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Mechanisms of obesogens and their impact on adipose tissue, hormones, and inflammation

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ABSTRACT

The complex interactions of genetic, environmental, and behavioral factors that contribute to obesity, a pervasive global health issue, continue to be a severe concern for people all over the world. This manuscript

examines the field of obesogen research, seeking to understand the mechanisms by which certain environmental chemicals contribute to the development of obesity. We explore the obesogenic effects by focusing on pathways such as inflammation, hormone interference, and the activation of peroxisome proliferator-activated receptors (PPARs). The text focuses on the significance of PPAR isoforms, especially PPARγ, and how they play a role in adipose tissue growth. We examine how obesogens such as tributyltin (TBT) and bisphenol A (BPA) influence these receptors. Additionally, we examined the impact of obesogens on hormonal regulation, including disruptions to leptin and adiponectin, and investigated the intricate relationship between chronic inflammation and obesity. In the methodology of our study, we utilized a systematic search to identify peer-reviewed articles of relevance. This search spanned various model systems, including in vitro, in vivo, and epidemiological studies, providing insights into the distinct advantages and limitations associated with each. Epigenetic modifications and the influence of obesogens on the development of adipose tissue, metabolism, and appetite control further enrich our understanding of this complex field. Finally, we assess the role of endocrine disruptors in amplifying the risk of obesity, emphasizing the heightened susceptibility during crucial developmental periods. This comprehensive review aims to contribute to the ongoing discourse surrounding obesogens, paving the way for targeted interventions and a more profound comprehension of the global obesity epidemic.

Introduction

Obesity, defined as a BMI of 30 kg/m^2 or more, is a global pandemic that affects children and adults in both developing and industrialized countries [1]. Obesity is the accumulation of excess body fat that can harm health. A person's body mass index (BMI), a measurement of body fat based on height and weight, is commonly used to determine it; interactions between hereditary, environmental, and behavioral factors typically cause obesity. Obesity can develop because of several reasons, including poor eating habits, inactivity, specific medical disorders, pharmaceutical use, and psychological concerns. Additionally, genetic predisposition may make some people more prone to acquiring weight.

Adipose tissue, body fat, is crucial in energy storage, hormonal regulation, and insulation. In the context of obesity, excessive accumulation of adipose tissue, especially visceral fat, contributes significantly to the health risks associated with obesity. Visceral fat found deep within the abdominal cavity surrounding vital organs like the liver, pancreas, and intestines is metabolically active and strongly linked to various metabolic disorders, including type 2 diabetes, cardiovascular disease, and inflammation. Adipocytokines, including leptin and adiponectin, are key signaling molecules secreted by adipose tissue, influencing various metabolic processes and inflammation. Leptin acts on the hypothalamus to regulate appetite and energy expenditure, while adiponectin enhances insulin sensitivity and has anti-inflammatory effects, contributing to overall metabolic health. Hence, understanding the mechanisms associated with visceral fat accumulation and its interactions with environmental factors, such as obesogens, is vital for examining the pathways involved in obesity-related diseases. Therefore, the present study aimed to investigate the mechanisms by which environmental chemicals, known as obesogens, contribute to the development of obesity, with a focus on pathways such as inflammation, hormone interference, and the activation of peroxisome proliferator-activated receptors (PPARs).

History of Obesity

Over 68 million people participated in a large-scale, systematic examination of the literature that found that 650 million adults aged 18 and older were obese and that at least 1.9 billion adults were overweight in 2015 [1]. Around 107 million children globally suffer from obesity. In many nations, childhood obesity is rising more quickly than adult obesity. Overweight or obesity caused 4 million deaths worldwide, with over 40% of these deaths occurring in those who were overweight but not obese. One hundred twenty million years of life with disabilities were lost worldwide in 2015 because of being overweight. Between 1980 and 2000, the obesity rate in the United States more than doubled [1].

