipocytes and adipocytes [43]. In vitro assays show numerous compounds with obesogenic properties can induce the Mesenchymal Stem Cells (MSCs) to differentiate into preadipocytes and adipocytes via PPARγ dependent pathways. TBT exposure to 3 T3-L1 preadipocytes induces them to differentiate into white adipose tissues (WAT) [44]. Bisphenol A (BPA), combined with insulin, can accelerate the conversion of 3 T3-L1 fibroblasts to adipocytes [45]. Even prenatal exposure to TBT in mouse shows preferential differentiation of MSCs towards the adipose lineage [43] (**Figure 2**).

From the studies available so far, it is evident that any ligand which can bind to PPARγ can induce adipogenesis and can be called obesogens. However, as human adipose tissue stores many of them, they can have a more significant cumulative effect. These additive effects are not well studied yet.

4.2 Other receptor-mediated

Obesogens are reported to act via other hormone receptors like estrogen receptor, androgen receptors and glucocorticoid receptors. Many studies have reported that they act via the nuclear hormone receptor-mediated pathways. Molecular cross talks with other signaling pathways have also been reported. Steroid hormones have an essential role in lipid storage and disposition of body fat. Estrogen based hormone replacement therapy is prescribed to women at their menopause to remodel their adipose depot. Foetal or neonatal exposure to phytoestrogens may induce

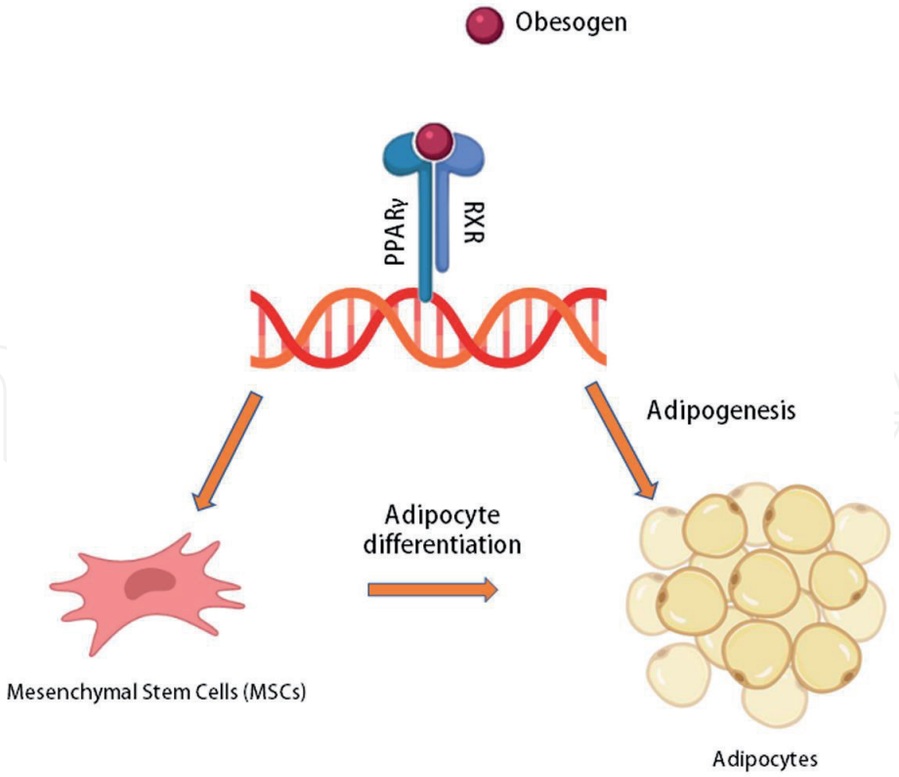

Figure 2.
PPARγ-RXR mediated action of obesogens.

obesity in later stages of life. Well-known phytoestrogen genistein, commonly found in soy-based foods, affects adipose tissue deposition in a dose-dependent and gender-specific manner [46].

