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Metabolism disrupting chemicals and metabolic disorders

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ABSTRACT

The recent epidemics of metabolic diseases, obesity, type 2 diabetes(T2D), liver lipid disorders and metabolic syndrome have largely been attributed to genetic background and changes in diet, exercise and aging. However, there is now considerable evidence that other environmental factors may contribute to the rapid increase in the incidence of these metabolic diseases. This review will examine changes to the incidence of obesity, T2D and non-alcoholic fatty liver disease (NAFLD), the contribution of genetics to these disorders and describe the role of the endocrine system in these metabolic disorders. It will then specifically focus on the role of endocrine disrupting chemicals (EDCs) in the etiology of obesity, T2D and NAFLD while finally integrating the information on EDCs on multiple metabolic disorders that could lead to metabolic syndrome. We will specifically examine evidence linking EDC exposures during critical periods of development with metabolic diseases that manifest later in life and across generations.

1. Introduction

Metabolic syndrome (MetS) is a complex condition characterized by insulin resistance, abdominal obesity, dyslipidemia, hypertension, and hyperglycemia; it is a risk factor for cardiovascular disease, T2D, stroke, chronic kidney disease and cancers [1,2]. Its prevalence is increasing along with the increase in obesity, and it is reaching epidemic proportions affecting between 24% and 34% of the adult US population [3].

In the medical community, epidemics of metabolic diseases have largely been attributed to genetic background and changes in diet, exercise and aging. However, there is now considerable evidence that other environmental factors may contribute to the rapid increase in the incidence of obesity, T2D and other aspects of MetS observed over the past three decades [4]. One environmental factor that has begun to receive attention is a class of chemicals that can interfere with the action of hormones including metabolic hormones. These compounds, termed EDCs, are found in a wide variety of consumer products, and exposures are often widespread [5] Of particular concern is evidence that exposure to EDCs during critical periods when adipocytes are differentiating and the pancreas, liver, brain, etc. are developing can induce effects that manifest later in life, often as overt disease.

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This review will examine changes to the incidence of obesity, T2D and NAFLD and its associated hyperlipidemia, the contribution of genetics and describe the role of the endocrine system in these metabolic disorders. It will then specifically focus on the role of EDCs in metabolic diseases, focusing on their role in the etiology of obesity, T2D and NAFLD while finally integrating the information on EDCs on multiple metabolic disorders that could lead to MetS. We will specifically examine evidence linking EDC exposures during critical periods of development with metabolic diseases that manifest later in life and across generations.

2. Metabolic diseases

2.1. Obesity

Obesity is a global epidemic that affects infants, children and adults [6]. The global prevalence of obesity has nearly doubled over the past three decades and in the US it is the highest recorded in human history [7]. For the first time worldwide, the number of obese and overweight people is greater than the number of those who are underweight [8]. This dramatic increase in the rate of abdominal obesity has been observed in both developed and developing countries [9,10].

Obesity among children and adolescents has similarly increased [6]. Approximately one third of US children are overweight or obese, and over 60% of obese children will become obese adults [11]. There is also an obesity epidemic among infants six months of age and younger; an age group where food choices and limited physical activity cannot explain this outcome [12].

The obesity epidemic is not limited to humans but has also been observed as upward trends in body weight among primates and rodents living in research colonies, as well as among feral rodents, horses and domestic dogs and cats [13].

Staggering health care costs are associated with treating the co-morbidities that typically accompany obesity [14] including cardiovascular disease, hypertension, dyslipidemia, liver and gallbladder disease, insulin resistance, hyperglycemia and T2D [9]. Obesity is also associated with neurodegenerative diseases, cancers and obstructive sleep apnea. Thus, determining the factors that contribute to obesity has become a major public health issue.

2.2. Type 2 diabetes

The American Diabetes Association (ADA) defines Diabetes Mellitus (DM) as: "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" [15]. DM can result from a deterioration in function and/or a loss of mass of pancreatic tissue [16]. T2D (formerly known as adult-onset or non-insulin-dependent diabetes or DM) accounts for 90–95% of diabetes cases and is characterized by increased insulin resistance and pancreatic beta cell dysfunction. More than 11% of individuals in the US older than 20 have diagnosed or undiagnosed T2D [7] and another 35% are estimated to be pre-diabetic. The World Health Organization (WHO) estimates that 347 million people globally suffer from diabetes (90% of which is T2D) [17]. Adolescents and even children have experienced significant increases in the prevalence of this disease over short periods [14,18].

Obesity is the main environmental factor driving the increased incidence of T2D; 70% of the risk associated with T2D is related to weight gain. Obesity is associated with insulin resistance that promotes beta cell proliferation, leading to hyperinsulinemia typical of early stages of T2D and MetS. However, obesity is neither necessary nor sufficient to cause T2D; these conditions can occur independently. Indeed, 20% of adults with T2D were not overweight and 57% of obese individuals do not have T2D [19].

2.3. Nonalcoholic fatty liver disease and hyperlipidemia

Liver is the central organ for lipid metabolism. Nonalcoholic fatty liver disease (NAFLD), characterized by excess triglyceride accumulation within hepatocytes, or steatosis, is considered by some to be the hepatic manifestation of obesity and MetS. NAFLD is the most common liver disease, and it affects 25% of the global population [20] and almost 8% of children [21]. NAFLD and its more severe form, nonalcoholic steatohepatitis (NASH), are associated with increased liver-related and overall mortality [20], and NAFLD is a risk factor for cardiovascular disease [22]. The metabolic condition most commonly associated with NAFLD is hyperlipidemia (69%), although NAFLD is also associated with obesity (51%), MetS (43%) and T2D (23%) [20]. NAFLD was initially thought to occur predominantly in women [23] but increasing evidence indicates that males and perhaps post-menopausal females are more susceptible to NAFLD [21,24].

Hyperlipidemia is an elevation in blood triglycerides (hypertriglyceridemia), cholesterol (hypercholesterolemia), phospholipids, or a combination thereof. While there is an association between NAFLD and hyperlipidemia, not all patients with one disorder are affected by the other. The prevalence of hypertriglyceridemia in US adults is 25%, although it declined from 33% in 2001–2004 [25]. Total and LDL cholesterol have also been declining, and these favorable changes may be attributed to increased awareness and utilization of lipid lowering medications [26]. Among adolescents and US children, the prevalence of hyperlipidemia was 20% (1999–2012) [27].

2.4. Metabolic syndrome

The International Diabetes Federation estimates that 20–25% of the world's adult population have MetS, which it defines as: "a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure" (https://www.idf.org/metabolic-syndrome). The etiology of MetS is still a matter of research but insulin resistance and central obesity are significant contributors. Although there is still substantial debate, it is likely that components of MetS arise from insulin resistance. When insulin resistance occurs, there is an increase of fasting glucose and impaired glucose tolerance, often due to the abnormal expression of gluconeogenic enzymes. This metabolic state induces further insulin release, ultimately resulting in hyperinsulinemia. Hyperinsulinemia then simulates transcription factors such as Srebp-1c in the liver, which drive hypertriglyceridemia and hepatic steatosis [28]. In addition, the overproduction and secretion of insulin by pancreatic β-cells can result in their exhaustion and death, initiating the onset of T2D. The most prevalent form of insulin resistance is associated with abdominal obesity and dysfunction of adipose tissue, indicating an important central role for obesity in MetS.

2.5. Genetic contributions to metabolic diseases

2.5.1. Genetic factors in obesity

While the hereditary origins of obesity have long been assumed, a genetic contribution to obesity became evident only in the last two decades [29]. Evidence from twins and animal studies indicates that genetic factors account for 40–70% of the variation in BMI [30–33]. Although several single genes are linked to obesity, studies have confirmed that the genetic basis of high BMI is mainly polygenic (i.e., resulting from polymorphisms in several genes that are associated with appetite and metabolism) or results from single nucleotide polymorphisms [SNPs] rather than a single gene mutation [34]. Three SNPs are significantly related to obesity: one in FTO (fat mass and the obesity-associated gene), one near

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TMEM18 (transmembrane protein 18) and one near *MC4R* (melatocortin 4 receptor) [29,34–36]. Only rare forms of obesity, usually parts of genetic syndromes, result from a single gene mutation or chromosomal abnormalities such as Prader- Willi and Bardet-Biedl syndromes [37]. Because many people who carry genetic variants linked to increased BMI are not obese, it is anticipated that other environmental factors can influence these genetic predispositions.

2.5.2. Genetic factors in diabetes

Genetic factors are involved in the development of both type 1 and T2D. The most prominent genetic factor known to be associated with type 1 diabetes is located in the region of chromosome 6 that contains the highly polymorphic HLA class II genes and controls immune responsiveness [38]. Recently, whole-genome investigations have detected more than 20 other genetic variants associated with type 1 diabetes [39].

Twin and family studies have provided strong evidence that T2D also has a solid genetic predisposition [40–42]. Genome wide association studies (GWAS) identified genetic variants associated with T2D; most of the loci identified are related to lipid metabolism, obesity and β-cell pathways [43,44]. *TCF7L2* demonstrated the strongest effect of >70 loci associated with the disease [43]. Similar to the genetic basis for obesity, it is assumed that predisposition to T2D involves multiple genes and SNPs.

2.5.3. Genetic factors in lipid disorder metabolism

Genetic predisposition to several lipid metabolism disorders was demonstrated based on twin and family studies with estimates that 40% to 80% of the variance in blood lipid levels results from genetic polymorphisms [45–47]. Familial hypercholesterolemia is an autosomal dominant disease characterized by elevated blood low-density lipoprotein levels (LDL). More than 150 mutations in the LDL receptor gene and in genes encoding the proteins apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9) and low density lipoprotein receptor adaptor protein 1 (LDLRAP1) that interact with the LDL receptor, are associated with the disease [48,49].

High levels of very low-density lipoprotein (VLDL) and triglycerides characterize hypertriglyceridemia. The hereditary form of this disease can result from mutations in genes that regulate the metabolism of triglyceride rich lipoproteins such as apolipoprotein A5 (APOA5) LPL, apolipoprotein C2 (APOC2), lipase maturation factor-1 (LMF1) and glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1). Hypobetalipoproteinemia is an autosomal dominant disease associated with low levels of LDL cholesterol and APOB-containing lipoproteins. Mutations in APOB and PCSK9 genes are common among patients [50].

2.5.4. Genetic factors in NAFLD

Genetics have also been shown to contribute to variability in the occurrence of NAFLD [51]. In recent years, GWAS have identified two major genetic determinants associated with NAFLD. The most significant genetic linkage identified to date is a SNP in the gene patatin-like phospholipase domain-containing 3 (PNPLA3), a gene involved in the remodeling of hepatocellular lipid droplets [52]. This variant alters the mobilization of fatty acid, inhibits the activity of lipases and can cause hepatocellular accumulation of triglycerides [53]. Carriers of this genetic variant have increased susceptibility to liver damage when exposed to environmental stressors [53]. Another SNP in transmembrane six superfamily member 2 (TM6SF2) has been linked with NAFLD. This gene variant is located on chromosome 19 and associated with increased hepatic triglyceride content and lower serum lipoproteins [54,55].

3. Overview of tissues and hormones controlling metabolism

The endocrine system controls the tissues and organs that regulate weight and metabolism. Hormones and growth factors including estrogens, androgens, glucocorticoids, insulin and thyroid hormones (among others) regulate the pathways that control the number and content of adipocytes as well as appetite, satiety and energy balance [56–59]. Other hormones affect metabolism via actions in the gastrointestinal tract [ghrelin, cholecystokinin (CCK), glucagon like peptide (GLP-1)], the pancreas (insulin, glucagon), muscle (insulin), liver (glucagon, insulin, FGF21), adipose tissue (leptin, adiponection, and a variety of other factors), immune system, and brain [Neuropeptide Y (NPY), agouti related protein (AgRP), pro-opiomelanocortin (POMC), alpha melanocyte-stimulating hormone (alpha MSH)] [56–60]. These and other hormones, growth factors and neurotransmitters control the hedonic pathways in the brain that regulate food reward mechanisms, food cravings and addiction [61–63]. They also control glucose and lipid levels via pancreatic, muscle and liver responses. The pancreas responds to rising blood glucose levels by releasing insulin, which then promotes glucose uptake into tissues. It also responds to falling glucose levels in the blood by releasing glucagon, which acts on the liver to stimulate glycogenolysis and gluconeogenesis to raise blood sugar. The liver also regulates glucose and lipid metabolism via a number of nuclear hormone receptors including aryl hydrocarbon receptor – AhR, pregnane x receptor – PXR, and the constitutive androstane receptor – CAR.

Below we focus on the endocrine control of adipogenesis, glucose homeostasis and liver lipids.

3.1. Neuroendocrine control

The neuroendocrine hypothalamus, together with some structures in the brainstem, plays a key role in the regulation of energy balance through the integration of peripheral signals and onward signal transmission (Fig. 1). Peripheral signals conveying information about meal processing, gastrointestinal activity, and changes in energy stores access the brain via a number of routes, crossing or by-passing the blood-brain barrier from the systemic circulation, or changing the firing rate of vagal or other sensory nerve fibers. In the medulla, the nucleus of the solitary tract and the area postrema are key sites for the integration of these peripheral signals and for sending them to other integration sites located in the hypothalamus (for reviews see [64,65]).

