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Review

Obesogens: Definition, mechanisms of action, potential industrial chemicals and pharmaceuticals

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ABSTRACT

The incidence of obesity and related diseases has increased dramatically in the last decade. Some endocrine disruptors have been shown to interact with metabolic processes via various cellular mechanisms, and disrupt homeostasis in adipose tissue, resulting in weight gain and obesity. These chemicals are called "obesogens". Today, with the increased use of industrial chemicals, individuals are exposed to a mixture of chemicals at very low doses. Most of these industrial chemicals have been investigated for their possible endocrine-disrupting and obesogenic effects. Besides these chemicals, pharmaceuticals can also have similar adverse effects; however, limited studies have been performed to investigate such effects of drugs. Furthermore, there are few studies investigating the relationship between prenatal exposure to pharmaceuticals and childhood obesity. Therefore, to clarify the endocrine-disrupting and obesogenic effects of the pharmaceuticals, which are prescribed during pregnancy, mechanistic studies should be performed, and necessary precautions should be taken. In this paper, we reviewed the mechanisms of obesogens, briefly overview several well-known obesogenic industrial chemicals, and focused more on potential obesogenic pharmaceuticals.

Keywords: Endocrine disruptors, Obesogens, Adipogenesis, Lipogenesis, Pharmaceuticals

Endocrine Disruptors

The endocrine system consists of various glands that are found in many parts of the body, hormones which are secreted from these glands to the bloodstream, and receptors that respond by binding to these hormones (USEPA, 2021). Some natural (such as phytoestrogens and hormones) and/or synthetic chemicals (such as pharmaceuticals, pesticides, plasticizers) can cause adverse health effects by interacting with and disrupting normal functions of this system. These chemicals are called "endocrine disruptors" or "endocrine-disrupting chemicals (EDCs)" and defined by the World Health Organization (WHO) as "an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations" (Bashshur, Mandil, & Shannon, 2002). Recently Autrup et al. noted that "endocrine disruptors" is not a scientific term and suggested using the phrase "chemicals interfering with the endocrine system," which they believe better defines their specific effects (Autrup et al., 2020). They can be transferred to humans through the food chain and stored in fatty tissues. They can also be transferred through the placenta to the developing fetus and disrupt the developmental programming of the offspring even at very low levels (Newbold, Padilla-Banks, Snyder, Phillips, & Jefferson, 2007b). EDCs act through different mechanisms: 1) interacting / activating hormone receptors, 2) antagonizing hormone receptors, 3) modifying receptor expression, 4) altering signal transduction pathways in hormone-responsive cells, 5) leading to epigenetic modifications in hormone-producing / responsive cells, and 6) altering hormone synthesis / transport / distribution / metabolism (La Merrill et al., 2020). In the early 2000s, it was hypothesized that some EDCs may lead to the development of obesity by interacting with adipose tissue

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function. Studies have supported the hypothesis that exposure to these chemicals in the early and late stages of life can lead to the development of obesity (Casals-Casas & Desvergne, 2011; De Cock & Van de Bor, 2014; Newbold, Padilla-banks, Snyder, & Jefferson, 2005).

Obesity and Obesogens

The obesity rates in children, adolescents, and adults have been increasing drastically all around the world (Ritchie & Max, 2017). Obesity has been reported as a pandemic in the last decade (Hill, Wyatt, & Peters, 2012). Besides being an important health problem itself, obesity also is known as a contributory factor in other pathologies, such as insulin intolerance, hyperlipidaemia, depression and cardiovascular diseases (Newbold, Padilla-Banks, Snyder, & Jefferson, 2007a. Obesity is defined as "abnormal or excessive fat accumulation that may impair health" by the WHO and is assessed by Body Mass Index (BMI) (WHO, 2021). Although overeating, lack of physical activity and genetic factors are the main reasons for the development of obesity, these factors alone cannot be responsible for the dramatic increase in obesity and related diseases. Over the last decades the increase in both the use of industrial chemicals and obesity incidence has led to the hypothesis that these chemicals, especially those with endocrine disrupting effects, may be responsible for this dramatic increase by disrupting the processes involved in adipo- and lipo-genesis (Baillie-Hamilton, 2002). The chemicals that disrupt lipid metabolism and alter adipo- and lipo-genesis processes are called "obesogens" (Figure 1) (Grün & Blumberg, 2006a). Since the early stages of life, especially organogenesis, are highly sensitive to low doses of EDCs and obesogens compared to later periods, it has been suggested that exposure to these chemicals during early periods may change metabolic homeostasis and cause increased obesity in children and adolescents (La Merrill & Birnbaum, 2011). For better understanding the role of endocrine-disrupting obesogens especially in early stages of life, the possible mechanisms involved in obesity should be considered.

