Endocrine-Disrupting Chemicals in Obesity

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The incidence of obesity has dramatically increased over the last decades. Recently, there has been a growing interest in the possible association between the pandemics of obesity and some endocrine-disrupting chemicals (EDCs), termed “obesogens”.

Endocrine-disrupting chemicals | Obesity | Epigenetic | Bisphenol

1. Epigenetic Changes Induced by Obesogenic EDCs Exposure

Endocrine-disrupting chemicals (EDCs) are considered a heterogeneous group of natural (e.g., plant phytoestrogens) or synthetic compounds (e.g., industrial solvents, plastics, heavy metals, pesticides/herbicides) that cause health problems in an intact organism and its progeny by changing endocrine function. By binding to hormone receptors, EDCs influence downstream patterns regulated by specific hormones and lead to an imbalance in metabolism [1][2]. Dioxin and dioxin-like compounds, plastic components such as bisphenol A (BPA) and phthalates, parabens, and various flame retardants represent different examples of EDCs. Although heterogeneous, EDCs display some general characteristics shared by different components of the group. For instance, EDCs promote their adverse effects even at very low doses of exposure, and their action is stronger if it takes place during critical developmental periods, such as fetal life, infancy, puberty, and pregnancy [3][4][5]. In addition, the onset of disease promoted by EDCs is evident many years after the exposure [6]. Although EDCs show a very low affinity for hormone receptors compared to natural ligands, they can cause profound damage in several tissues. In general, since different classes of EDCs are released by human activities into the environment, they all together contribute to the development of a disease, and it is difficult to predict the detrimental effect associated with a specific EDC [7]. A possible association between the increase of global obesity and the spread of industrial chemicals into the environment was initially proposed in the early 2000s [8]. Afterwards, Grun and Blumberg introduced the term “obesogens” to indicate “xenobiotic chemicals that can disrupt the normal developmental and homeostatic controls over adipogenesis and/or energy balance” [9]. The effects of obesogenic environmental pollutants on adipose tissue expansion are stronger if the exposure happens during the prenatal or early-life period [10]. Obesogens target transcription regulators that are involved in the control of lipid homeostasis as well as adipocytes’ proliferation and differentiation. Due to their lipophilic property, EDCs accumulate in the adipose tissue over the years [11][12]. This produces a continuous spiral, promoting the EDC-induced expansion of adipose tissue and therefore the possibility to store larger amounts of additional EDCs [13]. Several obesogenic EDCs are known to affect the activity of a group of nuclear hormone receptors known as peroxisome proliferator-activated receptors (PPARs). Among those, PPARγ is considered the master regulator of adipogenesis, and it is

associated with the control of lipids and glucose metabolism [14][15][16]. PPARγ is therefore the main target of obesogenic EDCs. In addition, since PPARs heterodimerize with the retinoid X receptors (RXRs) to induce transcription, RXRs can also be a target of obesogenic EDCs [17][18]. Although epigenetic effects of EDCs have been well described, the exact mechanisms by which they interfere with epigenetic marks still remain unknown. In general, it has been proposed as a global action, where EDCs affect the abundance or the activity of epigenetic regulators, such as DNA methyltransferases, and/or their cofactors, such as methyl donor SAM (s-adenosylmethionine), or they could have a gene-specific action, influencing the regulation of locus-specific epigenetic patterns.

2. Bisphenol A

Bisphenol-A (BPA) is an organic synthetic compound largely used in the manufacture of polycarbonate plastics and epoxy resins, two components used in many consumer products, including food containers, baby bottles, medical devices, and the lining of food cans [19]. BPA is one of the most produced chemicals worldwide; indeed, it has been estimated that the production of BPA each year reaches about 6 million tons [20]. Foods and water can be contaminated by BPA monomers because of its leaching from the plastic containers. BPA has been associated with many diseases such as diabetes mellitus, obesity, polycystic ovarian disease, cardiovascular disease, thyroid, reproductive and neurodevelopmental disorders, and cancers [21][22][23][24].