The hypothalamus participates in the regulation of food intake and body weight with two neuroendocrine components: the afferent peripheral system (stimulated in response to a meal) and the efferent system (regulating the feeding behavior and energy metabolism) [66,67]. The peripheral signals are the hormones insulin (secreted by the endocrine pancreas in response to changes in blood sugar), leptin (secreted by adipocytes in proportion to fat mass), ghrelin and orexin-A (secreted by the stomach and the gut) [68]. These hormones link the control of peripheral energy metabolism to the feeding behavior integrating neural units by modulating short term signals that determine meal initiation and termination as well as energy balance [69]. Two neurochemically-distinct populations of hypothalamic neurons located in the arcuate nucleus (ARC) are critical for the integration of signals of nutritional status, and influence energy homeostasis [70]. One neuron group expresses the potent orexigenic neuropeptide NPY and AgRP and shows high concentrations of binding sites for many hormonal and metabolic signals such as insulin, leptin and ghrelin [71]. An increase in NPY release results in increased food intake and decreased energy expenditure. Another set of ARC neurons expresses the neuropeptide precursor POMC, which is processed

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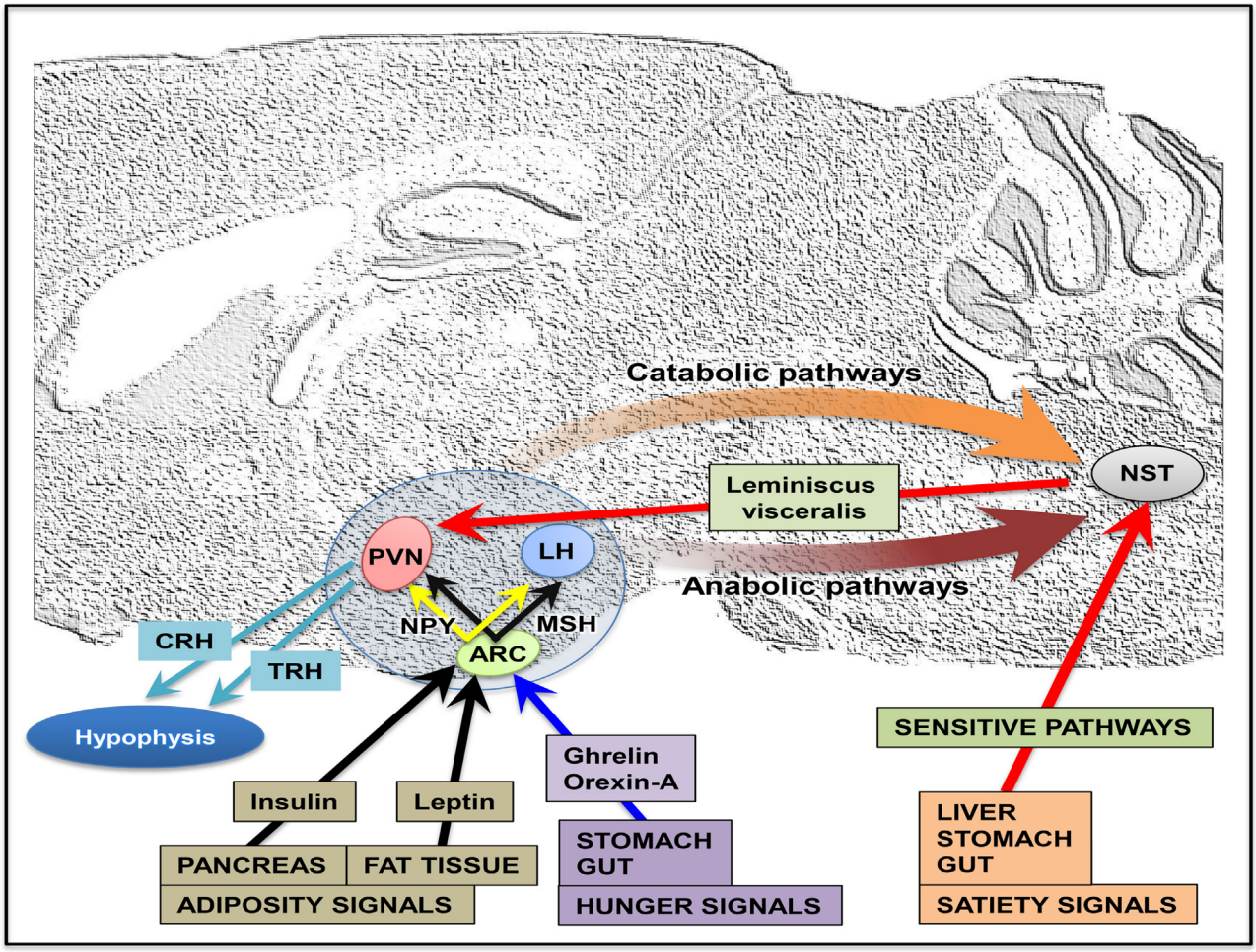

Fig. 1. Schematic illustrating the neuroendocrine control of energy balance (modified from Schwartz et al. Nature 404, 661-71, 2000).

to melanocortin peptides; activation of these neurons decreases food intake and increases energy expenditure [72–74]. These two populations of neurons thus exert opposite effects on energy intake and interact on several levels. The current hypothesis is that as adipose stores increase, both insulin and leptin levels increase along with POMC expression, while NPY synthesis and activity are inhibited and food intake is reduced. Conversely, when NPY synthesis and release are increased and POMC is decreased, the result is an increase in food intake [75–77]. Dysfunction of the NPY system has been implicated in obesity and T2D in humans [78,79]

Peptidergic neurons in the ARC project to other hypothalamic nuclei such as the paraventricular nucleus (PVN), dorsomedial hypothalamus, lateral hypothalamic area (LHA), and perifornical area [80,81]. These secondary centers process information regarding energy homeostasis. In particular, the PVN receives NPY/AgRP and POMC/METSH/CART projections and contains secondary neurons which are involved, for instance, in emotional and stress responses, which have been shown to be physiologically involved in energy homeostasis (i.e. thyrotropin releasing hormone (TRH) and corticoid releasing factor) [82]. In addition, the liver (an important integrator of nutrient metabolism) produces an endocrine satiety signal (fibroblast growth factor 21, FGF21), that suppresses the consumption of simple sugars, and reduces sweet-seeking behavior, by acting centrally at the level of the PVN [83].

Estradiol, in addition to its function as a gonadal hormone, is involved in the regulation of metabolism through the modulation of food intake, body weight, glucose/insulin balance, body fat distribution, lipogenesis and lipolysis, and energy consumption. The central metabolic action of estradiol at the brain level occurs primarily in the ARC of the hypothalamus where it targets directly the POMC neurons and indirectly the NPY cells [84]. Estradiol represses the synthesis of NPY and AgRP and thereby has an inhibitory function on food intake [85–88]. Recent data have shown that leptin and estradiol may use a common pathway to regulate energy metabolism, namely the STAT3 pathway in POMC neurons [87,88].

This integrated pathway between reproductive and metabolic functions is confirmed by recent findings on the role of brain kisspeptin and its receptor KISS1R (reviewed by [89]), originally identified based on their endocrine functions of regulating puberty and fertility, through actions on hypothalamic gonadotropin releasing hormone production [90]. Emerging evidence demonstrates a significant role of kisspeptin for regulating glucose homeostasis, insulin secretion, as well as food intake and body composition [91], with deficient kisspeptin signaling resulting in decreased locomotor activity and increased adiposity in a sex-dependent manner [92]. Organization and function of the kisspeptin-Kiss1R system is sex-specific, and sex steroid hormones play a crucial role in determining such sexual dimorphisms [93,94]. The kisspeptin system is therefore a potential target of endocrine disruption; in rodent studies, exposure to EDCs altered the kisspeptin system in a region-, sex- and compound –specific manner, and induced effects on the timing of pubertal onset, estrous cycles, and socio-sexual behaviors [95–97].

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3.2. Adipose tissue

Adipose tissue is the key regulator of energy balance and nutritional homeostasis and consists of white, brown and beige fat. It is an endocrine organ with more than 20endocrine, paracrine and autocrine secretions. The adipose tissue consists of several depots located in subcutaneous, intra-abdominal (visceral) and intrathoracic areas. Visceral adipose tissue depots are metabolically different from subcutaneous compartments [98]. Intra-abdominal (visceral) depots are associated with T2D and cardiovascular disease while subcutaneous depots seem protective against these diseases [99].

White adipose tissue stores energy as triglyceride and also signals to other organs on the status of energy reserves via hormones, growth factors and cytokines [100]. Two major secretions of white adipose tissue are leptin and adiponectin. Leptin is secreted in proportion to fat mass; it acts on the brain to reduce food intake and increase energy expenditure. However, obese individuals typically have increased serum leptin levels due to leptin resistance [101]. Adiponectin is also secreted from adipose tissue and induces fatty acid oxidation in liver, improves pancreatic beta cell function, enhances peripheral insulin sensitivity, suppresses hepatic glucose production and reduces inflammation [102]. Adipose tissue also contains immune cells, from both the adaptive (B and T lymphocytes) or innate (macrophages) immune system thus it is an immune organ. Obesity is considered a proinflammatory condition in which both hypertrophied adipoctyes and resident immune cells produce and release proinflammatory cytokines, including IL-6 and TNFα, which are associated with chronic low-level systemic inflammation, insulin resistance and T2D. In contrast, in non-obese individuals anti-inflammatory cytokines including adiponectin, interleukin −10, and transforming growth factor beta (TGFb) are preferentially secreted which, among other functions, improve insulin sensitivity [103].

Brown adipose tissue is present throughout life, but with highest volume in newborns. It generates body heat via non shivering thermogenesis while beige fat appears to be bifunctional, changing to either white or brown fat depending on the stimuli [104]. The sympathetic nervous system controls lipolysis in white adipose cells and stimulates the cold response in brown adipocytes.

In response to excess energy, adipocytes enlarge and/or increase in number [100]. Excess fat in these cells results in tissue dysfunction which leads to the development of other diseases and conditions including inflammation, T2D, heart disease, fatty liver, reproductive problems and some forms of cancer depending somewhat on the site of the added adipose tissue (e.g. visceral or subcutaneous) [100].

In humans, adipose tissue develops by the 14th week of gestation [105] followed by a second period of increased cellularity that continues after birth and lasts through adolescence [106]. The number of white adipocytes is usually fixed after that time [100] however adipocytes are replaced at a rate of about 10% per year in adulthood [106], thus the tissue is not static. In mice, most subcutaneous adipogenesis occurs late in gestation and after birth; differentiation of gonadal fat only appears postnatally between birth and puberty [107]. Overall, fat mass can continue to grow due to high fat feeding which induces both hyperplasia and hypertrophy in rodents [107] with the hyperplasia occurring in the visceral tissue. Adult mice that are challenged with a high fat diet accumulate fat by hypertrophy in most adipose depots, with the exception of gonadal (visceral) fat which possesses higher capacity to expand by hyperplasia [107].

Specific genes play critical roles in fat cell development and control, including PPARγ and Runx2, often called the master regulators of fat cell differentiation [108] and sirtuins which play important roles in secretion of adipokines including leptin and adiponectin, hepatic glucose metabolism, insulin sensitivity and inflammation [109].

Adipocytes are derived from mesenchymal stem cells (MSCs), which can be neuroectodermal or mesodermal depending on where the fat body originates; differentiation of adipocytes requires a committed pre-adipocyte progenitor [110,111]. Visceral white adipose tissue (WAT) is primarily derived from the lateral plate mesoderm [112], brown fat is largely produced by the paraxial mesoderm [113], and cranial WAT from the neural crest [114]. Beige (a.k.a brite) fat arises from WAT (precursors or mature cells). Despite this common origin, beige fat is thermogenic, like brown fat, so it plays a different metabolic role than WAT and has a correspondingly different transcriptional program than WAT [115,116]. Mesenchymal stem cells harvested from adipose tissue or bone marrow can be made to differentiate into fat, bone, cartilage, and other lineages in culture [117]; commitment to each of these lineages is largely mutually exclusive and irreversible [118]. Transformation of an MSC into an adipocyte requires initial commitment to the adipose lineage, followed by terminal differentiation into a mature adipocyte (reviewed in [100,111]). Adipocyte commitment is mediated by transcription factors Zfp423 [119], Zfp467 [120], Schnurri2 [121], Tcf7l1 [111] and the mTORC1 effector S6K1 [122]. Collectively these genes function to sensitize cells to BMP2/4 signaling while inhibiting canonical Wnt signaling and promoting expression of the so-called master regulator of adipogenesis, PPARγ. Terminal differentiation is primarily controlled by PPARγ and CCAAT-enhancer-binding proteins (C/EBP) −α, −β, and −δ [123,124] which establish a sustained feedback loop. Treatment of committed pre-adipocytes with an “adipogenic cocktail” (glucocorticoids, cAMP agonists, and insulin) increases expression of PPARγ and C/EBP proteins and is marked by induction of metabolic genes and adipokines associated with mature adipocytes [124,125].

3.3. Control of glucose homeostasis

Regulation of blood glucose within the normal range is accomplished through the concerted action of several organs: glucose absorption by the intestine, glucose-dependent secretion of insulin and glucagon from the endocrine pancreas, regulation of glucose production by the liver, and glucose uptake and metabolism by peripheral tissues. All these processes are further regulated by the neural system.

3.4. Pancreas

The endocrine pancreas is comprised of the pancreatic islets of Langerhans, a heterogeneous population of 1000–3000 cells, where the predominant cell type is the insulin-releasing β-cell. Other cells include α-cells, responsible for glucagon secretion, and δ-cells, responsible for somatostatin release, pancreatic polypeptide-producing cells (PP-cells) and ε-cells that produce ghrelin [126,127]. While β- and α-cell populations represent about 70–80% and 20% respectively of the total islet cell number in rodents, in humans the pancreas is comprised of 40–45% α-cells and 50% β-cells [128] and up to 10% δ-cells.

The number of β-cells rapidly expands *in utero* and in the neonatal period and then replication occurs only at very low levels in adult rodents [129] and humans [130]. β-cells replicate throughout life after physiologic challenges like high blood sugar, peripheral insulin resistance and pancreatic injury and their mass is controlled by insulin, placental lactogen and prolactin (reviewed in [131]). The liver may also control β-cell proliferation via a novel hormone, betatropin [131], which is upregulated in pregnancy and in the ob/ob and db/db diabetic mouse.

The regulation of blood glucose starts when glucose is taken up by β-cells where it undergoes intermediary metabolism. Insulin

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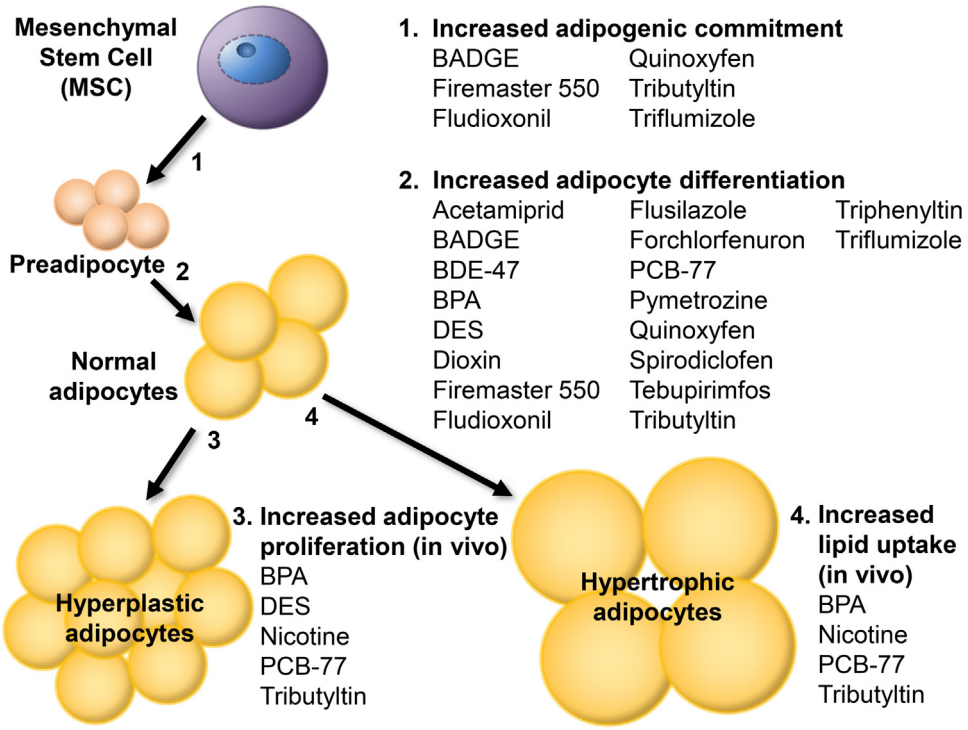

Fig. 2. Mechanisms of Adipocyte Formation and Sites of Action of Metabolism Disruptors.