Between 1980 and 2010, the US's obesity prevalence more than doubled, rising from 13.4%

to 35.7%. According to the latest recent data, the prevalence of obesity grew globally, reaching 37.7% in 2014 and 39.8% in 2016 [1]. Obesity affects black (46.8%) and Hispanic (47.0%) people disproportionately, while black (54.8%) and Hispanic (50.6%) women bear the brunt of the load. In 2012, more than one-third of young people in America were overweight or obese; by 2016, that number had dropped to 18.5 percent, with the oldest age group (those between 12 and 19 years old) having the greatest incidence of obesity (20.6 percent).

Obesogens

According to Ribeiro et al. [2], the word "obesogen" was created to designate substances, such as Endocrine-Disrupting Chemicals (EDCs), that can encourage obesity in humans and animals. EDCs are exogenous substances that interfere with the body's normal homeostasis and encourage adipogenesis and fat buildup. They are also exogenous substances that impede hormone function [3].

Obesogens are widely present in our environment and various daily items, including fungicides and food packaging [4]. These substances may exert their effects in several ways, including nuclear receptor binding that alters transcriptional regulation, interference with steroid hormone function, and disruption of the neuroendocrine system's regulation of average metabolic balance. Endocrine disruptors are also among the most popular and extensively researched obesogens.

Individual obesogens encompass a wide range of substances identified as contributors to obesity by disrupting normal metabolic processes [2]. These substances include chemicals in plastics, pesticides, food additives, and personal care products. For example, bisphenol A (BPA), commonly found in plastics and food containers, has been linked to obesity due to its ability to interfere with hormone signaling related to metabolism. Similarly, many household products' phthalates may disrupt endocrine function and contribute to weight gain. Organotins, used in pesticides and antifouling paints, have also been implicated as obesogens [4]. These compounds can disrupt hormonal balance, increasing fat accumulation and metabolic dysfunction.

Obesogens' Sources and Classes

About 20 different chemical substances have been identified as obesogens thus far. Most are human-made compounds intentionally or mistakenly released into the environment, while some are natural (like phytoestrogens) [5]. These substances can be breathed, applied topically, or taken orally.

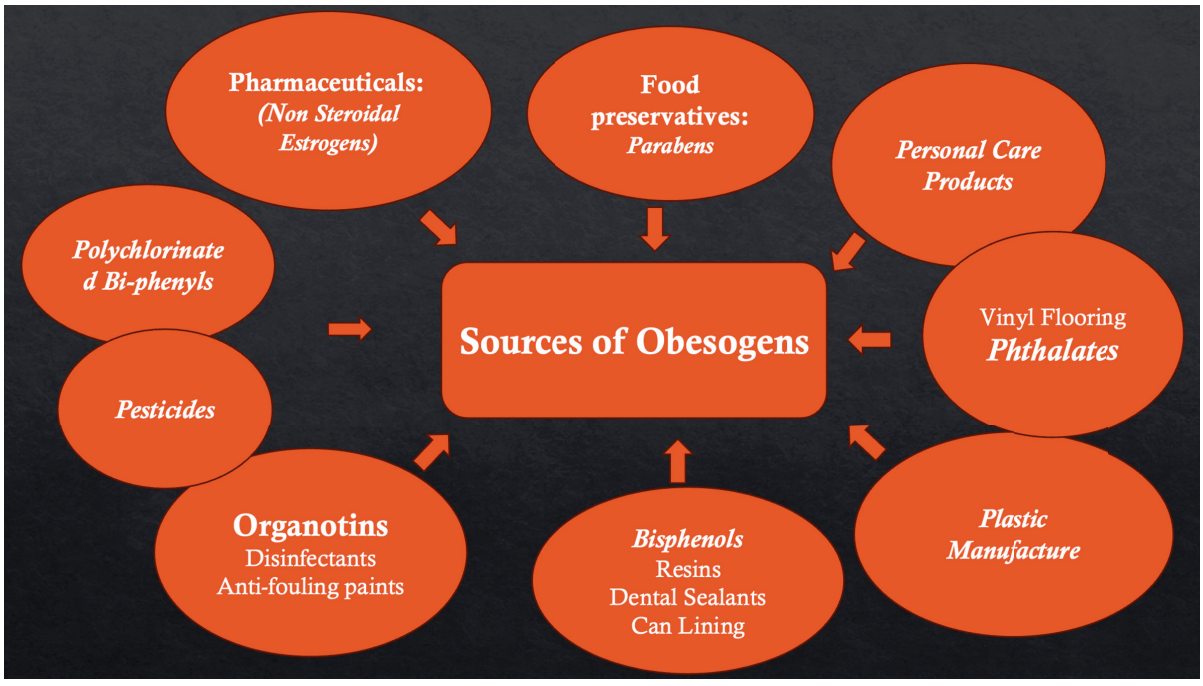

Figure 1. Sources of Obesogens.