Mechanisms of Obesogens

Obesogens can alter adipose tissue function and increase adiposity by disrupting various cellular processes, thus they can act through distinct mechanisms. In this review, we will focus on five main mechanisms that can lead to obesity.

Adipogenesis

Adipose tissue is comprised of various cell types, such as endothelial and blood cells, fibroblasts, preadipocytes, adipocytes, and macrophages. Among these, the main adipose tissue-forming cells are mature adipocytes. The process of differentiation of preadipocytes and precursory stem cells to mature adipocytes through a transcriptional cascade is called "adipogenesis" (Sarjeant & Stephens, 2012). Various transcriptional factors are involved in this process (Figure 2). The main and crucial transcriptional factors regulating the adipogenic gene expressions are peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT enhancer-binding protein alpha (C/EBPα) (Miettinen, Sarkanen, & Ashammakhi, 2008). PPARγ is a member of the nuclear receptor superfamily of ligand-activated transcription factors and is mainly expressed in adipose tissue. After forming a heterodimer with retinoid X receptor (RXR), PPARγ binds to its response element on promoter regions of genes and regulates the transcription of target genes involved in adipogenesis by increasing their mRNA expression (Lefterova & Lazar, 2009). C/EBPβ and C/EBPδ are also the regulators of adipogenesis and all of them are expressed in adipocytes. During adipogenesis, C/EBPβ and C/EBPδ together induce the expression of the main regulators PPARγ and C/EBPα. These regulators, mainly PPARγ, bind to the promoter regions of genes and promotes adipogenesis (Moseti, Regassa, & Kim, 2016; Richard, White, Elks, & Stephens, 2000). In addition to these adipogenic regulators, there are pro-adipogenic factors that induce PPARγ expression levels and stimulate adipogenesis. There are also anti-adipogenic factors that suppress the adipogenesis processes in adipocytes (Rosen & MacDougald, 2006; Sarjeant & Stephens, 2012). In brief, obesogens can disrupt this transcriptional cascade in adipocytes and thus lead to fat accumulation, resulting in obesity.

Lipogenesis

Lipogenesis is the formation of fatty acids and triglycerides, which is regulated by hormonal, nutritional and transcriptional factors (Kersten, 2001). Triglycerides are produced mainly in the liver, but they can also be generated minorly in adipocytes. Lipogenesis takes place in adipocytes in two different pathways:

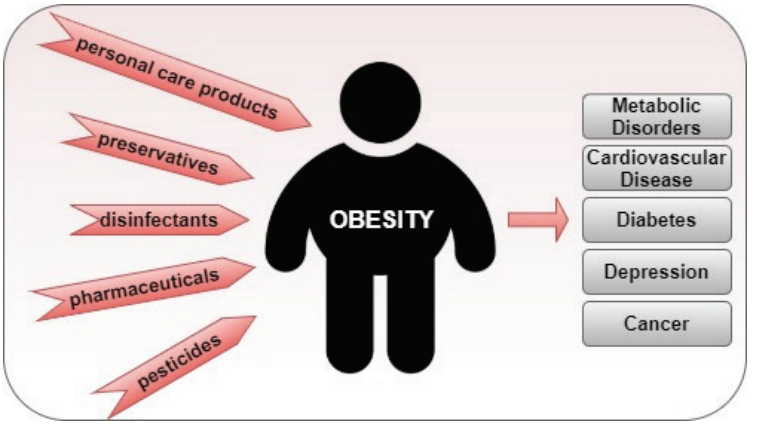

Figure 1. Obesogens and their negative impacts on human health.

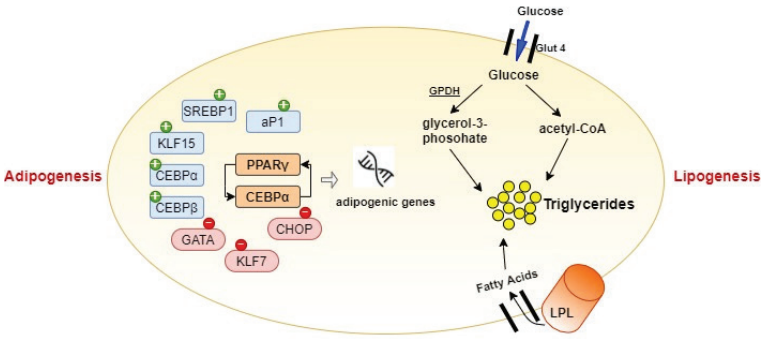

Figure 2. Adipo- and lipo-genesis pathways in adipocytes. PPARγ; peroxisome proliferator-activated receptor gamma, C/EBP; CCAAT/enhancer-binding protein, KLF; kruppel-like factor, aP1; activator protein 1, SREBP1; sterol regulatory element-binding protein 1, CHOP; transcription factor homologous to CCAAT/enhancer-binding protein, GPDH; glycerol-3-phosphate dehydrogenase, LPL; lipoprotein lipase.