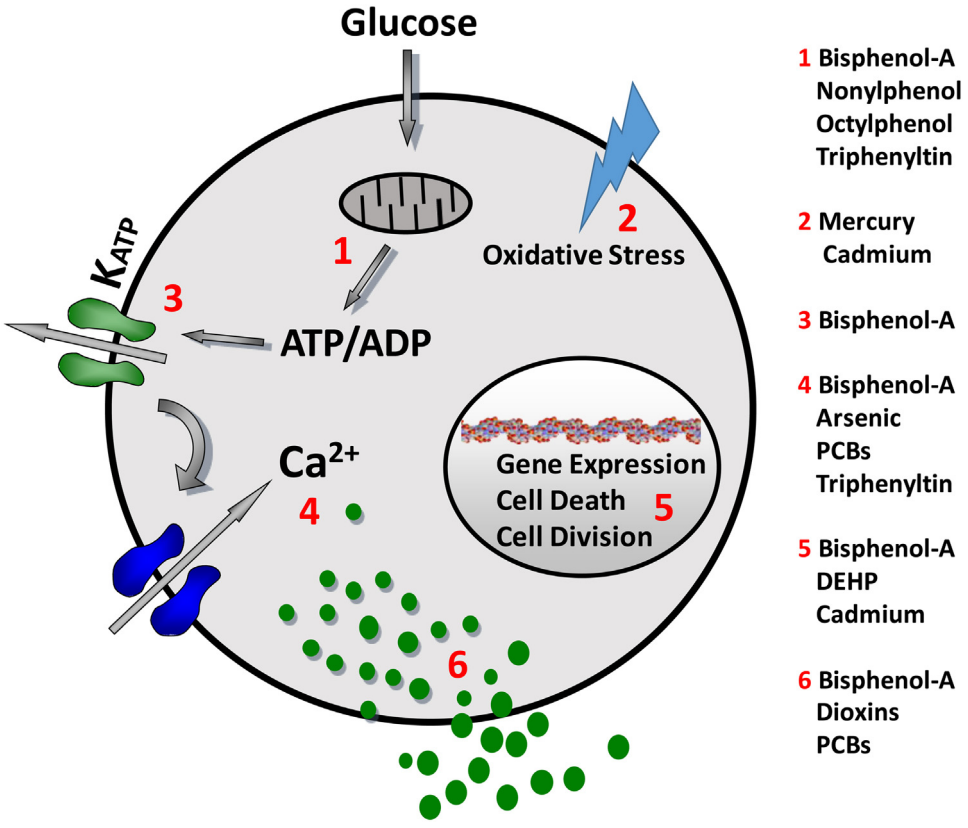

Fig. 3. Regulation of pancreas beta cell control of blood glucose and sites of action of metabolism disruptors.

release takes place after glucose metabolism increases the ATP/ADP ratio, which closes plasma membrane ATP-sensitive K^+ (K_{ATP}) channels that are responsible for the resting membrane potential. This results in cellular depolarization and ultimately insulin release from the cell. Insulin secreted into circulation then binds to receptors on the surface of target cells in the periphery to facilitate

glucose uptake and metabolism. Impaired β-cell insulin production results in a rise in blood glucose levels that over time can lead to the development of diabetes (See Fig. 3). This metabolic transition can arise from frank β-cell destruction as seen in type 1 diabetes or to β-cell dysfunction arising from increased synthetic demand resulting from peripheral insulin resistance as in T2D.

Glucagon is another key glucose-regulating hormone. It is secreted by α-cells in response to falling blood glucose levels and principally stimulates the liver to increase glycogenolysis and gluconeogenesis to raise circulating blood sugar [132,133]. When extracellular glucose concentrations rise to levels required for insulin release, glucagon release decreases [134]. Several paracrine and neural mechanisms also inhibit glucagon release [127,135–138]. While pure hyperglucagonemia is a rare cause of diabetes, disruptions in the autoregulatory feedback loop linking insulin and glucagon secretion is thought to result in inappropriate glucagon secretion in both type 1 and T2D [139].

3.4.1. Liver

The liver is the principal location of glucose storage as glycogen, and the main source of glucose for all tissues. Because the pancreatic veins drain into the portal venous system, every hormone secreted by the pancreas must traverse the liver before entering systemic circulation. The liver is a major target for pancreatic insulin and glucagon action as well as their site of degradation. In fact, 70% of hepatic glucose output occurs via liver glycogenolysis and 30% via gluconeogenesis.

Insulin promotes glycogen synthesis and decreases its breakdown after enhancing the transcription of glucokinase and the activation of glycogen synthase through changes in its phosphorylation state. Insulin increases transcription of the glucokinase gene and other enzymes involved in glycolysis such as phosphofructokinase and pyruvate kinase, promoting glycolysis [140]. Insulin also inhibits gluconeogenesis by decreasing phosphoenolpyruvate carboxykinase (PEPCK) and fructose-1, 6-biphosphatase (FBPase) gene expression. As a result, insulin inhibits glucose production during the fed state, keeping glucose levels within the normal range. At the same time, high glucose levels inhibit glucose-6-phosphatase and decrease the activity of glycogen phosphorylase; all together, these processes considerably reduce the conversion of glycogen to glucose.

Insulin also promotes the storage of fat by stimulating lipogenesis. It inhibits the oxidation of fatty acids by decreasing fatty acid transport into the mitochondria. Additionally, insulin stimulates fatty acid synthase (FAS). All together, these pathways promote the formation of triglycerides that can either be stored in the liver or exported as very low density-lipoproteins (VLDL).

On the other hand, glucagon signaling in the liver plays a key role during fasting, as well as in the adaptive response to hypoglycemia. After binding at its receptors, glucagon activates the cAMP/PKA pathway, which decreases glycolysis via a modulatory action on pyruvate kinase [127]. Glucagon increases gluconeogenesis after up-regulation of glucose-6-phosphatase and PEPCK through the activation of coactivators such as CREB-binding protein (CBP), P300, PGC-1 and TORC2 [134,141–144]. In addition, glucagon also activates ketogenesis. All these effects favor hepatic release of glucose to maintain normal blood glucose levels during fasting. Glucagon also promotes the oxidation of fat in the liver, increasing the activity of the citric acid cycle and the generation of ketone bodies. Moreover, there is a glucagon-induced decrease of triglyceride, VLDL, cholesterol and fatty acid synthesis mediated by PPARα [145].

3.4.2. Skeletal muscle

Skeletal muscle is the major site of insulin-mediated glucose usage; it can clear up to 70% of the blood glucose pool. Unlike the liver, glucose transport in skeletal muscle is insulin dependent via the recruitment of the glucose transporter GLUT4 to the membrane. Insulin activation of hexokinase and glycogen synthase enhances glycogen synthesis. Activation of phosphofructokinase and pyruvate dehydrogenase enhances glucose breakdown and oxidation. The action of insulin in glucose utilization allows the muscle to store fat as triglycerides that together with glycogen can be used as sources of energy during exercise and heat generation.

3.4.3. White adipose tissue

Similar to skeletal muscle, insulin promotes recruitment of GLUT4 to the membrane and accelerates glucose transport into adipocytes. It then induces the breakdown of glucose to generate triglycerides. These triglycerides are stored in fat together with those delivered via the circulation as chylomicrons and VLDL. In addition, insulin inhibition of triglyceride lipase decreases triglyceride breakdown. Insulin decreases lipolysis through inhibition of hormone sensitive lipase in a cAMP-dependent manner [146,147]. Insulin promotes the synthesis of lipoprotein lipase (LPL), which is exported to the endothelial cell plasma membrane. Once anchored there, LPL cleaves triglycerides from VLDL and chylomicrons into glycerol and fatty acids that are taken up by nearby adipocytes to form triglycerides.

Although the role of glucagon in WAT is controversial, recent results point to a role in lipolysis [127]. This lipolytic action has been attributed to glucagon-induced release of fibroblast growth factor 21 (FGF21) [148] as well as to signals from the sympathetic nervous system [149].

3.5. Importance of insulin resistance

Insulin resistance is present in many cases of obesity and T2D. However, most insulin-resistant individuals do not develop hyperglycemia due to compensatory increases biosynthesis and the release of insulin as well as increases in pancreatic β-cell mass. For example, obese subjects secrete 2–5 times more insulin in response to glucose, while athletes secrete 2–5 times less insulin [150]. Insulin resistance developed during puberty and pregnancy is counteracted by adaptation of β-cell mass and function, with sex and maternal hormones playing important roles [151–155]. Insulin sensitivity, therefore, regulates β-cell function; insulin resistant subjects, whether they are obese or lean, have greater insulin response and lower insulin clearance than insulin-sensitive individuals. In order for insulin resistance to lead to T2D, β-cells adaptation must fail [156]. Regulation of β-cell mass may occur by hypertrophy of existing cells and proliferation. Glucose, non-esterified fatty acids, incretins, and neuronal signaling are involved in increasing β-cell mass and function, yet when glucose and lipids are increased for longer than normal β-cell are killed which generates the onset of T2D [157,158].

The ability of pancreatic β-cells to integrate responses to changes in insulin sensitivity likely involves increased metabolism and metabolic signals. These include signaling molecules from adipocytes (e.g. NEFAs signaling via GPR40) as well as and fatty acyl-CoAs that augment insulin release via the exocytotic machinery and protein kinase C (PKC). Leptin, adiponectin, and proinflammatory cytokines such as TNFα, IL-6 and monocyte chemoattractant protein (MCP-1) from macrophages and other cells infiltrating adipose tissue have a role as well [157]. Pancreatic α-cells are responsible for glucagon production and release. Thus alterations in the pancreatic α-cell function can also contribute to T2D [127]. Unlike β-cells, the mass of pancreatic α-cell does not decrease in T2D, resulting in an increased α-to-β cell ratio; this altered ratio also contributes to higher plasma levels of glucagon and therefore to hypoglycemia.

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Thus, when β-cells are healthy, their adaptive responses counterbalance insulin resistance and preserve normal glucose tolerance. However, if β-cell dysfunction occurs due to genetic causes, environmental perturbations, or both, then the individual is more prone to develop impaired glucose tolerance, high fasting glucose levels, and ultimately T2D.

3.6. Liver control of xenobiotic and intermediary metabolism

The liver is the largest and most metabolically complex organ in the human body. Hepatocytes make up over 80% of total liver mass and play a critical role in intermediary energy (lipid, carbohydrate, amino acid) and xenobiotic metabolism (Phase I–III metabolizing enzymes). Other liver-specific cell types include Kupffer cells, biliary epithelial cells, sinusoidal endothelial cells, and stellate cells. These cells have specialized functions ranging from protection against infection, bile duct flow, endocytosis and fibrosis. The liver arises from the hepatic diverticulum of the foregut during the fourth week of gestation. Hepatoblasts are bipotential progenitor cells arising from foregut endodermal cells that differentiate into hepatocytes and cholangiocytes.

The liver is the principal organ for xenobiotic detoxification. Ligand-activated xenobiotic receptors induce foreign compound metabolism by cytochrome P450s. For example, the aryl hydrocarbon receptor (AhR) induces expression of CYP1A1, the constitutive androstane receptor (CAR) induces CYP2B10, and the pregnane X receptor (PXR) induces CYP3A4. In general, chemical ligands are metabolized by the P450 s that they induce. In addition to foreign compound metabolism, xenobiotic receptors play an important role in the control of hepatic lipid and carbohydrate metabolism. It was recently proposed that activation and cross-talk of xenobiotic receptors by foreign compounds is a molecular initiating event in hepatic steatosis [159]. Likewise, interactions between environmental compounds and xenobiotic receptors regulate, in part, hepatic carbohydrate metabolism including gluconeogenesis and insulin resistance [160,161]. These mechanisms appear to account for the wasting syndrome associated with some dioxin-like chemicals that activate the AhR [161].

Owing to its critical role in xenobiotic and intermediary metabolism, the liver is a principle target organ for chemicals resulting in the development of steatosis. Steatosis may progress to steatohepatitis (steatosis with superimposed hepatic inflammation), cirrhosis and hepatocellular carcinoma, and ultimately liver-related death if liver transplantation does not occur. In the clinic, steatohepatitis is named according to its etiology: alcohol (alcoholic steatohepatitis, ASH), cancer medications (chemotherapy associated steatohepatitis, CASH), excess dietary lipids or carbohydrates (NASH), and industrial chemicals (toxicant associated steatohepatitis, TASH) [162,163]. While disease mechanisms vary by etiology [164], steatosis is invariable associated with an imbalance of hepatocyte lipid synthesis, oxidation, uptake, and efflux via VLDL [159].

3.7. Thyroid control of metabolism

The thyroid gland, located in the neck, is one of the largest endocrine glands in the body. It plays a crucial role in normal growth and development, energy homeostasis and regulation of adult metabolism. The main hormones secreted by the gland are Thyroxine (T_4), which has limited biological activity and triiodothyronine (T_3) which is more potent but with a shorter half-life. T_4 is converted to T_3 by the enzyme thyroxine 5′-deiodinase [165]. Thyroid hormones are regulated by thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland, which in turn is regulated by TRH produced by the hypothalamus [166,167].

Tight interaction exists between thyroid function, weight control, and obesity [168]. Mild differences in thyroid function can be associated with changes in body weight and fat mass [168,169]. Even small variations in serum TSH, within the reference range of the assay, were associated with differences in body mass; higher levels of TSH were associated with increased BMI [170–172]. There is an inverse correlation between free thyroxine (fT4) values and body mass index (BMI), even when fT4 values remain in the normal range [173,174].