Tributyltin – a Model Obesogen

One of the earliest identified obesogens is tributyltin (TBT), currently the subject of extensive research. To encourage the commitment and differentiation of adipocytes, TBT binds to and activates Peroxisome Proliferator-Activated Receptor (PPAR) and Retinoid X Receptor (RXR) nuclear receptors involved in regulating gene expression related to lipid metabolism and adipogenesis. Studies conducted in vitro proved that TBT exposure induced the activation of PPAR and RXR, which led to the differentiation of murine 3T3-L1 adipocytes into adipocytes [6]. Additionally, 3T3-L1 preadipocytes treated with TBT created defective adipocytes with altered lipid metabolism and gene expression [2]. According to in vivo studies, TBT exposure enhanced fat accumulation and hepatic steatosis in rodents, fish, snails, and Daphnia. TBT administration during pregnancy led to F1 mice with larger adipose depots and a bias in Mesenchymal Stem Cells (MSCs) toward the adipose lineage rather than the bone lineage [7].

Surprisingly, exposure to TBT during pregnancy can have lasting effects on future generations. Pregnant F0 dams exposed to environmentally relevant (nanomolar) levels of TBT in the drinking water showed increases in adipose depot weight, adipocyte size, adipocyte number, and the propensity of MSCs to differentiate along the adipogenic rather than the osteogenic pathways in F1, F2, and F3 offspring. With various substances in other labs, transgenerational increases in obesity were also documented [8]. According to Lima et al. [7], an epigenetic mechanism was probably responsible for these effects.

A second TBT exposure experiment revealed that the effects of prenatal TBT exposure on fat depot size persisted at least through the F4 generation. When dietary fat was substantially increased (from 13.2 to 21.2% kcal from fat), the F4 male offspring of pregnant F0 mice exposed to TBT developed greater fat mass than their control counterparts. Furthermore, when put back on the regular low-fat diet, these animals did not lose weight during the fast and kept the extra fat [9].

It is critical to remember that current toxicology risk assessment paradigms, which include direct chemical exposure, may only partially detect the risks associated with chemical exposure, given the transgenerational impacts of TBT and other obesogens [10]. Generations that are directly exposed may show few or no significant phenotypes, and it has been suggested that the best way to assess risks is to combine traditional toxicological analysis with a generational toxicology analysis that considers the effects on future generations [11].

Mechanism of Action of Obesogen

Research into the specific mechanisms of obesogens is still in its infancy. A recent study found that inflammation, hormone interference, and the peroxisome proliferator-activated receptor gamma (PPARγ) are all essential contributors to the development of obesity [13]. There are additional obesogen-related possible pathways; however, the paper does not discuss all of them. The following section will focus on the significance of these three pathways in obesogenic effects. To further emphasize the distinctions between exposures to obesogens that are persistent versus non-persistent, as well as those that are developmental (in utero) and non-developmental, more study is likely required [12].

Activation of Peroxisome Proliferator-Activated Receptors (PPARs)

Peroxisome proliferator-activated receptors (PPARs) are steroid-free nuclear hormone receptors. There are currently three recognized isoforms of PPAR, which are: (1) PPARα, (2) PPARβ/δ, and (3) PPARγ. A separate gene encodes each isoform. PPARs interact with the nuclear receptor 9-cis retinoic acid receptor (RXR) to produce their heterodimers [14] [15]. These heterodimers modify the expression of the target genes. The heterodimer binds to specific response sites called peroxisome proliferator response elements (PPRE) in the promoter region of target genes [16]. When a ligand and receptor come into contact, the receptor's conformation is altered, which causes co-transcriptional factors to be attracted. The target gene's mRNA expression rises as a result [17].