Neonatal exposure of DES to female mice led to weight gain in adulthood. However, this effect can be sex-biased. While some EDCs may act directly via cellular steroid receptors by inducing estrogen synthesis, other EDCs may act indirectly. It is established that adipose tissue is a site of estrogen synthesis. The adipocyte cytoplasm contains the enzyme cytochrome P450 aromatase, which plays a vital role in converting estrogen from androgen. It is now reported that several EDCs can impair intracellular aromatase activity [47]. This action may raise intracellular estrogen levels in adipocytes and lead to obesity irrespective of the sexes [48]. It is reported that TBT can directly reduce the activity of the aromatase enzyme in adipose tissue at high doses, leading to reduced estradiol levels and down-regulation of the ER target genes. TBT also has an inhibitory effect on 11β-hydroxysteroid dehydrogenase 2, which leads to reduced inactivation of cortisol. It is believed that increased glucocorticoid levels could influence adipocyte differentiation and regulation of metabolism [40].

Some obesogens, especially the persistent organic pollutants (POPs), act via the ligand-activated transcription factor aryl hydrocarbon receptor (AhR). AhR activates xenobiotic-metabolizing enzyme cytochrome P450s. They can promote adipogenesis indirectly by changing PPARγ expression.

4.3 Other mechanisms

In some recent studies, researchers found that they are not linked to activation of any nuclear hormone receptors; instead, they followed some novel mechanisms, which make their mechanism of action more complex. Those include epigenetic modifications, impairment of thermogenesis and dysbiosis in gut microbiota. Some of these mechanisms will be discussed in the following sections. Some recent

studies correlated COVID-19 pandemic to the obesogenic exposures, that is also being discussed in this chapter.

4.3.1 Epigenetic modifications

Epigenetics is defined as the study of heritable changes in phenotype resulting from environmentally influenced modifications of genome. Epigenetic modification can alter gene expression during development and cellular differentiation in response to environmental factors such as chemical contaminants. These modifications include DNA methylation at cytosine residues of 5′ to guanine sites (CpG sites), chemically modifying histone proteins and noncoding RNAs interference [49]. DNA methylation was considered a key mechanism responsible for adult diseases with developmental origins [50]. DNA methylation changes are responsible for the transgenerational effects of exogenous exposed individuals to chemicals and nutrition deficits [51]. For instance, the obesogen pesticide TBT induced changes in DNA methylation and histone modification invitro. Various reports have documented the environmental chemicals, including obesogens, led to an epigenetic modification in vivo and obesogen phenotype even in unexposed generations. TBT exposure in 3 T3-L1 mice preadipocytes invitro resulted in increased adipocyte differentiation along with decreased DNA methylation levels. Increased differentiation level towards the adipogenic lineage was observed in adipose-derived stromal cells (ADSCs) isolated from TBT exposed mice perinatally but at the cost of decreased osteogenesis. ADSCs exposed to TBT were associated with increased adipogenesis marker genes, such as PPARγ target gene Fapb4, where methylation level decreased in the promoter region. However, PPARγ mRNA levels were increased, but DNA methylation at its promoter region had no effects [43]. A possible reason for this lack of epigenetic regulation might be that EDC exposure during differentiation process causes DNA histone demethylation. Ultimately, PPARγ, which is under the control of H3K27me3, causes the gene to be promptly up-regulated. Importantly, prenatal exposure to TBT has been recently shown to cause the transgenerational inheritance of adiposity. It remains to be determined whether these transgenerational effects are related to permanent changes in DNA methylation profiles or other epigenetic processes.

4.3.2 Impairment of thermogenesis

Recent advances found in understanding adipocyte function was the presence of thermogenic brown adipose tissue (BAT) in adult human beings in a dispersed manner, not as found in concentrated discrete depots in human infants. Another discovery of white adipose tissue can also be induced to produce thermogenic fat called beige or brite fat. Increased mitochondria production is responsible for differentiation of both bona fide brown adipocytes and beiging of white adipocytes. This thermogenesis relies on the capacity to dissipate energy in the form of heat through uncoupling of cellular oxidative phosphorylation and ATP synthesis via Uncoupling protein 1 (UCP1) or sometimes through shivering. Some of the evidence has documented how some obesogens impede the production and function of thermogenic adipocytes. For instance, perinatal exposures to DDT in mice have long term-effects on thermogenesis regulation in their female offspring. When female offspring reached up to 6 months of age, they showed reduced energy expenditure & ultimately decreased thermogenesis capacity. However, no change in their physical activity was observed. Thermogenesis impairment was due to the decreased expression of PPAR-γ co-activator 1α (Ppargc1a), a master regulator