1) catabolism of glucose to triglycerides, and 2) conversion of lipoproteins to fatty acids and triglycerides (Figure 2). In the first pathway, circulating glucose enters adipocytes by insulin stimulation and undergoes the glycolysis pathway. Pyruvate formed through glycolysis turns to acetyl-CoA, then enters the Krebs cycle in mitochondria and turns into malonyl CoA via various enzymatic reactions. Malonyl-CoA turns into acyl-CoA, fatty acids, and triglyceride molecules mediated by fatty acid synthase (FAS) and other multiple enzymatic reactions. In addition, glucose is converted into glycerol 3-phosphate by glycerol-3-phosphate dehydrogenase (GPDH) enzyme in the glycolysis pathway and finally turns into triglyceride molecules with further reactions (Romao & Guan, 2014; Vernon & David J. Flint, 2011). Lipoprotein lipase (LPL) is an important enzyme found in adipose tissue, secreted by adipocyte cells, and bound to capillary endothelium. In the second pathway of lipogenesis, circulating lipoproteins formed in the liver are hydrolysed by LPL and turned into fatty acids and monoacylglycerol. These fatty acids are taken into adipocyte cells and accumulate in these cells in the form of triglycerides (Richard et al., 2000). Obesogens can disrupt glucose metabolism in adipocytes and change gene transcription of key enzymes involved in lipogenesis, causing excessive lipid accumulation and increasing the size and number of adipocytes (Chamorro-García et al., 2013; Yang et al., 2018).

Estrogen and estrogen receptor mediated mechanisms

Estrogen is the key hormone involved in the development of female reproductive organs. In postmenopausal women, while estrogen synthesis in ovaries is diminished, its local synthesis in adipose tissue is increased (Mauvais-Jarvis, 2011). Physiologically, estrogen binds to the nuclear estrogen receptor (ER) in cells and the ER signaling pathway is activated by the binding of this homodimer to the estrogen response element in promoter regions of related genes. Estrogen can also regulate gene expression indirectly via binding to the G-protein coupled ER (GPER) located on the cell membrane (Sharma & Prossnitz, 2021). GPER is expressed in various tissues, such as the liver, reproductive organs and adipose tissue (Sharma & Prossnitz, 2017). While reproductive functions are regulated by nuclear ERs, energy homeostasis and metabolic processes are mainly modulated by GPER (Mauvais-Jarvis, 2011). Studies have shown increased fat accumulation, adiposity and body weight in GPER knockout mice (Davis et al., 2014; Sharma et al., 2013). The possible reason for this is reported as a decrease in thermogenic gene expression and leptin hormone sensitivity (Davis et al., 2014). Pre-adipocyte 3T3-L1 cell line also expresses GPER. One study reported that lipogenesis is inhibited and accordingly fat accumulation is reduced by incubating the cells with estradiol (Zhu, Yuen, Sham, & Cheng, 2013).

It has been shown that estrogen also regulates lipid metabolism in adipose tissue and inhibition of estrogen synthesis in ovariectomized mice, resulting in obesity (Pedersen, Børglum, Mø11er-Pedersen, & Richelsen, 1992). Estradiol treatment in 3T3-L1 cells *in vitro* and ovariectomized animals *in vivo* was found to reduce fat accumulation by inhibiting LPL expression and lipogenesis (Homma et al., 2000). Estradiol is reported to exert biphasic effects, decreasing LPL expression at high concentrations while increasing it at low concentrations (Palin et al., 2003). Obesogens can cause adiposity and lipid accumulation by changing the expression of ERs, altering estrogen hormone levels, mimicking these hormones, and thus leading to weight gain through these mechanisms.