PPARs target genes involved in fat storage, transport, and metabolism like fibroblast growth factor 1 (FGF1), G protein-coupled receptor 81 (GPR81), adiponectin (PPARγ), and CPT-1 (PPARα) as typical targets in the exploration of obesogenic pathways [19]. Regarding adipose tissue growth, PPARγ is the transcription factor that has been the subject of most research. According to Huang et al. [18], thiazolidinedione

medications used to treat type 2 diabetes target PPARγ to improve insulin sensitivity while also causing adipogenesis. It has been established that many obesogens activate the PPARγ/RXR heterodimer in vitro, in utero, and in vivo. Tributyltin (TBT) is an extensively researched obesogen that upregulates this gene. Uncertainty surrounds whether the effects result from activating the RXR domain, the PPAR domain, or both [80]. Since TBT-activated transfected Cos7 cells in the presence of a PPAR antagonist, TBT likely activates the PPAR/RXR complex via binding to the RXR domain [80].

Additionally, it has been demonstrated that RXR activation, rather than PPARβ/δ activity, is necessary for mesenchymal stem cell commitment to the adipogenic lineage [20]. However, further research is required to back up this assertion. Bisphenol A (BPA, a plastic monomer), triflumizole (a fungicide), phthalate monoesters (plasticizers), Firemaster 550 (a flame retardant), and dioctyl sodium sulfosuccinate (DOSS), an ingredient in the oil dispersant COREXIT, are additional obesogens that have been shown to function at least partially through PPARγ/RXR activation [80]. Several obesogens likely activate the PPARγ /RXR heterodimer in different ways, and more investigation is required to pinpoint the precise molecular pathways. Understanding how these obesogens affect the PPARγ /RXR heterodimer may help to understand how to reverse their effects [21].

An additional isoform of PPAR is PPARα. It is mainly in skeletal muscle, brown adipose tissue, the liver, and the heart. It is essential for the liver's fatty acid metabolism. Other natural ligands include oxidized phospholipids, proteins that break down lipoproteins, and fatty acids [44]. There is growing evidence that it functions in adipose tissue and is a target for obesogens despite being largely present in the liver and skeletal muscle. According to Cordeiro et al. [22], PPARα improves insulin sensitivity and helps rodents control their body weight.

Antagonists reduce insulin resistance and body weight in male mice. Adiponectin mRNA expression increases in PPARγ-deficient mice; however, this is thought to result from an increase in adipose tissue mass or an attempt to counteract a concurrent increase in leptin production [43]. Regarding obesogens, PPARα has not been examined as extensively as PPARγ, although recent research indicates that there may be an impact. Aspartame and MSG (monosodium glutamate) decreased the expression of the PPARγ gene in mice. TBT was discovered to activate PPARγ in transfected HeLa cells, and mice exposed to TBT in utero showed increased PPARγ mRNA expression [44].

One mechanism causing the obesogenic effects may be increased expression of PPARα, which is known to boost insulin sensitivity. However, according to Loh et al. [23], the obesogen bis (2-ethylhexyl) phthalate (DEHP) enhanced mRNA expression of PPARα in liver tissue while lowering expression in visceral fat in mice. The mechanisms of obesogens are likely more complex than what is now understood. Therefore, more research will be required before any definitive conclusions can be drawn [43].

Hormone Interference

Exogenous chemicals that mimic or obstruct hormone function can significantly affect metabolic processes' efficiency. Tightly controlled hormones, such as androgens and estrogens, have a significant impact on the function of adipose tissue. Males with lower BMIs have higher testosterone levels [24]. Many phthalates, which are thought to be antiandrogens, have been connected to human obesity. BPA behaves as a xenoestrogen. The progeny of mice who are perinatally exposed to BPA are noticeably bulkier. Dichlorodiphenyldichloroethylene (DDE), a metabolite of the common pesticide dichlorodiphenyltrichloroethane (DDT), has also been shown to have estrogenic effects. Babies gain weight quickly after being exposed to it during pregnancy. Phthalates, polybrominated biphenyl ethers (PBDEs), and BPA have also been shown to reduce thyroid levels in the blood [25].