3.8. Sexual dimorphism and metabolism

In humans, there are important sex differences in the incidence and health consequences of obesity; men and women differ in the patterns of fat deposition, fat mobilization, utilization of fat, and the consequences of both excess and insufficient fat stores. Gonadal hormones appear to play a crucial role in shaping such differences. Women suffer fewer obesity-related disorders than men do. In fact women are resistant to free fatty acid-induced insulin release and are therefore less prone to T2D before menopause but the prevalence of these disorders increases dramatically after menopause [175]. The prevalence of T2D is higher in men before puberty compared to reproductive age females. It is noteworthy that T1D has a male predominance as well [176]. Androgens, adiposity and disease are clearly interrelated in humans.

These asymmetries in energy balance traits probably reflect evolved adaptive differences due to differential investment and costs of reproduction in male and female mammals and are mainly shaped by gonadal hormones either during development (organizational effects) or at adulthood (activational effects) (for reviews see [177–179]). Development and maturation of brain circuits involved in the regulation of food intake and metabolism occur during the perinatal period. The current literature argues that there are multiple critical periods in which hormones organize energy balancing traits; besides the fetal and neonatal stage, the peripubertal period is also a time window when sexually dimorphic eating behaviors are established [180]. Sex differences in body fat composition and distribution, energy expenditure, orosensory physiology, taste and smell preference, food intake, binge eating, susceptibility to diet induced obesity, responses to leptin-, ghrelin,- or insulin- induced hyperphagia, POMC gene expression in the ARC nucleus, and many other traits are well documented (reviewed in: [181–183]).

The POMC, melanocortin system, is sexually dimorphic [184]. In adults, females have increased responsiveness to leptin and decreased responsiveness to insulin in comparison to males. These differences are estrogen dependent [185], and they are perinatally organized by testosterone [186]. The NPY/AgRP circuit is also sexually dimorphic. In particular, *in situ* hybridization studies demonstrated sex differences in the distribution of NPY mRNA-containing cells in the rat ARC, and its modulation by testosterone in males [187]. Also, NPY immunoreactivity is sexually dimorphic in the ARC, the dorsomedial hypothalamus, and the PVN [188]; NPY-Y1 receptor expression is higher in females compared to males [189].

Male mice have higher levels of daily food intake, post-fast hyperphagia and leptin-induced hypophagia compared to female mice, and these behavioral differences are related to sexual dimorphisms in the ARC as far as the number of ARC cells containing NPY, AgRP, and POMC. Females perinatally treated with testosterone or DHT show male-like levels of food intake, post-fast hyperphagia and POMC gene expression and projection [186].

Estrogens play a pivotal role in regulating energy homeostasis, especially in female mammals, either by acting directly on the brain or through activation of estrogen receptors (ER) on adipocytes. Estrogens protect against increased adiposity/obesity through their effects of suppressing appetite and increasing energy expenditure;

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estradiol suppresses feeding by enhancing the potency of other anorectic signals (leptin, apolipoprotein, BDNF, cholecystokinin) and by decreasing the potency of orexigenic signals such as ghrelin and melanin concentrating hormone [87,185,190,191]. The liver is a major target for estrogen action in female mammals and the activity of the liver ERα is strictly associated with ovarian activity [192]. In the liver, ERα regulates fertility in response to protein consumption and controls lipid and cholesterol synthesis in relation to the reproductive cycle [193]. Since the liver is the major organ for the control of energy homeostasis, the activity of hepatic ERα also influences the synthesis and secretion of the signaling molecules necessary for coordinated responses among liver, fat, muscles and brain [192].

In mammals, including humans, the liver is a sexually dimorphic organ and exhibits major differences in the profile of steroid, lipid, foreign compound metabolism [194], and gene expression. These differentially expressed genes regulate a wide range of biological processes; accordingly, many enzymes, such as steroid hydroxylases belonging to the cytochrome P450 (CYP) superfamily, are expressed in the liver in unique, sexually biased patterns [195]. Such differences have implications for sex-related steroid metabolism, xenobiotic metabolism and pharmacokinetics, and differential susceptibility to some liver diseases [23,196]. The sexual dimorphism of liver gene expression is established and maintained, in part, by the temporal pattern of pituitary GH secretion, which is sex specific in many species (episodic in males and more stable in females) [197]. GH secretion is affected by brain and lactotrope dopamine 2 receptors (D2Rs) [198]. A link exists between obesity, growth, and dopaminergic systems located within the central nervous system and in other tissues [199–201].

4. Environmental contributions to obesity, T2D, and dyslipidemia

The global pandemic of obesity, T2D and MetS is often causally linked to marked changes in diet and lifestyle, namely increases in dietary intake of high energy diets and concomitant reduction in physical activity levels [202]. However, it is clear that the susceptibility to these diseases is not that simple. Indeed there have been multiple environmental factors that have been linked to the increase in these metabolic diseases including stress, lack of sleep, adenoviruses, childhood antibiotics [202–205] and exposure to environmental chemicals [206]. While all of these environmental stressors likely play some role in the epidemic of metabolic diseases, we focus here on exposure to environmental chemicals, especially EDCs and the role they might play in disease etiology. Indeed, the current rise in metabolic diseases correlates with substantial increases in environmental chemical production and exposures over the past four decades [207–209].

4.1. Overview of endocrine disrupting chemicals

In 2012, the Endocrine Society defined EDCs as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" [210]. This definition is a more simplified version of the one originally proposed by the US EPA, that EDCs are "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes" [211]. At the global level, the WHO/UNEP definition of EDCs is "an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in intact organism, or its progeny or (sub) population [212]. Although EDCs were first identified as agonists or antagonists of estrogen, androgen and thyroid hormone receptors [213], EDCs disrupt hormonal signaling systems by interfering with a variety of hormones through numerous mechanisms. EDCs can disrupt normal hormone levels by inhibiting or stimulating the production and metabolism of hormones, or changing the way hormones are transported to target tissues.

The effects of EDCs, like those of hormones, can occur at very low levels [214–217]. Other principles of hormone action are similarly expected for EDCs including their ability to induce tissue- and time-dependent effects and strong evidence that responses to EDCs can be non-monotonic (often referred to as biphasic or U-shaped responses) [5,210,215,218,219]. Some EDCs are persistent and can bioaccumulate in tissues [220,221]. With more than 85,000 registered chemicals in commerce, most of which are poorly studied; current estimates have identified approximately 1000 chemicals that meet the criteria of an EDC [213,222].

Decades of work from both basic and clinical endocrinology have revealed that the disruption of hormones can have detrimental effects on a variety of diseases [223] [223,224]. A number of recent "state of science" reviews of the EDC literature, as well as large reviews of hundreds or thousands of EDC studies, draw strong conclusions about the association between EDC exposures and diseases [210,215,218,223,225–228]. These conclusions are drawn from observational human epidemiology studies and controlled laboratory animal studies, as well as additional support from wildlife studies, *in vitro* mechanistic studies, and *in silico* studies. In 2015, a review of the EDC literature by scientists in the Endocrine Society found that there was strong evidence for a role of EDCs in the etiology of metabolic diseases, although these diseases were generally examined individually [229]. Some of these conclusions were challenged, with groups contesting the strength of evidence linking EDC exposures to endocrine-related diseases [230–235]. However, whereas some useful criticisms were put forward, these challenges typically resulted from a lack of understanding of the endocrine system, as well as of endocrine disruption as an effect on a complex regulatory network of the organism [219,236–241]. On the contrary, the need to fully appreciate the impact of EDCs is apparent considering the health care costs associated with inaction [9,228].

A number of relevant factors can influence whether significant effects are observed in experimental studies of EDCs and these factors can affect the strength of the evidence for an effect. First, measurement of body weight alone is now recognized to be an inadequate measure in experimental rodent studies to assess the effects of chemical exposure on adipocyte endpoints [242]. Second, the endocrine milieu of males and females is different, and thus it should be expected that sex-specific effects are often observed because of EDC exposure, particularly for compounds that interfere with sex hormones. Third, the specific type of feed used in animal experiments can affect sex hormone levels in pregnant females and fetuses, and consequently result in significant differences in phenotype, including the potential to modify effects of chemical exposures [243,244]. Indeed, natural diet components and EDCs may interact in several ways [245].

One relevant challenge concerns the publication of apparently "conflicting" results on EDCs. Independent replication of results is the accepted standard for assessing validity of findings in research, thus the issue of non-replication of findings in some EDC studies must take into account the issues described above (sensitivity of endpoint, sex-specific effects, influence of animal feed), as well as the appropriate use of positive controls [246–248,249], and/or negative control groups [250,251], and the range of dose levels used [219,252]. There also appears to be a relationship between the source of funding and the likelihood of identifying effects of EDCs [237,248,253]. Thus, rather than labelling results as "conflicting" the factors involved in the apparent failure to replicate certain findings should be assessed [246,254].

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4.2. EDC exposures: sources & routes

As noted above, approximately 1000 chemicals have been identified that meet the criteria of an EDC [213,222]. These compounds are used in a wide range of consumer products including food packaging, building materials, pesticides, clothing and upholstery, personal care products, detergents and other cleaning agents, thermal paper, plastics and medical equipment [210,215,226,227,255,256]. Some chemicals used in industrial processes lead to unintended contamination of food, water and air. Thus, routes of exposure can include oral, dermal, and inhalation, as well as subcutaneous and intravenous (via medical equipment).

The US CDC's National Health and Nutrition Examination Survey (NHANES) is a nationally representative biomonitoring program which assesses, among other things, exposures to environmental chemicals in the general population [257].The CDC has documented widespread exposures to a number of EDCs (e.g. [258–263]). Importantly, a large number of chemicals are not examined, and thus the number of exposed individuals, as well as the typical levels of exposure, remains unknown. Although the sampling of infants and young children is limited in the context of NHANES [264], other studies have revealed the presence of environmental chemicals in placenta, amniotic fluid and umbilical cord blood, documenting exposure throughout the most critical stages of development as well as across the lifespan (e.g. [265–271]).

4.3. Vulnerable windows of exposure and metabolic disorders

The concept that adult diseases could have a fetal basis was highlighted by the work of David Barker who proposed a hypothesis, which was expanded to the Fetal Basis of Adult Disease and has now been restated as the Developmental Origins of Health and Disease (DOHaD) hypothesis [272–274]. The core DOHaD hypothesis is that there are critical windows during development, and environmental disruptions during these life stages can lead to subtle changes in gene expression, tissue organization, or other levels of biological organization that lead to permanent dysfunction leading to increased susceptibility to disease. Unlike birth defects and neonatal diseases, these dysfunctions manifest later in life mostly as increased vulnerability to common diseases including obesity [275–277]. Barker and others showed that low birth weight (LBW) babies resulting from maternal malnutrition developed increased susceptibility to diseases in adult life including coronary heart disease, obesity, stroke, T2D, osteoporosis, increased blood pressure, dyslipidemia, impaired glucose metabolism and metabolic dysfunction (reviewed in [273,278]).

Barker's focus on nutrition was preceded by the iatrogenic event involving the prescription of diethylstilbestrol (DES) to millions of women from the 1940s through the early 1970s to prevent miscarriage. Not only was DES shown to be ineffective, it increased the incidence of a rare cervical cancer. Animal studies confirmed it is a transplacental carcinogen and the effects, including other deformities of the reproductive tract and increased incidence of mammary cancer, shown to result from developmental exposure in animal models, have now been confirmed in human studies. The DES tragedy remains one of the best examples of the long-latency adverse health outcomes associated with fetal endocrine disruption and was a clear example of DOHaD, with adverse health outcomes associated with the alteration of normal endocrine function during development [279,280].

The observation that alternations in human development affects the risk of non-communicable diseases later in life is confirmed by epidemiology studies focusing on both nutrition and environmental chemical exposures [276,281–283]. Developing organisms are extremely sensitive to perturbation by chemicals including EDCs because hormones and growth factors control development. Alterations of their levels during development by EDCs leads to tissues with abnormal gene expression, numbers of cells, location of cells, imbalance between cell types, as well as altered organ structure and hormonal signaling that lead to increased susceptibility to disease/dysfunctions across the life course [281,284]. Adverse effects may be most pronounced in the developing organism and occur at concentrations of the chemical that are far below levels that would be considered harmful in the adult [285,286]. Some of the reasons for this increased sensitivity include the fact that the protective mechanisms that are available to the adult, such as DNA repair mechanisms, a competent immune system, detoxifying enzymes, liver metabolism, and the blood/brain barrier are not fully functional in the fetus or newborn. In addition, the developing organism has an increased metabolic rate as compared to an adult, which, in some cases, may result in increased toxicity [286].

Another critically important reason for the increased sensitivity of the developmental period to EDCs (as well as nutritional deficits) is that epigenetic signaling regulates gene expression which controls development. Epigenetic changes provide biochemical evidence of the deleterious effects of adverse conditions during development and subsequent disease including metabolic diseases [287]. Some aspects of epigenetic signaling (e.g.DNA methylation, histone marks, chromatin remodeling and noncoding RNAs) are likely involved in the mechanisms responsible for altered programming of tissue development by EDCs that lead to obesity [288–290]. Since hormones and growth factors control development, signaling errors caused by hormones expressed at the wrong time or concentration can cause alterations in gene expression in tissues, and these abnormal expression patterns become permanent due to epigenetic signaling [290–292].

There are now credible data that supporting the claim that many chronic diseases including obesity, T2D and MetS can be linked to epigenetic changes in cells and tissues during development that manifest in altered tissue development as a result of early environmental factors (stress, drugs, nutrition, environmental chemicals) [293–295]. Extensive data from animal and human studies show that developmentally induced disease outcomes often are not immediately apparent but manifest later in life [277,296,297].

There are now data that show that environmental factors can account for disruption of individual or multiple systems involved in metabolism depending on the timing of exposure. For example, exposure to a chemical during the fetal or perinatal period can permanently alter the functioning of mesenchymal stem cells and lead to disruption of adipocyte function [298]. Altered adipocyte function is likely to affect other organs/tissues due to hormonal and paracrine action. This brief chemical exposure might also impact differentiation of the pancreas, heart, brain, liver or any other component of the complex regulatory system impacting the various components of metabolic disease [275].

4.4. Obesogen hypothesis overview (historical)

In 2002, Baille-Hamilton wrote the first article relating environmental chemicals to obesity. Her article, "Chemical toxins: a hypothesis to explain the global obesity epidemic", suggested that the current obesity epidemic was associated with the increase in production of environmental chemicals [299]. She reviewed published studies showing associations between exposure to a variety of environmental chemicals, including some pesticides, solvents, plastics, flame retardants and heavy metals, and increased weight gain; because these studies originally focused on weight loss and toxicity, their effects on weight gain had gone unnoticed. In 2006, Grun and Blumberg, published their now classic paper, in which they coined the term "obesogen" followed by a 2009 review "Endocrine disruptors as obesogens" [300]. They noted the existence of chemicals that alter regulation of energy balance to favor

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weight gain and obesity and proposed that obesogens derail the homeostatic and reward mechanisms important for weight control, such that exposed individuals have increased susceptibility to weight gain despite normal diet and exercise.