Glucocorticoid mediated mechanisms

Glucocorticoids (GCs) are hormones that are secreted from the adrenal gland and regulated by the adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH). GCs play roles in various physiological processes, such as regulation of blood pressure, modulation of key enzymes involved in lipid and glucose metabolism, and anti-inflammatory reactions (Moraitis, Block, Nguyen, & Belanoff, 2017). GCs produce biological responses by binding to cytosolic glucocorticoid receptors (GRs). Thereafter, ligand-bound complex is transferred to the nucleus and regulates the expression of genes by binding to the specific glucocorticoid response elements (Heitzer, Wolf, Sanchez, Witchel, & DeFranco, 2007). GCs have been shown to stimulate adipogenesis locally in adipocytes and promote their proliferation (Wu, Bucher, & Farmer, 1996). Therefore, in adipogenesis assays GCs are often used as adipogenic agents. Cortisol secretion elevates as a result of the increase in positive feedback of hypothalamic pituitary adrenal (HPA) axis with obesity (Peeke & Chrousos, 1995). The underlying mechanism of hypercortisolism in obese patients is described as increased levels of 11β-hydroxysteroid dehydrogenase type-1 (11βHSD1) enzyme, which is responsible for converting the inactive form, cortisone, to the active form , cortisol (Rask et al., 2001; Wake et

al., 2003). Another possible mechanism for the involvement of the glucocorticoid pathway in obesity is corticosteroid binding globulin (CBG) deficiency in obese individuals. With the decrease in CBGs, excess cortisol levels cannot be cleared, causing increased proliferation of mature adipocytes (Janesick & Blumberg, 2012). In brief, obesogens may lead to obesity by interacting with the HPA axis, competing with ligands binding to GR, or by disrupting the GC pathway by altering expression of key enzymes and modulating lipid metabolism as described.

Epigenetics

Genetic factors are also known to play an important role in the development of obesity. However, genetics alone are unlikely to be responsible for the dramatic increase in worldwide obesity cases in such a short time. Therefore, the risk of obesity seems to be increasing as a result of the interaction between environmental and genetic factors (Obri, Serra, Herrero, & Mera, 2020). Environmental factors can induce epigenetic modifications through changing gene activities by causing structural changes in genes associated with weight gain, without any changes in DNA sequences (Stger, 2008). The main epigenetic modifications are: 1) DNA methylation (addition of a methyl group to the 5th carbon of a cytosine), 2) histone modifications (changes in chromatin structures by post-translational modifications of histone proteins), 3) interference of non-coding RNAs (regulation of post-transcriptional gene expression through different mechanisms such as negative regulation of mRNA degradation, chromatin remodeling) (Obri et al., 2020). Some obesogens can cause changes in the expression of key genes which play roles in adipo- and lipo-genesis pathways via these modifications (Janesick & Blumberg, 2012). As EDCs bind to nuclear receptors, they can alter the epigenetic programming of obesity via changes in chromatin structure. As described above, PPARγ is a key factor for adipogenesis and regulates the expression of genes involved in this pathway. Some EDCs which are PPARγ ligands can cause obesogenic effects via one of the described epigenetic modifications in PPARγ or target genes (Stel & Legler, 2015). For example, tributyltin, a well-known obesogen, has been demonstrated to cause a decrease in methylation of PPARγ or target genes and consequently results in abnormal genomic responses and obesogenic effects (Bastos Sales et al., 2013). Furthermore, exposure to obesogens in the early stages of life may cause epigenetic changes that lead to transgenerational effects (Rissman & Adli, 2014).

Detection of Obesogens

To investigate the mode of action of possible obesogens, various *in vitro* and *in vivo* models are used. In this review we summarized the frequently used models. *In vitro* models are commonly preferred because of their simplicity, cost effectiveness and advantage of high-throughput screening. 3T3-L1 mouse embryo fibroblast cells are pre-adipocytes and commonly used in *in vitro* obesogen screening studies. In a proper growth media, these cells have the ability to differentiate into mature adipocytes which accumulate triglycerides (OECD, 2012). Mouse bone marrow-derived mesenchymal stem cells are also used widely in adipogenesis assays (Janesick et al., 2016). The difference of species can cause difficulties in extrapolation of the results to humans and might be a disadvantage for the use of 3T3-L1 and mouse-derived stem cells (Griffin, Pereira, DeBari, & Abbott, 2020). Human adipose-derived mesenchymal stem cells are also preferred in the *in vitro* model (Cohen, Cohenour, Harnett, & Schuh, 2021; Foley, Clewell, & Deisenroth, 2015) which does not need an extrapolation step. Besides *in vitro* models, animal models are important to study the kinetics and systemic effects of the obesogenic compounds. Rodents are widely used to detect the obesogenic effects of chemicals. Frequently C57BL/6J (Chu, Malinowska, Jura, & Kozak, 2017; Koya & Kanasaki, 2011) and CD1 mice (Moazzam, Jarmasz, Jin, Siddiqui, & Cattini, 2021; Newbold, Padilla-Banks, Jefferson, & Heindel, 2008) are used as *in vivo* models for obesity studies. For better understanding the mechanisms of the action of the obesogenic compounds, all information from *in vitro* and *in vivo* models should be combined.