Decreased thyroid hormone levels bring on an increase in BMI. Obesogens also affect leptin and adiponectin. Zhang et al. identified Leptin to cause satiety and boost skeletal muscle and brown adipose tissue glucose absorption; Hyperinsulinemia and obesity are caused by leptin mutations. Leptin resistance, however, can result from hyperleptinemia, which is common in obese people [26]. Scherer et al. first identified adiponectin, which improves insulin sensitivity. Several obesogens have been shown to have an impact on these hormones. TBT lowers serum

adiponectin levels and raises plasma leptin levels in mice, leading to the overexpression of the leptin gene [27].

DEHP lowers the mRNA levels of leptin and adiponectin in mice. Male mice exposed to DOSS during pregnancy have higher plasma leptin levels. Genistein, an isoflavone found in soy, increases leptin mRNA expression, male mouse adipose tissue accumulation, and insulin resistance. DEHP has also been shown to increase serum leptin levels [28]. It was shown that the plasticizer benzyl butyl phthalate (BBP) boosted the expression of the adiponectin protein in differentiated 3T3-L1 cells. Adipocyte growth is additionally reliant on glucocorticoid receptor activation. Sargis et al. demonstrated improved adipogenic differentiation by employing BPA, dicyclohexylphthalate (DCHP), endrin, and tolylfluanid to activate the glucocorticoid receptor [29]. Although it is unclear how each obesogen will act and how hormone impact will function, obesogens typically target hormones. In addition, there may yet be unknown hormonal targets.

Inflammation

There is a link between chronic inflammation and obesity. Although there is a link between inflammation and the growth of fat tissue [30], it may also result from epigenetic changes brought on by environmental and lifestyle variables. Male mice exposed to DOSS in utero demonstrated increased body mass, visceral fat mass, upregulated inflammatory gene expression (Cox2, Nox4), and increased plasma levels of IL6. Like humans, TBT treatment in rats elevated PPARγ, additional ovarian fat mass, and increased inflammation in the reproductive system. Increased body weight and uterine inflammation were observed following TBT administration in a comparable research study of female rats [31]. Increased IL-6, TNF-, and IL-1 gene expression in white adipose tissue and increased fat mass rate were seen in male BPA-exposed mice. Variousized 3T3-L1 preadipocytes also show increased expression of IL-6, TNFα, MCP-1, and CXCL1 after exposure to either TBT, BPA, or mono-ethylhexyl phthalate (MEHP, metabolite of DEHP) [32].

An Il-17 antibody may slow down inflammation and prevent the BPA obesogenic effects, according to Mittelstraß and Waldenberger's [58] study on male mice, suggesting that inflammation may be a substantial factor in this effect. It has also been demonstrated that several obesogens cause an increase in immune cells in adipose tissue [58]. The mRNA expression of CD68, a marker for filtration-associated macrophages, increased in female lambs exposed to BPA. Furthermore, gonadal white adipose tissue from mice exposed to BPA during pregnancy included more macrophages. BPA has also been shown to encourage macrophage self-renewal. Even though BPA is one of the obesogens that has received the most attention, there are additional obesogens. Additionally, there is proof of a connection between inflammation and the PPARγ and PPARα genes [33]. In addition to being elevated during inflammation, these molecules function as negative feedback loops because they compete with transcription factors for proinflammatory genes. Thiazolidinediones, an anti-diabetic medication, inhibits tumor necrosis factor (TNF) and activates PPARγ [34]. Although research in this field is still in its infancy, data suggests that inflammatory cells and gene expression play a role in obesogenic pathways.

Model Systems

Epidemiological studies, in vitro and in vivo systems, and model systems are currently used to assess the mechanisms of obesogenic action. Each kind offers unique benefits and drawbacks for developing mechanisms. The following paragraphs go over typical systems for each category and their advantages and disadvantages [13].

In Vitro Models

Compared to other model systems, in vitro models have several advantages. To be more biologically relevant, they might employ human cell types. They are often also simpler, faster, and more convenient as an effective obesogen screening method before in vivo investigations, cheaper, and parallelizable (for tests with medium to high volume) [35]. In vitro screening methods are already available to evaluate traits like adipocyte maturation and lipid metabolism to identify possible obesogens [36]. These simulations mostly employ mouse 3T3-L1 preadipocytes. These cultures have been crucial in revealing some of the molecular processes underlying adipogenesis.