The obesogen hypothesis makes two important points. First, susceptibility to obesity starts during development (*in utero* and the first few years of life). Second, susceptibility to obesity is due in part to the influence of a specific subclass of EDCs that alter developmental programming, and thus disrupt the set point for weight gain later in life.

"Obesogens" are defined functionally as chemicals that promote obesity by increasing the number of fat cells and/or the storage of fat in existing adipocytes. Obesogens can also act indirectly to promote obesity by shifting energy balance to favor calorie storage, by altering basal metabolic rate, by altering gut microbiota to promote food storage [301], and by altering hormonal control of appetite and satiety [298,302–305]. New obesogenic chemicals are being identified at an increasing rate. The obesogen field has recently expanded to include chemicals that cause or lead to diabetes [306] as well as altered lipid metabolism and fatty liver [307].

4.5. The metabolism disrupting chemical (MDC) hypothesis

In 2015 the Parma Consensus Statement proposed that the Obesogen hypothesis should be expanded, considering newer evidence of chemicals that increased susceptibility to T2D, liver lipid abnormalities and MetS [308]. The Parma Statement proposed a name change to 'metabolic disruptor hypothesis', which we further propose should be termed 'metabolism disrupting chemical (MDC) hypothesis' to distinguish the role of chemicals from other metabolic disruptors such as nutrition and stress. The MDC hypothesis postulates that environmental chemicals have the ability to promote metabolic changes that can result in obesity, T2D or fatty liver in animals including humans; these metabolic alterations may play an important role in the global epidemics of obesity, T2D and MetS. In the study of liver disease etiology, the MDC hypothesis provides, for the first time, a framework for the integration of different etiology of steatohepatitis (ASH, CASH, NASH, and TASH). Alcohol, chemotherapeutic medications, fructose, dietary fatty acids, and industrial chemicals are all MDCs; while they disrupt hepatic metabolism differently the pathologic end result is the same [162,163].

For the remainder of this manuscript we will focus on MDCs as chemicals that can alter any aspect of metabolism and describe the current state of the science.

5. MDCs and metabolism-relevant diseases

5.1. Adipogenesis, subsequent weight gain and obesity

A number of MDCs have been shown to significantly alter the function (gene expression, hormone secretion) of white adipose tissue, adipose tissue mass (adipocyte number and/or volume), or body weight in animal models after developmental exposures (Fig. 2). Epidemiological studies also support the identification of obesogenic MDCs [309,310] and these studies focus mainly on weight gain and (body mass index) BMI as endpoints. This is typical for a new field, where the focus is on descriptive studies that show that a chemical can have an effect on an endpoint or disease of interest (e.g. weight gain). In many cases, effects of MDCs on adult adiposity and/or body weight are reported to be significant for only one sex, consistent with the sexually dimorphic responses that are a common feature of EDCs and thus MDCs [226].

Nicotine is an MDC where there are compelling data for its obesogenic properties from both animals and human studies [7,311,312]. Maternal smoking in pregnancy is a risk factor for subsequent obesity in offspring [313] even when exposure is limited only to early pregnancy [314,315]. Although multiple mechanisms have been proposed, associations may be partly attributable to impaired fetal growth, which as Barker and colleagues noted is a risk factor for subsequent rapid growth and long-term obesity [316].

Developmental exposure in mice to DES [317] has also been shown to increase weight gain which is specific to females and does not appear until puberty [318]. In another study, prenatal exposure to DES resulted in an increase in number of adipocytes in the gonadal fat pad of male mice[319]. Two epidemiological studies also link DES exposure to obesity; prenatal exposure to DES is associated with an increased likelihood of childhood obesity at age 7y [320] and increased risk of adult obesity in women that was most evident at lower doses [321].

Bisphenol A (BPA) [322–324], a chemical used to make polycarbonate plastic, epoxy resins that line food and beverage cans, and as a developer in cash register receipts has been shown to increase weight gain and body fat after developmental exposure in rats [325–327] and mice [319,328–330]. Some studies have not shown effects of BPA on weight gain [97,331] including government standardized study designs e.g. guideline studies, [332,333]. The two guideline studies with CD-SD rats, which appear to be relatively insensitive to xenoestrogens [334], showed no significant effects for any outcome measure. Also in one mouse study reporting no significant effect of BPA on body fat[331], the control animals were obese due to the use of casein-based feed, which increases body fat in CD-1 mice [335,336]. These studies differ with regard to several aspects including animal strain, doses, developmental windows, and diet which are likely responsible for the discordant results (reviewed in [337]). Also a distinction needs to be made between studies that only measured body weight (for example [329]) which is recognized to be a poor indicator of significant changes in body fat in rodents [7] and studies that actually measured body fat.

Human studies have shown that prenatal exposure to BPA was associated with increased body fat at age 7 [338] or BMI by age 9 [339] or accelerated postnatal growth without a change in BMI between age 2–5 [340] consistent with the DOHaD prediction that light at birth babies would experience increased rate of growth in childhood[14,341]. Not all epidemiology studies report a positive relationship between an exposure and a health outcome [339,340,342–344] which is not uncommon for studies linking environmental chemicals with adverse outcomes in humans, possibly due to potential for multiple environmental "stressors" to interact with chemical exposures [342,345,346]. Because of considerable within-person variability [347–350] and because most studies typically have only one sample to characterize exposure, BPA exposures may have been substantially misclassified and peak exposures, which generally occur in the evening, may have been underestimated [348]; these misclassifications may have increased the likelihood of a false negative outcome. Stronger attention is also needed for potential confounding by diet, which is only one source of BPA exposure [256,351]. Moreover, since the developing organism is more susceptible to BPA effects, epidemiology studies must consider the lifestage when exposure is measured. The inconsistencies in the data notwithstanding, there are data from both animal and human studies that support the hypothesis that developmental exposure to BPA can lead to an increase in weight gain later in life in exposed offspring.

Phthalates are a class of chemicals that promote flexibility in plastic products such as tubing and vinyl flooring. Fragrances and a variety of household and personal care products including food packaging also contain a variety of phthalates. Phthalate metabolites have been shown to activate PPAR receptors and have antiandrogenic effects which may contribute to the development

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of obesity [352]. Prenatal exposure of mice to one phthalate, DEHP, results in increased body weight as well as increased body fat in male offspring; similar findings were reported in studies from different labs using different animal models [353–356]. Epidemiologic data linking prenatal phthalate exposures to obesity are limited and mixed [357–361]. Although daily exposure measurements are less variable than BPA, phthalates are also prone to exposure misclassifications. One recent study found evidence of a sex-specific effect, with high molecular weight phthalates — including DEHP — associated with reduced BMI z-scores among boys, but increased BMI z-scores among girls from Spain [359]. DEHP metabolites were associated with lower BMI z-scores in ethnically diverse boys from a US cohort [357], and in children of both sexes in another [358]. However, high molecular weight phthalates were associated with higher BMI z-scores in US children of Mexican American and African American descent, though not in Whites [362]. Phthalate exposure during pregnancy was also associated with increased triglyceride levels in cord blood and with increased body mass three months after birth in boys [363]. While more data are needed, these data support the conclusion that developmental exposure to DEHP and perhaps other phthalates, depending on their molecular weight, can lead to increased weight gain in animal and human studies.

Tributyltin (TBT) [364,365] is an organotin used as a fungicide; it is a retinoic acid X receptor and PPARγ agonist. Several laboratories have shown that TBT stimulates adipogenesis in preadipoctyes in vitro [366–368,369]. Prenatal exposure to TBT results in increased lipid accumulation, increased adipose tissue mass (due to both adipocyte hyperplasia and hypertrophy), and reduced muscle mass that persists into adulthood and across generations in mouse models [307,364] and increased adiposity in zebrafish [370]. A recent study explored organotins and weight gain in humans for the first time, finding placental TBT to be associated with a non-significant trend towards higher weight gain, but only in the first three months of life [371]. These limited data in humans warrant further investigation, whereas the animal data strongly support the notion that TBT exposure during development may play a role in the obesity epidemic.

Polycyclic aromatic hydrocarbons (PAHs) are a family of environmental chemicals that are byproducts of fossil fuel burning which includes diesel exhaust, air pollution and cigarette smoke [206]. Prenatal exposure to a nebulized PAH mixture 5 days a week for three weeks led to increased weight, fat mass and higher gene expression of PPARγ, fatty acid synthase and adiponectin in mice[372]. Developmental exposure in rats to PAHs in diesel exhaust have been shown to lead to increased obesity, insulin resistance and inflammation; these effects were observed only in adults fed a high fat diet, indicating a second hit was needed, and only in males, indicating a sexually dimorphic effect [373,374]. Specific exposure to benzo (a) pyrene during development also resulted in increased visceral adipose tissue weight in female offspring [375].The use of different model systems and exposures limits our ability to determine the importance of PAHs as an important contributor to obesity. There are limited human data on the association of childhood obesity with maternal exposure to ambient PAHs, however a study by Rundle and colleagues [376] shows children born to mothers with the highest PAH exposures during pregnancy had higher body weights both at 5 and 7 years of age. The extensive exposure of populations to air pollution necessitates a further examination of its overall effects and its specific contribution to increased risk of obesity.

The most consistent human evidence that prenatal MDC exposure is associated with obesity in offspring is for several organochlorine compounds: the in vivo metabolites of DDT (DDE), as well as hexachlorobenzene (HCB) [309,310,377,378]. Persistent organic pollutants (POPs) are a class of chemicals that bioaccumulate in tissues and magnify in the food chain [379]. They include some pesticides (DDT, HCB) and some industrial chemicals such as polychlorinated biphenols (PCBs). While the use of these chemicals is banned in many countries (PCBs, HCB and DDT) exposures exist due to their persistence in the environment. In some countries like South Africa DDT is still used thus current exposure also exists. Exposure during early gestation to some POPs, namely PCBs, HCB and DDT, can lead to the development of obesity later in life [380,310,378,381–385]. In rodent studies, prenatal exposure to DDT followed by a high fat diet for 12 weeks in adulthood led to the development of glucose intolerance, hyperinsulinemia, dyslipidemia and altered bile acid metabolism as well as reduced energy expenditure and impaired thermogenesis as measured by reductions in core temperature in female offspring [386]. Six separate epidemiology studies showed that prenatal DDE exposures were associated with increased BMI in the offspring at ages 1 and 3 [387], at age 4 [378] and between ages 5–7 [381], as well as increased overweight at age 6.5 [383], 7 years [377], and age 9 [388]. Prenatal exposure to HCB has been associated with rapid growth in the first 6 months of life and obesity in infancy and childhood [380,389]. Similarly, prenatal exposure to specific PCB congeners resulted in increased BMI at 14 months [384], at 1 and 3 yrs. of age [387], and age 5 and 7 [390].

Effects of several POPs on growth may be sex-specific. For example, some associations between PCBs and measures of general or central obesity are specific to girls [381,383,391] while the weight gain due to DDT/DDE occurred in boys or girls depending on the cohort and conditions of the study. In addition, it remains uncertain to what extent the effects of these chemicals on long-term growth may be due to indirect effects, dependent on the mismatch between a prenatal environment that can program offspring to survive in an environment that inhibits growth and the energy-dense diets available in the postnatal environment. Many POPs for which prenatal exposure is associated with obesity are also associated with smaller size at birth [382], and thus associations with obesity may be, at least in part, related to rapid postnatal growth in these children, similar to that observed in offspring of smokers and malnourished infants [314,384,385,392]. In contrast to the human data, there is a paucity of animal data on the role of POPs on obesity; this area requires future study.

Data are limited, and sometimes inconsistent, for associations between obesity and a number of chemicals in humans [310] and animals [206]. For example, prenatal exposure to perfluorinated compounds, chemicals used to repel grease stains in carpets and clothing, was not associated with subsequent adiposity in childhood [393] in a recent study, though a prior study found such an association at age 20y [394]. Similarly, in animal models, one study found *in utero* exposure to perfluorooctanoic acid (PFOA) led to weight gain in offspring in outbred CD-1 mice [395] whereas another inbred transgenic mouse model did not show any weight gain [396]. The animal [397] and epidemiological data on obesogenic effects of prenatal exposure to arsenic [398,399] while limited are consistent across species. Cd, Pb and As exposures are associated with smaller size at birth [400–403] which is a risk factor for subsequent weight gain and greater adiposity. Prenatal exposure to toxic metals is also related to higher leptin at birth [404,405]. Similarly, limited but consistent data suggest obesity-related effects of exposures to various flame retardants *in utero* in humans with some indication of sex-specific effects [406]. Developmental exposure of rats to Firemaster 550, a flame retardant mixture, was associated with weight gain later in life [407].

Taken together, these observations support the relevance of the MDC hypothesis with respect to weight gain in animal and human studies.

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5.2. MDCs and fat cell differentiation and development

Preadipocytes such as 3T3-L1 cells are often used as models to test the ability of chemicals to induce adipogenesis. A recent study used 3T3-L1 cells and MSCs to evaluate the effects of a collection of chemicals on adipogenesis and adipogenic gene expression [408]. This study found that several pesticides with different chemical structures and modes of action, zoxamide, spirodiclofen, quinoxyfen, fludioxonil, tebupirimfos, forchlorfenuron, flusilazole, acetamaprid, and pymetrozine all induced adipogenesis and adipogenic gene expression in 3T3-L1 preadipocytes, whereas quinoxyfen and fludioxonil were also able to induce adipogenesis and adipogenic gene expression in MSCs [408,409] (Fig. 2). Dioxins and PCBs acting via the AhR alter the expression of important genes related to adipogenesis, lipid metabolism and inflammatory factors [410–414]. Activation of PPARγ via exogenous ligands such as rosiglitazone or TBT strongly promotes adipocyte differentiation and maintenance, together with the expression of genes involved in lipid droplet formation, glucose uptake, fatty acid synthesis, and adipokine secretion [415,416]. Other studies have identified BPA [132,417,418], bisphenol A diglycidyl ether [419], aklylphenols [420], phthalates [353,354,369,421,422] and flame retardants [369,421,423,424] as well as organochlorine [425,426] and neonicotinoid pesticides [427] as chemicals that can promote adipocyte differentiation.