for thermogenesis related genes and type 2 iodothyronine deiodinase (DiO2) (the enzyme that catalyzes thyroid hormone T4 to convert into T3 which stimulates BAT thermogenesis) [52]. Secondly, Shoucri and his colleagues [49] found that TBT or rexinoids have inhibited adipocytes' production. Other EDCs increase thermogenesis by changing mRNA and protein levels of UCP-1. Adult mice exposed to PFOA and PFOS through diet (containing 0.02% w/w) for ten days exhibited BAT mitochondria activation for increased oxidative capacity and protein levels of UCP-1, resulting in decreased depots size of adipose tissue. PFOA exposure (80–40 μM) during in-vitro experiments activates UCP1 similarly as fatty acids. These examples indicate how obesogens influence obesity by impairing thermogenesis during the in-vitro and in vivo study. This intriguing area of obesogen epidemic and their mechanism remains to be elucidated. Through their Horizon 2020 programme, the European Union has funded several grants to establish new assays to assess EDCs effects on metabolic-end points and identify those chemicals that affect thermogenesis [53].

4.3.3 Gut microbiota dysbiosis

The gut microbiome is defined as "the totality of microorganisms, bacteria, viruses, protozoa, and fungi, and their collective genetic material present in the gastrointestinal tract" by molecular biologist Joshua Lederberg. Obesogen exposure could lead to obesity by altering the gut microbiome, a relatively novel mechanism which leads to obesity. It is well understood that obesity is correlated with gut microbiome composition [54]. Some experimental data shows that the transplant of gut microbe from obese mice can induce obesity in lean mice [55]. Conversely, the gut microbiome transplant from lean donors improved the metabolic disorder condition in obese mice [56]. It is evident from several experimental data that many obesogens induce the gut microbiome dysbiosis in zebrafish [57], mice [58] and human [59]. In mice, gut microbial dysbiosis was associated with increased fat accumulation or impaired lipid metabolism after exposure to triphenyl phosphate. Tributyltin exposure induces gut microbiome dysbiosis with increased body weight gain and dyslipidemia in mice [58]. Though, it is not yet apparent whether this metabolic disruption is a result of the gut microbiota dysbiosis or not.

Additionally, some microbial metabolites have also been reported as AhR agonists and antagonists [60, 61], as we are already aware that activating AhR inhibits adipogenesis. In contrast, inhibition of the activity leads to obesity and fatty liver disease. Two basic dietary emulsifiers, carboxymethylcellulose and P-80, were reported to initiate intestinal inflammation and gut microbiota dysbiosis, which led to metabolic disorder and increased body weight in mice [62]. These pieces of evidence suggest that inducing obesity via gut microbiota dysbiosis is possibly a potent mechanism for the obesogens to follow. However, to get more clues, this field needs to be studied further extensively.

4.3.4 Obesogens and COVID-19

The current outbreak of novel coronavirus has emerged as a worldwide pandemic in the past year, which is related to the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 [63]. Interestingly, a study in 2003 found a positive correlation between air pollution and extreme SARS in the Chinese population. Patients with SARS from regions with a high air pollution index (API) were twice as likely as those from regions with low APIs to die from SARS [64]. A finding based on US population found that long-term exposure to air

pollution resulted in a 6% rise in cardiopulmonary mortality risk. Some of these pollutants are potent obesogenic [65].

Human studies have even shown nitrogen dioxide (NO2), one of the components of air pollution, is correlated with higher fasting serum lipids among obese individuals, indicating that obesity can worsen the effects of air pollution [66]. Animal studies have also shown that air pollution particles' sensitivity early in life will contribute to increased visceral obesity, insulin tolerance, and inflammation, signaling NO2's function as an endocrine disruptor [67]. Since COVID-19 is similar to SARS in causing respiratory disease, exposure to NO2 can increase the mortality rate of patients with COVID-19. However, future studies are needed to validate this relationship.

5. Transgenerational effects

One of the most intriguing results in EDCs field came when a series of reports were published by Skinner and colleagues showing EDCs, including DDT and MTX, induce transgenerational obesogenic effects. During F1 generation, prenatally exposed individuals with anti-androgenic fungicide vinclozolin or estrogenic pesticide MTX were associated with disease in various organs in their F4 generation [68]. Similarly, when pregnant mice (FO generation) were exposed to environmentally relevant doses (nM) of TBT through drinking water, then effects on obesity were observed in F1-F3 descendants of exposed animals [69]. Notably, in a similar experiment, the pharmacological obesogen, Rosiglitazone, which can activate PPARγ, could not produce the same transgenerational obesity effects suggesting that different pathways in addition to PPARγ were required to generate transgenerational phenotype [69].