BPA interacts with several ERs, including ERα and ERβ, and these interactions regulate the expression of estrogen-responsive genes [25][26][27]. The relative binding affinity of BPA for these receptors is much lower than that of estradiol, although it binds with high specificity and a binding affinity constant (KD) of 5.5–5.7 nM to ERRgamma. This receptor represents the most recently identified member of the estrogen-related receptor (ERR) family, and it is present in the developing embryo and neonate. Therefore, it could be responsible for some for the effects of BPA during development [28]. Since both pancreatic islets and adipocytes express functional ERs [29], they become targets of BPA, which can induce insulin resistance, alteration in pancreatic beta-cell function, hepatotoxicity, and obesity [30]. Urinary BPA concentration in man has been associated with a high incidence of obesity [31]. In addition, a positive correlation between BPA urinary levels and insulin resistance was found in obese children regardless of BMI. This could be linked to the effect of BPA on the expression of adiponectin and resistin genes, as demonstrated in adipocyte cultures [32]. In these cells, BPA is capable of reducing adiponectin production and secretion and induce resistin expression, a condition that generally characterizes obese subjects, where adiponectin levels are usually reduced and resistin levels are elevated, determining insulin resistance [33].

Experiments conducted in 3T3-L1 cells (mouse fibroblast cells that can differentiate into adipocytes) and human adipose stromal/stem cells have demonstrated that BPA promotes the expression of PPARγ and c/EBPα, the two master regulators of adipogenesis, increases triglyceride content, and inhibits adiponectin release [30]. Globally, these effects stimulate adipogenesis. Interestingly, the adipogenic effects of BPA are mediated not only by estrogen receptors, but also by the influence on the activity of other enzymes, including 11beta-hydroxysteroid dehydrogenase type 1 [34], thyroid receptor/retinoid X receptor, or mammalian target of rapamycin signaling pathways [35]. BPA may induce changes in DNA methylation and determine histone modifications [36]. In vitro

studies conducted in 3T3-L1 cells exposed to BPA confirm that this compound decreases global DNA methylation and enhances adipocyte differentiation [36]. This study demonstrates that altered epigenetic gene regulation may play a role in the link between BPA exposure and obesity development. In male rats, early-life exposure to BPA is responsible for increased fat/lean mass and adulthood hepatic steatosis with reduced mitochondrial function. These alterations are accompanied by changes in the epigenetic regulation of genes involved in hepatic beta-oxidation, such as the carnitine palmitoyltransferase (*Cpt1a*) gene. Here, BPA exposure promotes the binding of several transcription factors induced by modifications in DNA methylation and histone marks, such as histones H3 and H4 acetylation (H3Ac, H4Ac), histone di-methylation on lysine 4 on histone H3 (H3Me2K4), and histone tri-methylation on lysine 36 on histone H3 (H3Me3K36). Therefore, BPA toxicity is determined by both DNA methylation and histone modifications [37].

3. Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic non-steroidal estrogen that was prescribed between 1940 and 1971 to pregnant women to prevent adverse pregnancy outcomes [38]. Studies conducted in animals have suggested that exposure to DES during the prenatal or perinatal period increased the susceptibility to develop obesity during growth [39]. One possible explanation is that early exposure to DES may alter the genetic and epigenetic programming of adipocytes and their distribution.

In mice, an increase has been reported in circulating levels of leptin and pro-inflammatory cytokines, such as interleukin 6 (IL-6), considered markers of adiposity, during the early phase of exposure to DES. In addition, DES exposure has also been linked to alterations in glucose metabolism accompanied by pancreatic beta-cell hyperplasia [39][40]. DES exposure may potentially determine epigenetic effects, although epigenetic mechanisms that associate DES with obesity are still unclear. Recent studies demonstrated that many long non-coding RNAs (lncRNAs) regulate adipogenesis [41] and lipid homeostasis [42] and are regulated by nutrient factors and metabolic hormones [43]. Interestingly, several cancer-related lncRNAs are dysregulated/co-expressed in obesity, suggesting that obesity-associated lncRNAs may promote cancers. Therefore, data associating miRNA induction by EDCs and obesity-induced cancers could represent a link between EDCs exposure, miRNA expression, and obesity onset. As an example, in a breast cancer cell line (MCF-7), Bhan and coauthors have demonstrated that BPA and DES induce the expression of oncogenic long non-coding RNA HOTAIR (HOX transcript antisense RNA) [44], a potential oncogene having a significant impact on tumor cell viability, proliferation, and invasion [43][45]. A recent study demonstrated that a sedentary lifestyle further increases circulating exosomal HOTAIR in obese subjects, but not in lean subjects [1]. Ectopic expression of HOTAIR in abdominal preadipocytes produced an increase in the differentiation and expression of key adipogenic genes including *PPARγ* and *LPL* (lipoprotein lipase), the main enzyme of lipid storage in adipocytes [46]. Thus, one possibility is that a large increase in HOTAIR expression as a consequence of BPA and DES exposure may drive an increase in the differentiation in abdominal preadipocytes determining regional adiposity.