In addition to differentiation of cell lines to adipocytes, it is also possible to regulate the fate of MSC to result in increased numbers of fat cells. Because multiple signaling pathways converge to regulate MSC fate, there are numerous opportunities for extrinsic factors to disrupt or modify differentiation. For example, the pesticides chlorpyrifos and carbofuran inhibited the ability of MSCs to differentiate into bone [428] although the potential to differentiate into fat was not tested. Treatment with the organotin TBT or the pharmaceutical rosiglitazone (ROSI) led to adipogenic differentiation of 3T3-L1 preadipocytes and MSCs in vitro [429,430] in a PPARγ-dependent manner [431]. The fungicides triflumizole [354] and tolyfluanid [431] also promoted adipocyte differentiation and gene expression in MSCs and 3T3-L1 cells. Prenatal exposure of pregnant mice to TBT or ROSI led to increased fat deposition at birth [364]. These exposures also diverted MSCs toward the adipogenic lineage at the expense of the osteogenic lineage [429]. Although adipogenesis and obesity have been the most studied outcome of exposure to obesogens and MDCs, it should be obvious that the bipotential switch between the adiopogenic and osteogenic lineages opens an entirely new field for the effects of MDCs on bone development and osteoporosis.

It is clear that chemicals can alter MSC lineage allocation in animal models; however, there are no studies that examine MSC lineage commitment in obese verses lean individuals. Nonetheless, it is worth focusing on the potential consequences of chemicals altering MSC lineage in humans. Obese individuals definitely have more fat cells than individuals of normal weight [106]. It is likely that obese individuals either were born with more fat cells because of prenatal programming or developed them early in life by mechanisms outlined above. It is probable that adipogenic stimuli (such as exposure to chemical obesogens or inappropriate diet) received perinatally or during adolescence permanently increased fat cell number. In turn, this creates an altered metabolic set-point that favors the storage of calories as fat. Once fat cell number is programmed, the number cannot be altered readily by diet, exercise, or even surgery [106]; many studies have documented the expansion of visceral fat depots in adults via increased adipocyte number [107,432,433] whereas permanent decreases in cell number accompanied by weight loss have not been documented. It is possible to successfully shrink the size of existing fat cells by faithful adherence to a restrictive diet and a vigorous exercise regimen. However, clinical studies repeatedly show that 83–87% of people who achieve significant weight loss regain the weight within a few years [434,435]. These data strongly suggest that obese individuals have altered metabolic set-points that favor calorie storage over the long term.

There is no evidence that lipid-depleted fat cells automatically undergo apoptosis. Indeed, it is difficult to envision how such a scenario would be favored over evolutionary time since healthy fat cells would be required for the organism to survive periods of fasting that regularly occur in hunter-gatherer societies. Moreover, expression of the satiety hormone, leptin closely parallels fat mass and small fat cells secrete the least leptin making it likely that shrunken fat cells would “crave to be filled” [436].

5.3. MDCs and neuroendocrine control of feeding and metabolism

Only a few studies have investigated the action of potential MDCs on neural circuits/cells and on the resulting feeding behavior and energy balance output. However, the neuroendocrine control of these features could be an important target of environmental chemicals.

Prenatal exposure to low doses of BPA alters the development of the POMC system in a sexually differentiated way [437]. The differences are evident when adult are exposed to a high-fat diet; in particular, males show reduced POMC fiber innervation of the PVN and increased NPY and AGRP expression in the ARC. Females exposed to BPA show reduced POMC expression and ERα expression patterns in the ARC similar to those seen in males, suggesting a masculinizing effect of BPA. Also, fetal exposure to BPA in mice alters food intake during puberty and in adulthood as well as leptin and insulin levels, which in turn regulate the NPY system [319].

Organotin compounds such as TBT have not only peripheral effects, but also may activate elements in the brain, in particular in a crucial region for the regulation of food intake, the ARC [438]. Adult mice exposed to TBT for 4 weeks show profound alterations of the leptin-NPY-NPY-Y1 receptor system [96,188]. Prenatal exposure to TBT also induces hypothyroidism in the progeny, while the acute treatment of pregnant females induces a dose-dependent increase of T3-independent TRH transcription levels [439] in the hypothalamus.

In summary, there are a number of important endpoints to study the effects of MDCs on the regulation of food intake and metabolism in the central nervous system. These include expression of the leptin receptor, ERα, thyroid hormone receptor (associated also with PPARγ), the POMC-CART system, the NPY-AGRP system and their receptor systems, and the dopaminergic system.

5.4. Sexually dimorphic effects

Because by definition they interfere with hormonal actions, sex specific effects are expected for many MDCs. A critical aspect regarding research on sex differences related to metabolic disease is that until recently, the majority of biomedical studies have focused only on males. With regard to the impact of MDCs on adipocity and metabolism, it is well known that females differ dramatically from males in subcutaneous fat deposition as well as in the endocrine function of adipocytes. For example, females have higher circulating concentrations of both leptin and adiponectin relative to males [176] Thus, while not all studies that examined a few outcomes of exposure in males and females report sex differences, one would expect on detailed examination to find sex differences. In this regard, some studies have demonstrated that MDCs can masculinize or feminize energy balancing traits depending upon type and dose of the tested chemical, the timing of exposure and the metabolic challenge. In experimental animals, sex-dependent differences in body weight in response to prenatal or early postnatal

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exposure to low doses of BPA or DES have been reported; both chemicals increased body weight in female rodents but decreased or did not affect it in males [326,440]. A recent study has examined in detail the energy balance traits of mice prenatally exposed either to a low or a high dose of BPA or to DES showing that exposure to BPA but not to DES hypermasculinized male and masculinized female mice (see also [437]). In addition, exposure to MDCs can diminish, eliminate, reverse or widen sex differences in behavior, thus interfering with normal sexual differentiation of the brain [441–444] which can also affect metabolic processes. For example, numerous studies have confirmed the ability of BPA to affect the rodent developing brain in a sex-specific manner (for review see [445] even at very low doses [446,447], indicating that the brain is a very sensitive target organ for BPA action. The cerebral cortex, hippocampus and hypothalamus are key sexually dimorphic regions in the rodent brain, and these brain areas can be affected by pre- and perinatal MDC exposure, with sex specific effects observable even before the increase in gonadal hormones during puberty. The developing hypothalamus has sex-specific vulnerability to BPA, with the preoptic area (POA) and mediobasal hypothalamus (MBH) being the most studied and robustly affected [448,449].

5.5. Type 2 diabetes (T2D)

Evidence that chemicals can disrupt the function of the endocrine pancreas dates to the early 1940s when alloxan, a glucose analogue which selectively destroys insulin producing cells in the pancreas, was shown to promote type 1 diabetes in rabbits [450]. This was followed by the discovery that streptozotocin similarly induced a diabetic state through selective β-cell destruction. Although humans are not exposed to alloxan or sreptozotocin, they are used in animal research on diabetes. Initial human evidence that synthetic chemicals promote the development of diabetes came from patients accidentally or intentionally exposed to pyrinuron (Vacor) [451]. Exposure to this rodenticide resulted in β-cell destruction and the development of type 1 diabetes [452]. More recently, a patient exposed to high levels of the fungicide chlorothalonil was reported to develop diabetic ketoacidosis, a condition arising from insulin deficiency [453]. These and other studies of environmental contaminants provide mechanistic insights into the pathways by which MDCs may promote diabetes pathogenesis through defects in β-cell physiology.

5.5.1. MDCs and beta cell survival and function

5.5.1.1. Cellular studies. A structurally diverse array of synthetic and inorganic toxicants disrupts β-cell survival and function in cell lines and isolated rodent islets. 2,3,7,8-tetrachlorodibenzodioxin (TCDD) reduces glucose-stimulated insulin secretion (GSIS) in isolated islets [412,454,455]. Similarly, DDT impairs both GSIS as well as insulin secretion in response to tolbutamide (a pharmacological insulin secretagogue) [456]. Among organotin compounds, triphenyltin was shown to disrupt cellular signaling in β-cells and impair insulin secretion in response to a variety of stimuli [457]. Similarly, inorganic contaminants including both inorganic and methylated arsenic [458–460], cadmium [461–463], and mercury [464] disrupt β-cell function (Fig. 2).

Interestingly, several compounds disrupt β-cell signaling and function in a manner that promotes insulin release. In the RINm5F cell line, a PCB mixture (Aroclor 1254) increased insulin secretion into the culture media, an effect recapitulated by coplanar PCB congeners [465]; TCDD also promotes continuous insulin release [466]. Interestingly, the insulin secretory effect resulted in a depletion of cellular insulin content by PCBs [465] and TCDD was proposed to promote β-cell "exhaustion" [466]. This suggests that prolonged exposure to these compounds could result in insulin deficiency.

BPA has been shown to augment GSIS; unlike TCDD and PCBs, low doses of BPA augmented β-cell insulin content in an ERα dependent manner [467]. A rapid action on insulin release was shown to be dependent on ERβ expression, and was confirmed in human as well as mouse islets [468,469]. Importantly, these effects of BPA may be representative of effects of other phenolic compounds because nonylphenol and octylphenol were also shown to augment GSIS in isolated rat islets [470].

In contrast to the extensive work examining MDC effects on β-cell physiology, less is known about the effects of environmental pollutants on α-cell biology. In early studies, cobalt was shown to be toxic to α-cells [471]. More recently, BPA has been shown to alter calcium signaling in α-cells [472]. Collectively, these data support the theory that the endocrine pancreas is an important target for the deleterious effects of MDCs on energy homeostasis.

5.5.1.2. Animal studies: exposures during adulthood. The strength of evidence supporting environmental toxicants altering β-cell physiology is reinforced by animal studies that examine the effects of whole-body exposure to a variety of MDCs on insulin secretion and glucose homeostasis. Although the focus of this review is on developmental exposure, in the case of MDCs exposures and T2D, it is important to also mention adult studies. These studies demonstrate a direct induction of insulin resistance without the need for an increase in weight or adiposity.

Adult mice exposed to TCDD exhibited reduced glucose-stimulated insulin release without concomitant hyperglycemia, an effect that was absent in AhR-null mice [454]. Furthermore, TCDD-exposed rats had islets depleted of insulin [412], similar to the depletion of secretory granules observed with chronic exposure to PCBs [473]. This contrasts with the effects of *in vivo* BPA exposure, which augments insulin release and increases β-cell insulin content in a murine model [467]. Oral administration of TBT was shown to promote hyperglycemia with reduced circulating insulin levels accompanied by increased islet apoptosis and reduced cellular proliferation, suggesting a β-cell defect as a contributing lesion to TBT-induced metabolic dysfunction [474].

The use of genetic models of type 1 and T2D have also unlocked the deleterious effects of MDCs on β-cell biology. In the db/db mouse model of T2D in which a defect in the leptin receptor promotes the development of obesity and diabetes, exposure to arsenic through drinking water enhanced the development of hyperglycemia with concomitant reductions in insulin levels, suggesting an arsenic-induced impairment in β-cell function [475]. The non-obese diabetic (NOD) mouse, in contrast, is a model of type 1 diabetes as these mice develop autoimmune inflammation of the pancreatic islets (insulitis) and insulinopenic diabetes. Chronic exposure to BPA modulates insulitis in female NOD mice with complex concentration-dependent effects [476].

5.5.1.3. Epidemiological studies in adult human populations. The effects of MDCs on β-cell physiology in adult human studies are limited. In a Northern Mexican cohort, inorganic arsenic exposure was associated with a reduction in β-cell function, with the effect amplified among those with T2D [477]. Along with larger epidemiologic literature linking arsenic exposure to diabetes [478–480], other studies have also found arsenic to be associated specifically with measures of β-cell dysfunction or reduced insulin secretion, more strongly than with measures of insulin resistance [481,482]. Epidemiological studies also suggest that BPA, phthalates, dioxins, and POPs including DDT metabolites and PCBs are associated with measures of altered glucose homeostasis including T2D [342,483–487]. In one recent study, urinary BPA concentration in US adults was associated with an increase in β-cell function, hyperinsulinemia and insulin resistance [488] preferentially in males. These results are similar to those obtained from studies performed in mice [467].

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Consistent with animal studies [489], a number of human studies —including studies among children and numerous studies in adults— suggest that DEHP is more strongly associated than are other phthalates with diabetes and other markers of impaired glucose metabolism [362,490–493], perhaps because of greater activation of PPARs. However, several other studies [494–496] found stronger evidence of associations with butyl phthalates, which have a weaker PPARγ affinity than do DEHP metabolites [497]. Because data thus far are limited, it is uncertain to what extent the mixed results in humans may be due to factors such as differences in exposures [494], measurement errors in estimates of exposure [347], or sex-specific effects [498]. Moreover, to date very few epidemiological studies have examined the developmental or perinatal exposures thought to have the most potent diabetogenic effects [499], though recent animal studies support adverse effects of ongoing exposures including those in adulthood [500,501]. Nonetheless, overall, these studies support the idea that MDC-induced disruptions in β-cell function may mediate some of the observed associations between environmental chemicals and diabetes in human populations.

5.5.1.4. Animal studies: gestational and perinatal exposures. While disruptions in glucose homeostasis due to diminished insulin action result from developmental exposure to several chemicals, evidence specifically linking MDCs to impaired β-cell function is less common (Fig. 3). In a rat model, females exposed to the phthalate DEHP throughout gestation and perinatal development exhibited hyperglycemia in the presence of reduced insulin levels [502]. Histological evaluation of pancreatic islets from weanlings revealed reductions in β-cell mass, reduced islet insulin content, and disruptions in β-cell ultrastructure [489]. In a similar model, restriction of exposure to days 9–21 of gestation, albeit to higher DEHP levels, similarly altered β-cell function and reduced insulin levels with hyperglycemia [503].

In the NOD model of type 1 diabetes, in utero and perinatal exposure to BPA increased the severity of insulitis at 11 weeks of age and increased the prevalence of diabetes at 20 weeks of age in female mice [504]. Interestingly, a recent study also demonstrated that BPA exposure during pregnancy promotes the development of glucose intolerance in later life through impairments in β-cell function and mass [505]. This suggests that exposures during pregnancy may alter the long-term metabolic trajectory of both the mother and her offspring. These studies support extending the view of 'developmental windows' beyond early life, as important periods of sensitivity to disruptions in β-cell function may be mediated by exposure to environmental toxicants during other critical periods, e.g. pregnancy.

Collectively, experimental evidence from cell lines to humans supports the endocrine pancreas as a target for disruption by diverse MDCs. Further work is required to determine the exposure conditions under which α- and β-cell physiology is disrupted in humans to better characterize the threat of exposures to MDCs to metabolic health.