However, it is still being determined if the 3T3-L1 cell line is adequate for evaluating adipogenic responses since they are fully committed to the adipocyte lineage [37]. Patient demographics and medical histories are unknown to researchers and contribute to large outcome variability [38]. Sex-specific distinctions are typically ignored even though gender is known to alter body fat storage and responses to obesogens.

Further study must concentrate on validating these models using primary cells or tissues from numerous known patient populations. Additionally, obesogens have depot-specific effects on adipose tissue. Visceral versus subcutaneous or brown versus white adipose tissue-derived cells may respond to obesogens differently [39]. Understanding the various responses of adipose tissue depots is crucial for identifying obesogenic consequences, as visceral adipose tissue is most directly linked to metabolic disease. [65].

To duplicate the effects of obesogens in vitro and better understand their effects under more physiologically appropriate conditions, researchers have begun examining 3D human tissue systems [66]. The in vivo adipose tissue environment may be replicated by using 3D adipose tissue systems, which can be extended for long-term culture (months to study the long-term effects of obesogens). These systems can be used to investigate cell migration and how obesogens are kept in adipose tissue. Adipose tissue may hold onto obesogens because it is primarily lipophilic [40].

3D models can include non-adherent mature adipocytes that cannot be grown using traditional 2D culture techniques. Like ASC differentiation, which also becomes non-adherent with time, they enable long-term in vitro research. The use of 3D models enables the development of more complex coculture systems [41]. Because different organs, including adipose tissue, the pancreas, the liver, or the thyroid play a role in the obesogenic processes, systems combining multiple cell types may provide more physiologically accurate data. They can research paracrine signaling as well. However, because 3D models include either synthetic or natural extracellular matrix (ECM), they are more expensive and sophisticated than 2D systems [42]. This introduces new factors, including pore size, mechanical characteristics, and cell binding domains. Furthermore, problems with flow rates, medium, and fluid/cell ratios are present in perfusion cultures [50]. Finally, most of the in vitro research is now 2D, which makes it difficult to compare outcomes from 3D cultures to already validated models [71]. Overall, 2D and 3D in vitro models of biological interactions and boundary conditions can be accurately controlled, enabling quantitative evaluations of mechanisms. Due to their ability to assess dose responses and combination effects concurrently, they are ideal for high-throughput screening. In vitro models offer high screening potential for obesogens despite having issues that must be fixed [52].

In Vivo Models

Animal models have the disadvantage of plainly not accurately reproducing human physiology. However, because they are suitable for analyzing whole-body kinetics and systemic effects that are impossible to investigate in vitro, animal models are a significant and often used tool for studying obesogens [53]. According to Huang et al. [18] and Talley et al. [54], complex interconnected pathways involving several organs, such as adipose tissue, liver, pancreas, muscle, and brain, control metabolism, and body weight. Human cell lines can be used in in vitro cell culture procedures, although replicating these systems' interdependence is still challenging. Long-term in vitro culture is challenging due to scaling ratios, common medium, and organ-specific ECMs unique to multi-organ models [55]. Even though more complicated in vitro models are the focus of considerable research, animal models are essential for discovering obesogens and understanding obesogenic pathways because they enable the investigation of organ cross-talk and systemic effects and, thus being crucial to comprehend the function of hormone interference and chronic inflammation [28].