4. Phthalates

Phthalates are diesters of phthalic acid and are used to improve the flexibility, transparency, and durability of plastic materials, such as polyvinyl chloride (PVC). For this reason, they are present in many consumer products, including children's toys, food and beverage packaging, and medical devices. Human exposure to phthalates is generally due to dermal contact with PVC and plastic materials that release phthalates or by inhalation or ingestion [47].

Mice models have shown that phthalates' metabolites represent one of the causes of the increasing incidence of metabolic disease and that a close correlation between phthalates, increased adipogenesis, and insulin resistance exists [48]. Indeed, during adipocyte differentiation, phthalates activate PPARγ receptors [49]. A recent study has demonstrated a correlation between urinary excretion of phthalates' metabolites and obesity in both males and females, and phthalates exposure in children increases the risk of obesity [50]. These effects can be determined by the anti-androgenic actions of these compounds, which low cause androgenic activity and are responsible for the development of overweight and obesity [51][52]. DNA methylation represents a potential mechanism by which phthalate exposure in utero may exert long-term effects. An example is the study conducted by Miura and collaborators on DNA methylation in the cord blood of 203 mother–child pairs after di-2-ethylhexyl phthalate (DEHP) exposure. The results obtained have identified increased methylation changes associated with prenatal DEHP exposure at the level of genes related to metabolism, the endocrine system, and signal transduction. Further, increased methylation changes associated with DEHP exposure may contribute to the effects of prenatal exposure to this chemical on fetal growth [48].

Among the phthalates, butyl benzyl phthalate (BBP) is ubiquitously present in multiple products and can enter cells, bioaccumulate, and lead to extensive exposure to humans. Studies showed that 3T3-L1 preadipocytes exposed to BBP were induced to differentiate into mature adipocytes [48][53][54] and were characterized by the induction of miR-34a-5p expression, a key miRNA involved in obesity. In parallel, a decrease in the expression levels of *Nampt* and *Sirt1*, two target genes of miR-34a-5p, is observed, along with another significant epigenetic regulator, Sirt3 [48]. Zhang and collaborators have demonstrated that BBP exposure may regulate insulin signaling by altering vital epigenetic regulators, such as long noncoding RNA H19, and their downstream pathways [55].

5. Organochlorine and Organophosphate Pesticides

Organochlorine pesticides (OCPs) are chlorinated hydrocarbons that were used from 1940 to 1960. Although banned in several countries, some of these compounds tend to persist in the environment and bioaccumulate [56], posing a serious risk to worldwide human health. OCPs have been substituted by organophosphates (OPPs) that are esters of phosphoric acid and are commonly used as insecticide [57]. The first largely used compound of this group and one of the mostly known is dichlorodiphenyltrichloroethane, or DDT. Due to their high lipophilicity, these compounds become stored in fatty tissue and may act as endocrine disrupters [56]. Their presence in human adipose tissue has been linked to obesity and insulin resistance, probably due to their interference in *PPARγ* gene expression, production of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), and anti-androgenic effect [58]. A recent study demonstrated that a breakdown product of DDT, p,p'-dichlorodiphenyldichloroethylene (DDE), enhances adipogenesis and intracellular lipid accumulation in 3T3-L1 cells through the up-regulation of

some proteins involved in lipid storage, such as fatty acid-binding protein 4 and sterol regulatory element-binding protein-1c [59]. Early-life exposure to OPPs has been associated with hyperinsulinemia and hyperlipidemia, characteristic features of a prediabetic condition. In addition, human ApoE-targeted replacement mice showed an increase in food intake and weight gain after chronic dietary exposure to chlorpyrifos, one of the most frequently used OPPs worldwide. This suggested that genetic factors may also modulate the response to toxic exposure to OPPs and the susceptibility to the development of obesity and other related metabolic dysfunctions [60].