5.5.2. MDCs, insulin action and glucose disposal

5.5.2.1. Cellular models. In addition to data demonstrating that MDCs disrupt insulin production, an increasing body of evidence suggests that a variety of MDCs have the capacity to impair peripheral insulin action. In diverse cell line and organ culture models of insulin-responsive tissues, an array of compounds have been shown to impair insulin signal transduction or insulin-stimulated glucose disposal, including TCDD [506,507], tolylfluanid [508], inorganic and methylated arsenic species [509,510], DEHP [511,512], and POPs [413]. In one model, BPA was also shown to inhibit insulin-stimulated glucose utilization in 3T3-L1 adipocytes [414] and another study showed that BPA can increase basal and insulin-stimulated glucose uptake in 3T3-F442A cells [409]. BPA also stimulated secretion of pro-inflammatory cytokines IL-6 and TNF while inhibiting the anti-inflammatory cytokine adiponectin from human adipoctyes in culture [513]. Collectively, these data suggest impairments in insulin action may result from exposure to a variety of environmental MDCs; however, dose, duration, and model system may alter the phenotypic response of some tissues to these compounds.

5.5.2.2. Adult animal studies. Evidence that MDCs disrupt cellular energy handling is supported by data from animal models in which multiple compounds have been shown to promote insulin resistance. For example, in vivo exposure to DEHP down-regulates expression of adipocyte insulin signaling intermediates [514], while rats exposed to BPA demonstrated a reduction of insulin signaling intermediates in both muscle [515] and liver [516]. Cadmium exposure has been shown to promote glucose intolerance with a specific reduction in adipose expression of Glut4 [517] and TCDD has been shown to also reduce glucose uptake in adipose and brain [518,519]. In addition, the fungicide tolylfluanid promotes glucose intolerance with concomitant global and adipose-specific insulin resistance, with the latter resulting from a specific down-regulation of insulin receptor substrate-1 (IRS-1) [520].

While less specific, a variety of studies have also shown that exposure to various organic and inorganic toxicants promotes global insulin resistance or glucose intolerance with associated shifts in serum insulin levels. For example, in vivo exposure to inorganic arsenic promotes glucose intolerance with concordant insulin resistance [475,521], including accentuation of the inherent insulin resistance of pregnancy [522]. Extended exposure to air pollution particular matter (PM2.5) for 24 weeks induced whole body insulin resistance in mice [523]. Acute and chronic malathion exposure resulted in increases in both glucose and insulin levels in rats [524]. Chronic exposure to POPs has also been shown to promote insulin resistance [500]. Similarly, BPA promotes insulin resistance in mice [467], and this effect can be observed with exposures as short as 8 days [525]. In addition to effects on β-cells, in vivo studies of TBT exposure in mice demonstrate hyperinsulinism [526].

While these studies emphasize the diverse array of compounds that can alter insulin action, key factors may modulate the ultimate metabolic phenotype. For example, female mice exposed to arsenic develop glucose intolerance; however, the etiology may be influenced by the background hormonal status of the animal as ovariectomized mice exhibit elevated insulin levels while those with intact ovaries have reduced insulin levels [527]. Furthermore, an animal's genetic background may also influence the phenotype. In one study, inorganic arsenic was shown to preferentially induce glucose intolerance in diabetic db/db mice but not non-diabetic mice [475]. Importantly, additional metabolic stressors such as high fat feeding may also modify MDC effects on energy homeostasis. Atrazine has been shown to promote insulin resistance, an effect exacerbated by a high fat diet [528]. BPA also promotes glucose intolerance and impair insulin action in a chronic model of exposure coupled with a high fat diet [529]. Interestingly, PCB77 and PCB126 were shown to impair glucose tolerance with the induction of systemic insulin resistance when coupled with a low fat diet; however, the effect of PCB77 on glucose tolerance was absent in the context of high fat diet but reemerged with weight loss [530]. Indeed, the evidence for diet-PCB interactions in promoting insulin resistance may be quite complex and congener-specific as exposure to the PCB mixture Aroclor 1254 induced insulin resistance in both lean and diet-induced obese states [531]. Similarly, in one epidemiology study, effects of PCBs on odds of diabetes appeared to be modified by intakes of fruits and vegetables [532]. Conversely, rats exposed to PM2.5 developed increased insulin levels and elevated HOMA-IR only in the context of a high fat diet [533] and Aroclor

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1260 administered to mice fed a high fat diet altered carbohydrate metabolism at multiple levels including glucose tolerance, insulin resistance/sensitivity, adipokines, pancreatic insulin secretion, and hepatic gluconeogenesis [534]. Taken together, this evidence suggests that the relationships between MDCs and dietary metabolic stressors are complex, with an ultimate phenotype that may be exposure-specific.

5.5.2.3. Animal studies: gestational and perinatal exposures. Various models have suggested that imbalances in insulin action can arise from MDC exposures during development. BPA enhanced the insulin resistance of pregnancy, with female offspring demonstrating higher insulin levels and males exhibiting glucose intolerance with systemic insulin resistance [535]. Insulin resistance was also observed in BPA-exposed rats [536], while another mouse model similarly demonstrated glucose intolerance with insulin resistance; however, the effect was observed only at low doses[319]. Metabolic stressors like high fat diet may be additive to the BPA-induced insulin resistance [329]. Indeed, high-fat diet potentiated GSIS impairments elicited by low doses of BPA given subcutaneously [537]. In the CD-1 mouse, however, developmental exposure to BPA did not alter glucose homeostasis in adult mice fed a normal chow or high fat diet [331]. Overall, these findings suggest that developmental BPA exposure can alter metabolism, albeit the ultimate metabolic phenotype may be modulated by genotype, diet and exposure patterns.

Additional studies have suggested that developmental exposure to other compounds can promote alterations in insulin action. For example, exposure to low doses of PFOA in midlife were shown to increase insulin levels [395], while PFOS exposure during gestation and early postnatal development resulted in glucose intolerance and insulin resistance [538]. Rats exposed to PFOS from gestation day 0 to postnatal day 21 also shown exhibited glucose intolerance with elevated insulin levels [539].

Developmental exposure to DEHP induces a complicated phenotype with the development of hyperglycemia with reduced insulin levels in female rats, while male offspring had elevated insulin levels but normal glucose tolerance [489]. In another model, DEHP exposure led to glucose intolerance with insulin resistance in the offspring, although this model also revealed central defects in β-cell function as well [503]. Sex-specific effects of DEHP on measures of insulin resistance have been reported in some epidemiological studies [493], but not others [540].

These data suggest that both adult and developmental exposures to various MDCs have the capacity to modulate insulin action globally as well as at the cellular level. This conclusion is further supported by a number of studies, not discussed, in which MDC exposure promoted glucose intolerance without examination of insulin levels or action. However, the precise mechanism(s) by which this common phenotype occurs remains somewhat obscure. Examining the totality of the data, several molecular pathways are implicated as potential mechanisms of altered insulin action. These include increased production of proinflammatory cytokines that induce insulin resistance such as TNFα and IL-6 [506,523,541], increased oxidative stress [464,475,514,524,542], and mitochondrial dysfunction [528], which may also increase oxidative damage. Further work is required to fully characterize the modes by which MDCs promote impaired insulin action to devise strategies to mitigate their adverse effects on global energy homeostasis.

5.5.3. MDCs and energy homeostasis

In addition to the effects of MDCs on insulin production and action, specific defects in intermediary metabolism have also been described for MDCs using a variety of model systems. For example, in the 3T3-F442a cell line, TCDD reduces expression of lipoprotein lipase [507], suggesting one mechanism by which MDCs may promote hypertriglyceridemia. PBDE exposure inhibits adipose glucose oxidation while augmenting isoproterenol-induced lipolysis [543], potentially increasing circulating free fatty acid levels, which are substrates for hepatic triglyceride synthesis.

Additional lipid abnormalities may be induced by perinatal exposure to 4-nonylphenol which has been shown to increase serum total cholesterol [420]. Disruptions in hepatic metabolic function were shown with subchronic exposure to malathion, which induced hyperglycemia with evidence of increased hepatic gluconeogenesis and glycogenolysis [544]. Chronic intake of DEHP impairs glucose tolerance with an alteration in glycolytic intermediates in both liver and muscle that were suggestive of impaired lactate as well as glucose handling [545]. In utero and lactational exposure to BPA in a rat model demonstrated a reduction in hepatic glycogen content at 21 weeks of age with evidence that the promoter for hepatic glucokinase was hypermethylated, suggesting a reduction in the expression of this key enzyme [536]. In a multigenerational rat model, BPA exposure in the F0 generation promoted glucose intolerance and insulin resistance in the F2 generation with an associated reduction in hepatic glucokinase expression and concomitant hypermethylation of the gene promoter [546]. Interestingly, adult mice exposed to BPA have also been shown to exhibit reduced hepatic glucokinase activity [547]. This suggests that disruptions in hepatic glucose handling may be a common mode by which MDCs promote metabolic dysfunction.

5.6. MDCs, hepatic steatosis, and hyperlipidemia

Developmental studies examining MDCs and liver health endpoints have been conducted in laboratory animals, but epidemiology studies examining the developmental basis of these diseases are lacking. This is likely due to the relatively long time to develop clinically apparent human liver disease owing to the slowly progressive nature of hepatic fibrosis. Compounding the problem, routine clinical biomarkers (e.g. alanine aminotransferase) may be insensitive for the detection of environmental liver disease[548] Novel biomarkers for fatty liver disease and fibrosis [549] are being developed for clinical use, and perhaps these could be applied to future environmental epidemiology studies. Due to the relative lack of epidemiological data on developmental MDC exposures in steatosis and hyperlipidemia, post-developmental studies (adolescent and adult) provide 'proof of concept' and thus are reviewed below.

5.6.1. Adult MDC exposures, steatosis and hyperlipidemia

Hepatic steatosis is likely to be the most common pathologic liver responses to chemical exposures [163]. Indeed, hepatic steatosis was noted in approximately 8–10% of rodent studies warehoused in the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) database and the Toxicological Reference Database (pesticide) [162,550]. Furthermore, in the Chemical Effects in Biological Systems (CEBS) data repository of the US National Toxicology Program (NTP), 329 rodent studies of 81 unique chemicals reported hepatic steatosis [550]. Whatever its etiology, hepatic steatosis is invariably associated with insulin resistance [163]. However, this interaction is complex as fatty liver disease is both a cause and effect of insulin resistance.

While some chemicals (e.g. vinyl chloride) appear to directly cause steatosis and steatohepatitis [551], other chemicals such as non-dioxin like PCBs merely modify the hepatic response to diet-induced obesity [534]. These chemicals may be a 'second hit' in the progression of diet-induced steatosis to frank steatohepatitis, which may further progress to cirrhosis and hepatocellular carcinoma. Many non-dioxin like PCBs interact with NR1 class nuclear receptors such as PXR and CAR [552]. However, the role of MDC-nuclear receptor interactions in fatty liver disease is likely to be

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complex, as PPARγ agonists (e.g. obesogens) have been proposed as treatments for non-alcoholic fatty liver disease and associated insulin resistance [553]. Nuclear receptor crosstalk especially at the liver X receptor response element is also likely to be important, but is currently understudied. Other proposed mechanisms include oxidative/carbonyl stress, endoplasmic reticulum stress, mitochondrial dysfunction, increased cytokine production, increased hepatic lipid synthesis/uptake and impaired VLDL synthesis and secretion [162,163]. Many of the environmental chemicals associated with steatosis are organochlorines. Of the compounds in the US Environmental Protection Agency's Integrated Risk Information System (IRIS) that induced steatosis in rodents following oral (dietary) treatment, the most potent (mirex, chlordecone, chlordane) were structurally similar, highly chlorinated molecules (>8 chlorines) [162]. While these data suggest that highly halogenated environmental chemicals could be of particular interest in steatosis, more data are required.

Key chemical classes identified in adult steatosis studies include solvents and volatile organic chemicals; POPs and pesticides; and metals [163,550]. Solvent exposures have historically been associated with steatosis and liver injury in the occupational health literature [551,554]. These data were recently reviewed by the Institute of Medicine and the National Research Council which concluded that there was "...evidence of an association between chronic exposure to solvents in general and hepatic steatosis that could persist after cessation of exposure" [555,556]. Unfortunately, it is difficult to assess biomarkers of prior solvent exposures, and epidemiological data on the impact of solvent exposures in human cohorts are lacking.

Exposure to BPA is associated with liver enzyme abnormalities reflective of liver injury in population-based studies [341,557], although pathologic data were not provided. Regarding dyslipidemia, non-significant trends were observed for BPA in pediatric NHANES populations [558]. However, prolonged (8-month) exposure of male mice to low BPA doses induced hypercholesterolemia with upregulation of key genes involved in cholesterol biosynthesis including sterol regulatory element-binding protein 2. Whole body *de novo* cholesterol synthesis was also increased as seen by the plasma lathosterol-to-cholesterol ratio [501]. Interestingly, the food contaminant 1,3-dichloro-2-propanol induced hyperlipidemia with increased LDL/HDL ratio in mice via the AMP-activated protein kinase (AMPK) signaling pathway [559].

Exposures to POPs and pesticides have been associated with fatty liver disease in adults. In the NHANES study, PCB exposures were associated with 'unexplained alanine aminotransferase (ALT) elevation', a surrogate marker for fatty liver [560]. The observed association between PCB exposures and ALT was subsequently confirmed in NHANES by two other independent groups using different statistical techniques; and also in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort [561–563]. Likewise, associations between organochlorine pesticides or their metabolites and liver enzymes have been seen for ALT [561] and gamma glutamyl transferase [564]. Perfluorinated chemical exposures were also positively associated with ALT in NHANES [565], and this association was more evident for PFOA exposures in obese adults [566]. Positive associations were also seen between both PFOA and PFOS exposures in adult participants of the C8 study (n = 47,092 subjects) [567]. Animal studies of PCBs [160–162,534,550,568], organochlorine pesticides [162], and PFOA [569] suggest that the liver enzyme abnormalities reported in these adult epidemiological studies could be due to fatty liver disease.

In population-based studies of hyperlipidemia, PCB exposures were associated with longitudinal increases in LDL cholesterol [570]. However, other studies reported nonlinear associations between PCBs and organochlorine pesticides with hyperlipidemia [571,572]. PCB treatment has been associated with hyperlipidemia in some [573], but not all rodent studies [548]. The chlorinated insecticide, lindane, interacts with ERβ [574], and high-dose lindane exposure (12 mg/kg × 20 days) in rats increased serum total cholesterol and triglycerides while decreasing HDL cholesterol [575]. On the other hand, TCDD decreased total cholesterol, LDL, and HDL in a rodent study suggesting an AhR-mediated serum lipid clearance and decreased hepatic efflux [576].