Industrial Chemicals as Possible Obesogens

The number and use of industrial chemicals are increasing day by day. Thus, the chances of individuals being exposed to these chemicals at very low doses in their daily lives are getting higher (Figure 1). Some chemicals such as pesticides, food preservatives and plasticizers are investigated largely in terms of their endocrine-disrupting and obesogenic effects. Comprehensive reviews have been published summarizing all studies (Darbre, 2017; Gupta et al., 2020). Therefore, only the well-known obesogens bisphenol A, phthalates, and tributyltin are reviewed in this section (Table 1).

Tributyltin

Tributyltin (TBT) is used in various fields of industry and is the most studied organotin compound with obesogenic effects. Due to its lipophilic properties, TBT bioaccumulates in animal and human tissues and can be transferred to the developing fetus through the placenta. TBT has one of the best-understood modes of action among obesogens, as a nanomolar affinity ligand of the PPARγ and RXR (Darbre, 2017). *In vitro* studies have shown that TBT increases preadipocyte differentiation and this effect is mediated by the activation of PPARγ (Kanayama, Kobayashi, Mamiya, Nakanishi, & Nishikawa, 2005; Kirchner, Kieu, Chow, Casey, & Blumberg, 2010; Li, Ycaza, & Blumberg, 2011). *In vivo* studies with TBT have shown that prenatal exposure in mice induces obesity in male and female offspring by increasing adipogenesis through PPARγ activation (Grün et al., 2006b. In addition, transgenerational obesogenic effects were observed in a multigenerational study *in vivo*. After female mice were exposed to TBT during pregnancy, an increase in adipose tissue weight, adipocyte hypertrophy and hyperplasia, and hepatic lipid accumulation were observed in the exposed F1 and F2 generations as well as the unexposed F3 generation (Chamorro-Garcia et al., 2017; Chamorro-García et al., 2013). To summarize, as an industrial product, TBT is a well-known obesogen that has been shown to exert its obesogenic effects through PPARγ and RXR activation.

Bisphenol A

Bisphenols are synthetic lipophilic chemicals widely used in the plastic industry. The most studied member, bisphenol A (BPA), is found in water bottles and food containers (Darbre, 2017). BPA was shown to induce the differentiation of preadi-

pocyte 3T3-L1 cells into mature adipocytes *in vitro* (Ahmed & Atlas, 2016; Masuno et al., 2002). Prenatal BPA exposure in mice showed adipogenic effects in the offspring (Manikkam, Tracey, Guerrero-Bosagna, & Skinner, 2013; Rubin et al., 2017; Somm et al., 2009). Somm et al. showed that increased adipose tissue weight of the female pups is associated with the overexpression of proadipogenic transcription factors. The majority of these proadipogenic genes upregulated by exposure to BPA are transcriptional targets of PPARγ itself, thus this connection between BPA and PPARγ needs to be better explored (MacKay & Abizaid, 2018). Like tributyltin, BPA induced transgenerational adipogenic effects *in vivo* (Manikkam et al., 2013; Rubin et al., 2017). A prospective epidemiological study has found no association between BPA levels and adipose tissue mass or lipid distribution, but a positive correlation between BPA levels and circulating levels of leptin and adiponectin. Changes in blood levels of these hormones suggest that BPA might exert its obesogenic effects by interfering with the hormonal control of satiety and hunger (Rönn et al., 2014). In summary, the obesogenic effect of BPA is demonstrated in experimental studies; however, the mechanism(s) underlying the obesogenic effect of BPA needs to be better elucidated.

Phthalates

Phthalates are used as industrial plasticizers. Important routes of human exposure include oral, inhalation and dermal routes, and placental transfer from the mother to the developing fetus. Experimental studies have focused mainly on diethylhexyl phthalate (DEHP) and its metabolite monoethylhexyl phthalate (MEHP). DEHP is short-lived and rapidly converted to MEHP by hydrolysis of one of the ester groups in the body (Casals-Casas & Desvergne, 2011). MEHP is a potent agonist of PPARγ (Maloney & Waxman, 1999) and was shown to increase preadipocyte differentiation *in vitro* (Feige et al., 2007). Prenatal exposure to DEHP caused increased body weight, visceral fat mass, circulating leptin, insulin, and glucose levels in mice (Hao, Cheng, Guo, Xia, & Ma, 2013). In a cross-sectional study, blood levels of several phthalate metabolites showed a positive correlation with abdominal obesity and insulin resistance in males (Stahlhut, Wijngaarden, Dye, Stephen, & Swan, 2007). In conclusion, phthalates are found in many products and are shown to induce adipogenesis mainly through PPARγ activation.