The most used animal model for obesogen research is rats. Several obesogens, such as TBT, BPA, triphenyltin, DEHP, DES, MEHP, polycyclic aromatic hydrocarbons, DDT, and nicotine, have been discovered utilizing murine models [55]. Mice share many diseases with humans regarding biology and anatomy [22]. Animal models can replicate complicated, inflammatory responses, making this especially helpful for disorders like obesity that have an inflammatory component. Furthermore, mice can be reared in controlled environments (such as with a high-fat/Western

diet) and have longer lifespans, which shortens the time required to conduct research [56]. They can also be genetically modified. Rats, zebrafish, and Xenopus laevi are some other typical in vivo models used to assess obesogens. Numerous insights into putative obesogens and various mechanisms of action have been gained using in vivo models to research endocrine disruption [57]. However, it is critical to consider the disadvantages of utilizing animal models. They sometimes replicate human physiology, as was previously mentioned [26]. Dose response may also apply differently to humans. It is also possible that the exposure window is odd. Mice treated to a specific quantity of one chemical over a few weeks may not accurately represent chronic variable exposure to several chemicals over many years in humans. In vitro research and epidemiological studies should be supplemented with data from animal models in order to make the most accurate findings about obesogens and their mechanisms of action [80].

Influence of Obesogens on Epigenetic Modifications

Epigenetic changes have garnered much attention recently among the numerous putative mechanisms governing gene expression in adipose tissue. Epigenetics is the study of changes in gene function that occur without a corresponding alteration in DNA sequence. Examples include the methylation of DNA, acetylation, methylation, phosphorylation, ubiquitination of histones, and interference with microRNA (miRNA) [59]. There is mounting evidence that early exposure to obesogens can alter the gene activity of tissues, which is crucial for regulating metabolism in long-lasting ways. Among other things, changes in DNA methylation, histone acetylation, and miRNA expression may be the root of these modifications [60].

The phthalate BBP has been demonstrated to generate histone changes that drive MSCs to differentiate into adipocytes at varying concentrations. These include decreased PPARγ methylation, increased H3K9 acetylation, increased expression of histone acetyltransferase and decreased expression of histone deacetylase, and decreased H3K9 dimethylation [83]. Lower PPARγ DNA methylation was seen in the offspring of pregnant mice exposed to PAH. In turn, exposure to BPA in various cells led to a reduction in histone H3K9 trimethylation and an increase in the production of miR-146a; however, MSCs have not yet demonstrated this [62].

Impact of Obesogens on the Development of Adipose Tissue, Metabolism, And Appetite Control

Adipogenesis

These include decreased PPAR methylation, increased H3K9 acetylation, increased histone acetyltransferase expression, decreased histone deacetylase expression, and decreased H3K9 dimethylation [65]. Lower PPAR DNA methylation was seen in the offspring of pregnant mice exposed to PAH. In turn, exposure to BPA in various cells led to a reduction in histone H3K9 trimethylation and an increase in the production of miR-146a; however, MSCs have not yet demonstrated this [64].

For instance, PCBs can cause adipogenesis and encourage the storage of fatty acids to create triglycerides by suppressing the production and function of leptin [87]. The results of in vitro research should be interpreted cautiously, however, as just one obesogen's influence was examined in one experiment, and there is a paucity of data on the effects of MSCs being exposed to multiple obesogens simultaneously. It is conceivable that interactions among different obesogens will have an additional impact on adipocyte growth [64].

Numerous in vivo investigations in vertebrates and invertebrates and particular research in people have shown that obesogens impact preadipocyte differentiation. Compared to mice who were not exposed, pregnant mice exposed to TBT had a higher likelihood of producing offspring with greater fat tissue [67]. Animals in adolescence and early adulthood revealed similar results. In turn, PBDE exposure during pregnancy and the first few years of life is connected to thyroid issues, an altered testosterone metabolism, and increased weight growth in both experimental animals and children. DEHP treatment of the mother or father Drosophila melanogaster caused the offspring's body weight to grow or decrease, respectively [68].

In mice, prenatal and neonatal exposure to diethylhexylphtalate increased the number of adipocytes, which in turn caused the offspring

and adult animals' body weight to increase [69]. In turn, higher body mass index (BMI) and waist circumference were found to be linked with higher urine quantities of phthalate metabolites in epidemiological investigations. Prenatal DDT and DDE exposure increased the risk of human obesity in epidemiological studies, much like prenatal DDT exposure increased rodent adiposity in succeeding generations [70]. However, the results of other animal and human studies regarding a potential link between exposure to BPA (and its analogs) and the development of obesity are inconclusive, and more research is required to clarify these findings. Urinary BPA levels did, however, positively correlate with BMI and waist circumference in children and adults [71].