Pesticides can be used as an example of how exposure to EDCs during development causes alterations in epigenetic gene regulation, leading to adipogenic or obesity-related effects. Studies in 3T3-L1 preadipocytes have demonstrated that tributyltin chloride (TBT) exposure is associated with a global DNA reduced methylation level, promoting adipocyte differentiation [36]. This phenomenon has also been observed in adipose-derived stromal cells (ADSCs) isolated from mice exposed in utero to TBT. These cells presented an increased trend to differentiate into adipocytes rather than osteocytes [61]. ADSCs are characterized by a demethylation in the promoter region of some PPARγ target genes, such as *Fapb4*. These cells are also characterized by an enhancement in PPARγ levels that is not accompanied by changes in DNA methylation levels. This increase could be due to a demethylation of lysine 27 on histone H3 (H3K27me3) after pesticides exposure [62].

6. Inhaled Pollutants

Toxic environmental particles represent a worldwide public health problem. They originate from a variety of sources, including industrial sources, automobile traffic, and natural disasters, such as volcanic eruptions and forest fires [63][64]. Generally, the classification of air pollutants is based on the source of their origin, their chemical composition, and the mode and space of their release that could be gaseous or particulate and indoor or outdoor. Regardless of their origin, these pollutants are a mixture of gases and particulate matter (PM) with toxic effects [65]. Data from large epidemiological studies have indicated an association between air pollution exposure and cardiovascular morbidity and mortality [66], as well as increased lung cancer risk [67][68]. Moreover, a meta-analysis study indicated that PM2.5 susceptibility to cardiovascular diseases is strongly influenced by obesity, suggesting that obese people show a higher risk of developing cardiovascular disease after exposure to inhaled pollution particles. Moreover, long-term exposure to PM enhances the expression of local pro-inflammatory mediators that translocate from the lung into the circulation, leading to an increase of the classic systemic inflammatory response that paves the way for the onset of obesity, type 2 diabetes, insulin resistance, and metabolic syndrome [69].

An association between PM2.5 exposure and nonalcoholic fatty liver disease (NAFLD) has also been described, and it is due to the potential of the pollutants to promote cytokines secretion from the Kupffer cells in the liver [15]. Moreover, systemic inflammation induced by inhaled pollutants activates the hypothalamic–pituitary–adrenal (HPA) axis that in turn inhibits somatotropic, thyrotropic, and gonadal axes, all exerting relevant effects on body composition and weight gain [70][71]. Thus, the dysregulation of the HPA axis caused by inhaled pollutants might cause such endocrine perturbations that impact body composition, leading to obesity and non-transmissible chronic disease onset.

Polycyclic aromatic hydrocarbons (PAHs), a family of air pollutants generated during incomplete combustion with both carcinogenic and endocrine-disrupting properties, may also influence obesity development. These substances bind to DNA and might alter the methylation state of PPARγ and PPARγ target genes, therefore acting as "obesogens" [72].

7. Flame Retardants

Flame retardants, such as polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs), are a group of EDCs generally added to manufactured materials, such as plastics, textiles, and surface finishes and coatings to prevent or slow the further development of ignition. A positive association between serum PBDEs and body mass index was found in several studies [73][74][75][76].

An example of how these EDCs can produce epigenetic effects associated with obesity development is given by the flame retardant BDE-47. This compound is responsible for a dose-dependent adipocyte differentiation and a reduction in global DNA methylation levels [36], as demonstrated in the *PPARγ2* gene promoter. Moreover, exposure to BDE-47 generally leads to the increased expression of different adipogenic genes, including leptin gene (*LEP*), although their expression levels are not linked to changes in DNA methylation [77].

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