In addition to TBT effects on obesity, Skinner lab has shown several environmental chemicals such as plasticizer (BPA, DEHP, DBP) [70], pesticides MTX [71], a mixed hydrocarbon mixture (jet fuel JP-8) [72] and the widely used pesticide DDT [73], induced transgenerational obesity in a rat model as observed in F3/F4 offspring of ancestral prenatal or perinatal obesogen exposed-FO individuals [71–73]. Although molecular mechanisms underlying transgenerational inheritance of obesity are currently controversial, researchers belonging to the EDC field believe that these obesogen effects are inherited in an epigenetic manner. This point has got stronger resistance in the genetics sphere [74].

6. Epidemiological evidence of obesogens

6.1 Human cohort studies

Epidemiological studies are of considerable significance for the association of disease effects with exposure to obesogens. Few cohort-based studies are available to date on the effect of obesogens in human populations. Since a considerable amount of evidence indicate that prenatal exposures predispose patients to obesity, epidemiological research concentrates on obesogenic measurements throughout pregnancy. Increase in child adiposity in multiple birth cohorts was associated with prenatal exposure to PFAS. At the same time, sexual dimorphism was sometimes linked with it [75–79]. A metapopulation analysis, including ten cohorts, suggests a 25% and 0.1 unit increase in weight and BMI, respectively, per ng/ml of PFOA concentration in maternal blood [80].

A research found that rising concentrations of maternal urinary phthalate during gestation doubled the risk of the offspring becoming overweight or obese

[81]. Cohort research on the impact of prenatal BPA exposure has also been correlated with increased waist circumference, BMI, and risk of obesity [82]. Studies of prenatal exposure to phthalates and bisphenols have not shown a consistent association with measures of childhood adiposity compared to studies of prenatal exposure to PFAS [83]. Two studies on the American population showed an association between serum concentrations of PFAS and weight gain irrespective of sexes [84]. PFAS, particularly perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFNA), were linked with alteration in metabolic rate [85].

Few studies have explored the longitudinal impacts on postnatal growth of prenatal exposure to other chemicals. Evidence risen over the past five years indicates that exposure to phthalates leads to adult weight gain, with most research conducted in women. Some studies by the Women's Health initiative reported a strong correlation between urine concentrations of phthalate metabolites and weight gain [86]. Again, it is to be considered that the effect of a single chemical mostly reflects the epidemiological studies conducted. However, naturally, obesogens ploy cumulative effect as mixtures. The WAT is the depot of obesogens in the human body. More studies should be designed to estimate the accumulative effect of mixtures in future.

6.2 In vitro models

In vitro models have several advantages over other model systems. Taking human cells lines for the study can be of great significance considering the physiological relevance. For screening new chemicals for potential obesogenic properties, in vitro studies are generally conducted before animal models. Several cell lines are used to study the obesogenic impacts of several compounds. Among the in vitro models, mouse embryo pre adipocyte 3 T3-L1 has been used extensively to check the effects of obesogens like TBT [87], BPA [88], BPS [89], genistein [90], phthalate [91], nonylphenol [92] and so on. Other cell lines include C2C12 (mice muscle cells) [93], HELA (human cervical cancer cells) [93], HEK293C (human embryonic kidney cells) [94], HepG2 (human liver carcinoma cells) [95], hASCs (human adipose-derived stem cells) [96], C57BL/6 (mice bone marrow stromal cells) [97], hESCs (human embryonic-derived stem cells) [98] etc.

6.3 In vivo models

Though animal models are not recommended to study certain chemicals' obesogenic potential, they do not mimic the human physiological systems. Still, in vivo model systems have certain advantages over in vitro systems as whole-body kinetics and systemic effects can be studied using animal models. Complex linked pathways involving multiple organs, including adipose tissue, liver, pancreas, muscle, brain, etc., regulate metabolism and weight. In understanding the role of chronic inflammation and hormone interference, in vivo experiment is particularly relevant. The most widely used animal model for the study of obesogens is rodents. Multiple obesogens including TBT [69], BPA [99], triphenyltin [100], DEHP [101], DES [102], polycyclic aromatic hydrocarbons, DDT, and nicotine, have been defined as murine models. Mice are identical biologically and anatomically to humans and share many common diseases. It is incredibly useful for diseases with an inflammatory condition, such as obesity, as animal models can mimic complex inflammatory responses. A transgenic model like obese or lean bodied mice can also be created by manipulating required genes. Other commonly used in vivo models include rats [103], zebrafish [104] and drosophila [105]. Many insights into possible obesogens and various modes of action were provided using in vivo models to investigate