Table 1. Summary of the known obesogenic chemicals / pharmaceuticals and their mode of actions.

Obesogens	Mode of action	References
Tributyltin	-PPARγ and RXR activator adipogenesis ↑ -transgenerational effects	(Kanayama et al., 2005; Li et al., 2011) (Chamorro-Garcia et al., 2017; Chamorro-García et al., 2013)
Bisphenol A	-adipogenesis ↑ -increased expression of proadipogenic factors -transgenerational effects -elevated serum leptin and adiponectin levels	(Ahmed & Atlas, 2016; Masuno et al., 2002) (Somm et al., 2009) (Manikkam et al., 2013; Rubin et al., 2017) (Rönn et al., 2014)
Phthalates	-PPARγ activator -adipogenesis↑ -weight gain -visceral fat mass, serum leptin, insulin, glucose levels ↑ -abdominal obesity, insulin resistance	(Maloney & Waxman, 1999) (Feige et al., 2007) (C. Hao et al., 2013) (Stahlhut et al., 2007)
Diethylstilbestrol	-PPARγ activator -adipogenesis↑ -lipogenesis↑ -weight gain -serum TG, leptin, glucose ↑	(Newbold, Padilla-Banks, Snyder, Phillips, et al., 2007b) (Hao, Cheng, Xia, & Ma, 2012b)
Thiazolidinediones	-PPARγ activator -adipogenesis ↑ -LPL ↑ -weight gain -BMI ↑	(Lehmann et al., 1995) (McTernan et al., 2002) (Mori et al., 1999)
Selective Serotonin Reuptake Inhibitors	-weight gain	(Arterburn et al., 2016; Blumenthal et al., 2014; Gafoor et al., 2018)
Atypical Antipsychotics	-lipogenesis↑ -impaired glucose, insulin tolerance -weight gain	(Raeder, Fernø, Vik-Mo, & Steen, 2006; Yang, Chen, Yu, & Chen, 2007) (Lord et al., 2017; Albaugh et al., 2011) (Verhaegen & Van Gaal, 2017)

PPARγ; peroxisome proliferator-activated receptor gamma, RXR; retinoid X receptor, TG; triglyceride, LPL; lipoprotein lipase, BMI; body mass index.

Pharmaceuticals as Possible Obesogens

Besides industrial chemicals, pharmaceuticals, which are generally used intentionally, might be potential obesogens and cause weight gain and obesity. Although several pharmaceuticals are reported to have either endocrine mediated adverse effects (such as gynecomastia, cryptorchidism, and sexual dysfunction) or effects on body weight, limited studies are performed to investigate their possible endocrine-related obesogenic potential. In this section, the potential pharmaceutical obesogens diethylstilbestrol, thiazolidinediones, selective serotonin reuptake inhibitors and atypical antipsychotics have been reviewed (Table 1).

Diethylstilbestrol (DES)

Diethylstilbestrol, a synthetic estrogen, is a well-known endocrine disruptor that was used against miscarriages during pregnancy between the 1940s – 1970s. Although it was reported to be ineffective for miscarriages in 1953, it continued to be prescribed until the 1970s (Schrager & Potter, 2004). Mothers who used DES during pregnancy were found to have an increased risk of breast cancer (Greenberg et al., 1984). Daughters exposed to DES *in utero* were demonstrated to develop vaginal and cervical cancers (Hoover et al., 2011). Moreover, urogenital abnormalities such as cryptorchidism and inflammation of the testes were associated with prenatal DES exposure in sons of the exposed mothers (Palmer et al., 2009). Recently, DES is also suggested to be a potent obesogen by disrupting lipid and glucose metabolism (Alonso-Magdalena et al., 2005; Newbold, Padilla-Banks, Snyder, & Jefferson, 2007a). Hao et. al. found that DES significantly induces adipogenesis and preadipocyte differentiation in 3T3-L1 cell lines and induces lipogenesis and triglyceride accumulation via increasing GPDH activity (Hao, Cheng, Xia, & Ma, 2012a). They also treated C57BL/6J mice prenatally with DES and observed increases in body weight, serum triglyceride and glucose levels, and induced expression of PPARγ and adipogenic genes. Newbold et. al. indicated that exposure to DES in early stages of development results in obesity later in life (Newbold, Padilla-Banks, Snyder, Phillips, et al., 2007b). They found enhanced body weight, serum insulin, triglyceride, leptin and adiponectin levels, and impaired glucose tolerance in prenatally treated CD1 mice. In an epidemiological cohort study, an association between prenatal DES exposure and obesity development in adult women was reported (Hatch et al., 2014). In another prospective pregnancy cohort study, use of DES was found to be associated with childhood obesity (Jensen & Longnecker, 2014). Consequently, DES is a model pharmaceutical product for obesity-related studies, and it has been suggested that exposure to some pharmaceuticals prenatally may cause obesogenic effects and related metabolic disorders later in life.