Adipose Tissue Metabolism

Cell culture tests have shown that several obesogens not only preferentially differentiate MSCs into preadipocytes but also interfere with the metabolism of mature adipocytes, causing them to become dysfunctional. Triglyceride accumulation was enhanced in 3T3-L1 cells that underwent TBT differentiation, while GLUT4 expression was downregulated. The TBT-treated cells also have fewer mitochondria, a slower rate of respiration, and reduced browning potential [72], being consistent with research showing that rats exposed to TBT during pregnancy have a greater propensity to form adipose tissue on a high-fat diet and a decreased ability to mobilize these depots after fasting [73].

TBT has been reported to alter the transcription of essential genes governing lipid metabolism and lipogenesis-related enzymes in the liver of exposed zebrafish (Danio rerio), indicating that it does not just have a lipogenic effect on mammals. TBT also reduces the ability of Daphnia magna eggs to transfer triacylglycerols, which encourages their buildup in adult individuals and lowers both adult and offspring fitness [94]. According to Pine [75], BPA analogs cause fat buildup in zebrafish larvae and late-onset weight gain in juvenile zebrafish.

2.5 Endocrine Disruptors

EDCs are defined as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body that are necessary for maintaining homeostasis and regulating developmental processes [73]. It has been demonstrated that early-life exposure to EDCs increases the chance of developing several chronic diseases, including diabetes and obesity. When exposure occurs during crucial developmental windows, sensitivity to the obesogenic effects of EDCs is exceptionally high [76] due to specific characteristics of the fetus and newborn, such as reduced expression of the cytochrome P450 enzymes that metabolize xenobiotic, that result in more tissue exposure than adults [77].

This ability also makes people more vulnerable to environmental stressors like EDCs, which can change several systems over time and raise the chance of becoming obese later in life [78]. In fact, exposure to obesogens in infancy may alter physiological functions that are important regulators of body mass, such as energy metabolism, appetite regulation, and adipogenesis. Thus, a frugal phenotype results in a higher risk of weight gain [77].

Conclusion

Numerous studies have shown that exogenous substances, including PPARs, affect gene expression, change hormone levels, and promote inflammation, all of which contribute to the rise in obesity rates. A deeper comprehension of obesogenic pathways will lead to better preventative and therapeutic approaches and the discovery of more potential obesogens [77].

Practical screening techniques for identifying and evaluating obesogen processes include in vitro models. They can help to pinpoint the changed molecular or gene expression pathways that result in altered adipocyte phenotype. Improvements to these models will aid in extrapolating in vitro to in vivo outcomes for humans. More comparisons to epidemiological research should be made to confirm in vitro and in vivo animal models. The most complete understanding of human obesogen exposures and effects is provided by epidemiological studies [79].

Implication and Future Direction

The implications and future directions of understanding the mechanisms of action of obesogens

have profound implications for public health, environmental science, and regulatory policies. One significant implication of unraveling obesogen mechanisms is the identification of potential therapeutic targets for obesity-related diseases. This knowledge opens doors for developing medications that counteract obesogenic effects, potentially providing novel treatment strategies for obesity and related metabolic disorders. Furthermore, the significance of early-life exposures is made clear by our understanding of obesogen processes. According to findings from the review, prenatal and early postnatal exposure to obesogens can have a long-lasting impact on a person's propensity to become obese in later life. This information highlights the urgent need for public health initiatives, regulations, and informational campaigns that reduce exposure, particularly during delicate developmental phases. It is crucial to put regulatory controls in place to restrict the use of obesogens in food production and consumer goods. Additionally, it highlights the necessity of thorough testing and safety assessments of chemicals before their release onto the market.

Future obesogen research should concentrate on discovering new obesogenic substances and comprehending their synergistic effects. It is also critical to investigate the long-term effects of obesogen exposure across generations. Studies that follow the health outcomes of people exposed to obesogens at various periods of life can shed important light on how obesogenic effects persist and intensify with time. Additionally, interdisciplinary study is crucial for developing a comprehensive understanding of obesogens. Toxicologists, endocrinologists, epidemiologists, and decision-makers working together can hasten the pace of discovery and its conversion into valuable applications.

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