endocrine disruption. They may not replicate human physiology, as discussed earlier. Mice exposed to a specified amount of one particular molecule over weeks sometimes does not reflect a chronic variable exposure in humans to multiple chemicals over the years. In detecting obesogens and discerning mechanisms of action, animal models play an essential role. However, they should be combined to draw the most reliable conclusions with knowledge from in vitro studies and epidemiological studies.

7. Strategies for change and future directions

The obesity epidemic first continues in the US and afterwards expands worldwide; therefore, it becomes a dire need to understand the predisposition and related disorders' mechanisms. It becomes of utmost importance to study the extent to which the obesogen exposure influences obesity in humans and establishes the risk factors related to obesity. The risk factors include oxidative stress, inflammation, disrupted circadian rhythms, mitochondrial dysfunction and dietary composition. These interactions may be critical in the effects of obesogen exposure. Evidence documented in the obesogen research area shows that their effect mainly depends on the level and timing of exposure, especially critical windows of exposure during fetal development. Hence, it is crucial to reduce or avoid exposure to obesogens, specifically during pregnancy. However, there is no technique to determine if the individuals have been exposed to any obesogens during their development. It will be a "Holy grail" to identify biomarkers of exposure in obesogen research and establish links among obesogen exposure and other factors related to obesity. The obesogen hypothesis opened a new field into obesity by linking EDCs research with developmental disease origin. The obesogen hypothesis is still in the dearth of research. It requires more studies in the mechanism, developmental time windows and diet interaction. The effects of obesogens are related to epigenetics.

However, we still need more research to understand the mechanism and how the effects get transmitted to forthcoming generations. For instance, how does the obesogen exposure of pregnant Fo female mice lead to obesity in upcoming F3 and F4 unexposed males? There is an extreme lack of data on how obesogen exposure programs adipose tissue dysfunctional that could readily store but not mobilize fat. The obesogen sphere is almost 15 years old only. Much has been studied related to potential effects of EDCs and obesogens. The most substantial evidence for chemical obesogens existence may be the variety of pharmaceuticals that have the side effects of making patients obese. Several international and national workshops have been held to understand the potential role of EDCs in obesity and related metabolic disorders [53]. Thus, various policies and strategies should investigate the magnitude of environmental obesogenic pollutants on the obesity epidemic and the regulatory actions required on such chemicals to improve public health.

8. Conclusion

The majority of evidence that indicates the role of EDCs in driving obesity provides a mechanistic explanation of the obesity epidemic and a management strategy. The role of exogenous chemicals in growing rates of obesity through gene expression regulation (such as PPARs), hormone changes, and inflammation is supported by ample evidence. While overeating, combined with lack of exercise,

is undoubtedly a significant contributor to the increase in obesity that can be addressed by decreased calorie intake and increased exercise, it may be that reducing exposure to obesogenic EDCs may also contribute to reducing obesity in the population, especially during the early stages of life. More knowledge of obesogenic pathways will improve prophylactic and therapeutic strategies. The extensive exposure of the human population to so many EDCs with obesogenic action needs evaluation. In vitro models are useful screening devices for detecting and testing obesogenic mechanisms, notably, changes in gene expression or molecular pathways. Improvements to these models will improve human extrapolation in vitro to in vivo as well. However, animal models remain a valuable and typically physiologically precise method for studying obesogenic inter-organ pathways, including hormone interference and inflammation. More epidemiological studies should be made to confirm in vitro and in vivo animal models and provide unparalleled insight into human obesogen exposures and effects. Integrating the data collected from all three of these model systems would result in better-informed choices of compounds that can be used to replace obesogens in food production, packaging, etc. It will, essentially, reduce the economic burden of obesity.

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Conflict of interest

The author declares that there is no conflict of interest.

Author contributions

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Author details

Archisman Mahapatra, Priya Gupta, Anjali Suman and Rahul Kumar Singh*
Department of Zoology, Molecular Endocrinology and Toxicology Lab (METLab), Institute of Science, Banaras Hindu University, Varanasi, India

*Address all correspondence to: rks.rna@gmail.com

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