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs) are insulin-sensitizing agents that were developed against type 2 diabetes mellitus. Rosiglitazone, troglitazone and pioglitazone are members of TZDs that decrease insulin resistance. Troglitazone has been withdrawn due to its hepatotoxicity and rosiglitazone use has been restricted because of its potential to increase cardiovascular risks (Lebovitz, 2019). *In vitro* studies have shown that TZDs are potent PPARγ agonists that promote adipogenesis in preadipocytes and mesenchymal stem cells (Fürnsinn & Waldhäusl, 2002; Hausman, Poulos, Pringle, & Azain, 2008; Lehmann et al., 1995). Troglitazone was shown to induce the differentiation and proliferation of 3T3-L1 cell lines in the presence of a suitable hormone cocktail and increase the expression of the adipogenic key regulator C/EBPα (Tafuri, 1996). *In vitro* studies with rosiglitazone demonstrated that this anti-diabetic agent promotes differentiation of the preadipocytes via increasing the expression levels of LPL and this can be the possible reason behind weight gain with rosiglitazone treatment (McTernan et al., 2002). Krichner et.al. showed an increase in lipid accumulation and differentiation capacity of adipose-derived stromal stem cells in 8-week old C57BL/6j mice, which were exposed to rosiglitazone *in utero* (Kirchner et al., 2010). Haliakon et. al. demonstrated increased body weight in rats treated with pioglitazone and they commented that pioglitazone stimulates the adipocyte differentiation with the induction of adipogenic factors, especially C/EBPα (Haliakon et al., 1997). In a study with type 2 diabetes mellitus patients, troglitazone treatment caused a significant increase in BMI and subcutaneous fat rather than visceral fat (Mori et al., 1999). Moreover, epidemiological studies have shown that treatment with pioglitazone also causes significant increases in the body weight of the patients (Aghamohammadzadeh et al., 2015; Chawla, Kaushik, Singh, Ghosh, & Saxena, 2013). Thus, this group of antidiabetics is known to increase body weight due to their agonistic effects, especially on PPARγ in adipose tissue.

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are among the most prescribed antidepressants worldwide, and members of this pharmaceutical group are sertraline, citalopram (and its S-stereoisomer escitalopram), fluoxetine, fluvoxamine, and paroxetine (Hansen, Larsen, Sørensen, Halling-Sørensen, & Styrishave, 2017). SSRIs exert their pharmacological effect by inhibiting the reuptake of serotonin in the presynaptic neuron, thus elongating the effect of serotonin in the synaptic cleft. Recent *in vitro* and *in vivo* studies have demonstrated that SSRIs might have ED effects. In two different microsome-based *in vitro* activity assays, five SSRIs were shown to reduce the estrogen level by inhibiting the aromatase enzyme (Jacobsen, Hansen, Nellemann, Styrishave, & Halling-Sørensen, 2015). All five SSRIs were found to disrupt steroid hormone synthesis in *in vitro* steroidogenesis assay performed with the H295R cell line (Hansen et al., 2017; Jacobsen et al., 2015). In male rats, sertraline was found to inhibit the production of steroid hormones in the testis and adrenal glands (Munkboel, Larsen, Weisser, Kristensen, & Styrishave, 2018), and cause a decrease in sperm count and motility *in vivo* (Atli et al., 2017). Müller et al. reported *in vivo* and *in vitro* estrogenic activity of fluoxetine (Müller et al., 2012). Following the results by Müller et al., Montagnini et al. conducted a similar experiment and showed that sertraline and escitalopram had no effect on the uterus weight, thus they suggested that sertraline and escitalopram did not show *in vivo* estrogenic activity described for fluoxetine (Montagnini et al., 2013). In epidemiological studies, sexual dysfunction was reported in 30-60% of the patients using SSRIs (Gre-

gorian Jr, Golden, Bahce, Goodman, & Kwong, 2002). Another epidemiological study reported alteration in hormone levels such as a decrease in testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) levels and an increase in prolactin hormone levels in adult men receiving SSRI treatment (Safarinejad, 2008). Epidemiological studies also showed long-term treatment with SSRIs causes weight gain in adults (Arterburn et al., 2016; Blumenthal et al., 2014; Gafoor, Booth, & Gulliford, 2018). However, there are no *in vitro* nor *in vivo* studies in the literature investigating the mechanism of these effects or showing a relationship between prenatal exposure to SSRIs and their possible effects on obesity later in life.

Atypical antipsychotics (AAs)

Atypical antipsychotics (AAs) are relatively newer antipsychotics, preferred in the treatment of various psychiatric disorders due to their limited neurological side effects. AAs exert their pharmacological effects by antagonizing 5-HT2 receptors as well as dopamine D2 receptors, and thus, have a better side-effect profile than typical antipsychotics. However, *in vitro* studies have demonstrated that clozapine and olanzapine induce SREBP mediated lipogenesis in cultured human liver cells (Raeder, Fernø, Vik-Mo, & Steen, 2006) and 3T3-L1cells (Yang, Chen, Yu, & Chen, 2007). Olanzapine administration resulted in impaired glucose tolerance, increased food intake, altered physical activity and energy expenditure in female mice (Lord et al., 2017). Another *in vivo* study with male rats showed that olanzapine administration impaired glucose and insulin tolerance, and increased adipose tissue mass, however, did not increase body weight or food intake (Albaugh et al., 2011). In epidemiological studies, AAs are shown to cause weight gain in 80% of the patients. The mechanisms behind these effects are unknown, although a recent study suggested that AAs might affect the hormonal control of satiety and hunger through the hypothalamus and alter food intake, leading to excessive calorie consumption and obesity, as well as exacerbation of insulin resistance (Verhaegen & Van Gaal, 2017).

Future Directions

All around the world, people are exposed to chemicals and pharmaceuticals both unintentionally and intentionally. These exposures are not only limited to adults, but children and even developing fetuses can also be affected. Many pharmaceuticals, such as analgesics, antibiotics and antidepressants, can be used during pregnancy, and many of these drugs are known to pass through the placenta to the developing fetus. Possible teratogenic effects of the pharmaceuticals are tested preclinically during the drug development process. However, prenatal exposure may lead to adverse effects like endocrine modulation and/or obesogenic effects, that may emerge later in life. In the early 2000s, it was hypothesized that prenatal exposure to chemicals and/or pharmaceuticals may play an important role in childhood obesity and related metabolic syndrome (Casals-Casas & Desvergne, 2011; De Cock & Van de Bor, 2014; Janesick & Blumberg, 2011).

Paracetamol is known as a "safe" drug and is commonly prescribed during pregnancy for pain relief. However, recent *in vitro* and epidemiological studies have shown it that may have endocrine-disrupting effects, such as decreased testosterone secretion, impaired semen quality in men, and reduced anogenital distance in sons exposed prenatally (Albert et al., 2013; Buck Louis, Chen, Kim, Smarr, & Kannan, 2017; Lind et al., 2017). In addition, an epidemiological study has demonstrated a positive relationship between prenatal exposure to paracetamol and childhood obesity (Murphy et al., 2015). However, contradictory results are also reported; Liew et. al. have found no significant association between the use of paracetamol and childhood obesity (Liew et al., 2019). Therefore, there are conflicts about the relationship between prenatal paracetamol exposure and obesity, and no *in vitro* and *in vivo* mechanistic studies have been reported so far. Similarly, as detailed above, various epidemiological studies have reported that some SSRIs might cause weight gain in adults but no reports showing the relationship between prenatal exposure and childhood obesity have been reported (Arterburn et al., 2016; Blumenthal et al., 2014; Gafoor et al., 2018). Another drug, used commonly during pregnancy against preeclampsia, is alpha-methyldopa and is shown to have endocrine-related adverse effects such as gynecomastia in epidemiological studies (Piersma et al., 2009). However, its potential for endocrine-disrupting and obesogenic effects in children who were exposed prenatally have not been investigated. As such, to prevent childhood obesity and related diseases, the endocrine-disrupting and obesogenic effects of other pharmaceuticals, especially the ones widely used during pregnancy, should be investigated.

In conclusion, many studies have mostly focused on the potential endocrine-disrupting and obesogenic effects of industrial/environmental chemicals and their adverse effects on human health but there are few studies investigating such effects of commonly prescribed drugs during pregnancy and their role in childhood obesity. With further studies, effects of these drugs should be investigated, and mechanistic studies should be performed to enlighten their mode of action.

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