Metals/metalloids have also been associated with abnormal liver function and hyperlipidemia. In Bangladesh, drinking from arsenic contaminated wells was associated with increased ALT [577]. Chronic arsenic exposures were also associated with increased triglycerides in a cross-sectional study [578]; in rats, arsenic increased serum cholesterol, triglycerides, free fatty acids and phospholipids in association with increased oxidative stress and hepatic mitochondrial damage [579] as well as ALT when combined with an obesogenic agent [580,581]. Lead and mercury exposures were associated with the fatty liver surrogate biomarker, 'unexplained ALT elevation' in adult NHANES [560]; and lead, but not mercury, was associated with ALT, plasma triglycerides and LDL, in Iranian adolescents [582]. In mice, however, methylmercury markedly and specifically increased total and LDL cholesterol [583]. Cadmium exposures were also associated with ALT in adult Korean NHANES participants [584] and Iranian adolescents [585].

Animal studies suggest that the observed ALT elevations in the adult/adolescent populations following exposures to arsenic [581], mercury [586], and cadmium [587] may be due to fatty liver disease. Thus, data implicate post-developmental exposures to specific volatile organic compounds/solvents, plasticizers, POPs, and metals/metalloids in hepatic steatosis and dyslipidemia.

The herbicide, atrazine, is a chloroplast inhibitor which has also been associated with mitochondrial dysfunction and NAFLD in rodents [528,588,589] Respiratory routes of exposure have also been associated with the development of fatty liver disease via the lung-liver axis. For example, air pollution and particulate matter were associated with steatohepatitis in rodents [590,591], though mechanisms including toll-like receptor activation. However, confirmation in human studies is required. While smoking has not historically been considered to be a clinically significant factor in the pathogenesis of liver disease, recent data demonstrate a link between active and secondhand smoke in the development of both adult and pediatric NAFLD [592–595].

5.6.2. Developmental MDC exposures and hepatic steatosis

Given the liver's importance in toxicology, it is somewhat surprising that only scattered evidence exists to characterize pathways and patterns of its altered functional development. Nevertheless, a number of rodent studies suggest that specific developmental perturbations to liver programming may influence the long-term predisposition to steatohepatitis and MetS. Of great interest is the multi-generational effect of maternal high-fat feeding, which may prime steatohepatitis in adult mice offspring [596–598] (Fig. 4). These effects result from mechanisms similar to those observed in adult steatohepatitis studies including increased lipogenic gene expression with mitochondrial dysfunction and decreased beta oxidation, due in part, to altered PPARα/PPARγ expression; microRNA changes; increased oxidative stress with reduction in hepatic antioxidant enzymes; and increased inflammation.

Likewise, maternal exposures to chemicals have been associated with altered hepatic metabolism and steatosis in offspring. Exposure throughout gestation and perinatal development to BPA may further exacerbate the nonalcoholic steatohepatitis-like phenotype in male rats that were fed a high-fat diet post-weaning; in particular, BPA worsened the accumulation of lipids in hepatocytes as well as liver inflammation and oxidative stress fibrosis [599]. Liver

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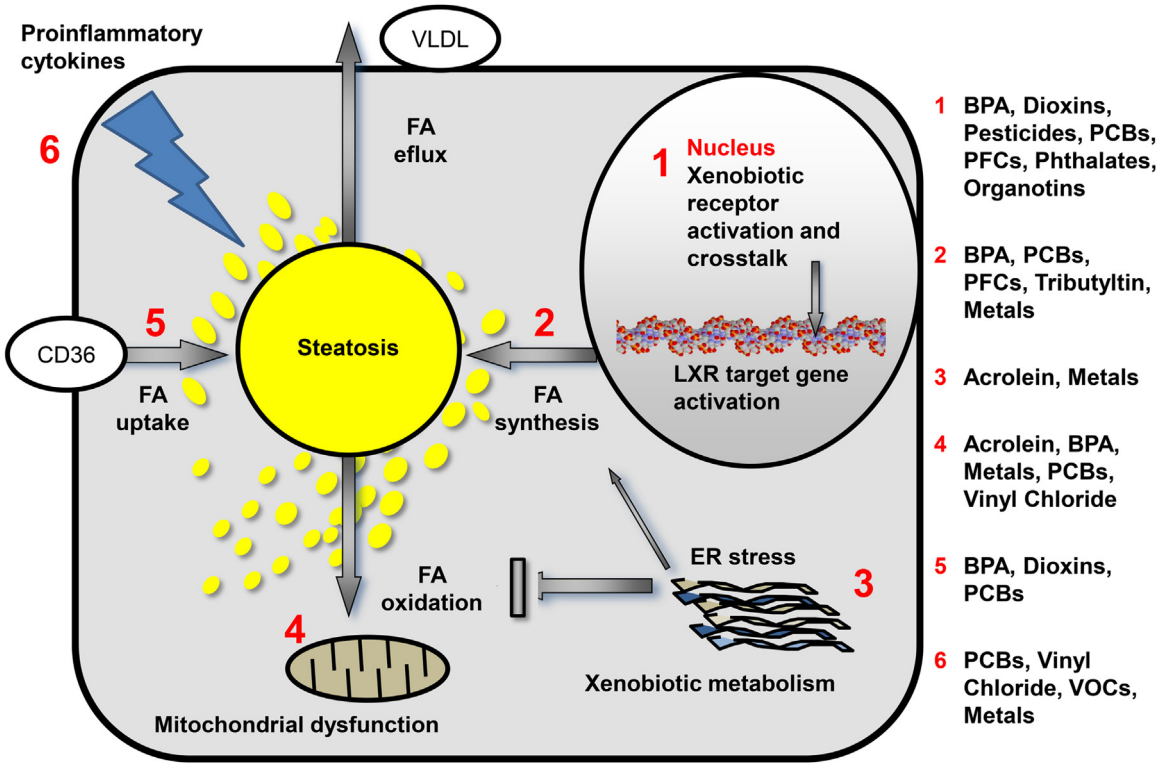

Fig. 4. Regulation of hepatic lipid metabolism and sites of action of metabolism disruptors.

function markers were unimpaired in BPA-exposed rats kept on a standard diet; however, these animals showed effects suggestive of subtle alterations of liver programming, such as moderately increased steatosis and altered expression of insulin signaling elements.

Epigenetic changes may be a hotspot in altered liver programming: developmental BPA exposure alters gene methylation in mouse liver, in particular concerning genes relevant to metabolism and stimulus response. As observed for other molecular and cellular effects of EDCs, the effects of BPA were different at low and high dose levels (0.05 and 50 mg/kg bw, respectively) [600]. Overall, the findings suggest that the developmentally-induced altered liver methylome increased insulin resistance phenotypes in adults. Some of these effects may have been related to hepatic changes including altered nuclear receptor expression (PPARα/PPARγ) key regulators of energy metabolism, mitochondrial dysfunction, and DNA methylation.

Gestational exposures to, DEHP, also resulted in hepatic steatosis in offspring as well as decreased glycogen storage in males, but with a delayed shift to glycogen-dependent metabolism of the mature hepatocyte [601]. This phenotype could stem from the DEHP-PPARα interactions influencing expression of lipid metabolism genes such as microsomal triglyceride transfer protein [602]. However, DEHP also interacts with other nuclear receptors including CAR and PXR. While there is no direct evidence of the involvement of CAR and/or PXR in the DEHP-induced effects on liver metabolic programming, nevertheless, their involvement is plausible and deserves attention for potential human disease relevance. While DEHP is a less potent human than rodent PPARα activator, it more potently activates human CAR [603].

While probably best characterized for plasticizers (BPA, DEHP), developmental exposures to other toxicants including benzo[a]pyrene, TBT, PBDEs, and pesticides have also been associated with development of fatty liver disease and/or abnormal hepatic lipid metabolism in rodents [365,375,550,604]. Rats perinatally exposed to polybrominated diphenyl ether 47 (PBDE-47) had increased blood cholesterol levels [605]. Altered blood cholesterol was likely a result of reduced hepatic Cyp7a1 expression, a critical enzyme for the conversion of cholesterol into bile acids [604,605]. Exposure to BDE-47 and DE-71 (a commercial mix of PBDE) resulted in transcriptomic enrichment of genes of lipid metabolism in rat livers [604,605], including long-term systematic activation of pathways of α, ω, and β-oxidation of fatty acids.

Overall, the available evidence indicates that liver programming may be an important target for MDCs that increase predisposition to MetS. Relevant morphological changes include increased lipid accumulation and depleted glycogen storage in hepatocytes; changes at molecular or biochemical levels may include altered methylation patterns, altered nuclear receptor cross-talk, mitochondrial dysfunction, and enhanced free radical production. However, more data are needed to define the set of chemicals that result in steatosis and dyslipidemia following developmental exposure and the mode of action of these chemicals in fatty liver disease. While the animal study data are compelling for developmental BPA exposures and steatosis, significant knowledge gaps exist for other MDCs. Epidemiological data are also very limited in this area.

5.7. MDCs and metabolic syndrome

As noted above there are MDCs that can result in obesity, T2D or lipid disorders. What is striking is that when multiple endpoints were examined within individual studies, in many cases an MDC caused disruptions in multiple disease pathways leading to what could be called MetS. Table 1 shows that indeed many EDCs should be characterized as MDCs as they can cause multiple disease/dysfunctions, even when not all of the metabolic endpoints were measured in the same experiment. We highlight examples here to show that indeed there are MDCs that can affect multiple tissues leading to multiple metabolic disorders and in some cases to MetS due to their ability to induce weight gain, glucose intol-

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Table 1
Metabolism Disruptors and Metabolic Disruption.

Chemical	Obesity	T2D	Lipid Disorders
Chemical	Obesity	T2D	Fatty Liver
Bisphenol A	***	***	***
DEHP	***	***	***
DDT/DDE	***	**	*
PBDE			*
PFOA	**		***
PFOS		*	***
TBT	***	***	***
Air Pollution	**	***	***
PAHs			
PCBs	*	***	***
TCDD		**	***
Cadmium		*	**
Atrazine		*	**
Arsenic	**	***	***
HCB	*		
Trifumizole	*		
Benzo(a) pyrene	*		**
Tolyfuanid	*	*	
Smoking/nicotine	***	**	***

This table has been developed from the literature cited in this review. The number of *** indicates the strength of the evidence. * indicates one manuscript animal or human, ** indicates one manuscript in animal and human or more than one manuscript in either animal or human and *** indicates more than one manuscript in both animal and human studies, or multiple manuscripts in animal studies.

erance and lipid disorders. These data indicate it is important to examine more than one endpoint and tissue to define an action of a suspected MDC.

The first example comes from developmental exposure to BPA, which can induce glucose intolerance and insulin resistance [329], and impairments β-cell function and mass [505]. Developmental exposure to BPA has also been shown to cause weight gain in offspring in some animal models and human studies (reviewed in [337]). BPA exposure throughout gestation and perinatal development exacerbates a nonalcoholic steatohepatitis-like phenotype in male rats that were fed a high-fat diet post-weaning; in particular, BPA worsened the accumulation of lipids in hepatocytes as well as liver inflammation and oxidative stress fibrosis [599].

Similarly, rats exposed to DEHP throughout gestation and perinatal development exhibited hyperglycemia in the presence of reduced insulin levels [502] along with reductions in β-cell mass, reduced islet insulin content, and disruptions in β-cell ultrastructure [489]. Sex-specific effects of DEHP on measures of insulin resistance have been reported in some epidemiological studies[493]. Gestational exposures to DEHP resulted in hepatic steatosis in offspring as well as decreased glycogen storage in males, but with a delayed shift to glycogen-dependent metabolism of the mature hepatocyte [601]. Prenatal exposure of mice to DEHP results in increased body weight as well as numbers and size of adipocytes in male offspring in several studies from different labs using different models [353–356].

DDT and its metabolites have been associated with increased risk of higher body weight, insulin resistance, T2D and dyslipidemia in human studies [572,606]. In rodent studies, female offspring exposed prenatally to DDT followed by a high fat diet for 12 weeks in adulthood developed glucose intolerance, hyperinsulinemia, dyslipidemia and altered bile acid metabolism as well as reduced energy expenditure and impaired thermogenesis [386]. DDT effects were also transmitted across generations resulting in obesity in the F3 generation [607].

PBDEs have also been associated with development of fatty liver disease and/or abnormal hepatic lipid metabolism in rodent studies [365,375,550,604]. Exposure to BDE-47 and DE-71 resulted in transcriptomic enrichment of genes of lipid metabolism in rat livers [604,605], including long-term systematic activation of pathways of α, ω, and β-oxidation of fatty acids. Developmental exposure in a rodent model to a specific PBDE mixture, Firemaster 550, resulted in weight gain in the offspring [407].

Prenatal exposure to TBT in mice promotes adipocyte differentiation that results in increased lipid accumulation and adipose tissue while reducing muscle mass that persists into adulthood and across generations [307,364]. It also increases adiposity in zebrafish [370]. One epidemiology study noted that prenatal TBT exposures were associated with a non-significant trend towards higher weight gain in the first three months of life [371]. In a transgenerational study, TBT resulted in hepatic steatosis through the F3 generation. Finally TBT was shown to promote hyperglycemia with reduced circulating insulin levels accompanied by increased islet apoptosis and reduced cellular proliferation, suggesting a β-cell defect as a contributing lesion to TBT-induced metabolic dysfunction [474].

Among the other chemicals summarized in Table 1, developmental exposure to PAHs in a rodent model induce obesity, insulin resistance and inflammation in adults on a high fat diet [373,374]. In a human cohort, children of mothers with the highest PAHs exposure during pregnancy had increased weight at 5 and 7 years of age [376]. Prenatal exposure to specific PCB congeners in birth cohort studies was shown to result in increased BMI in offspring [384,387,390]. Arsenic also deserves mention because of its specific association with insulin dysregulation and T2D and liver toxicity [475,521,527,581]

5.8. MDCs and transgenerational metabolic disruption

A variety of stressors including high-fat, high-sugar diets, low protein diets and environmental chemicals can induce transgenerational inheritance of metabolic diseases [608]. Several recent papers have shown that the effects of MDC exposure in pregnant F0 animals were propagated until at least the F3 generation (reviewed in [307,609,610]). This is significant because when exposures occur in the maternal lineage, the F0 and F1 animals are directly exposed to the chemical and the F2 generation is exposed as germ cells within the gestating F1 animals. The F3 generation is the first generation that has not received any direct chemical exposure; therefore, effects observed in F3 and beyond are considered to be transgenerational and permanent, and are distinguished from the multigenerational effects in F1 and F2 animals [611].

Exposure of pregnant F0 animals to low, environmentally-relevant levels of TBT in their drinking water led to increased fat depot size, MSCs reprogrammed toward the adipogenic lineage and hepatic steatosis through the F3 generation [365]. Effects on fat depot size were more pronounced in F1 females than F1 males. Prenatal TBT exposure permanently alters MSC cell fate in both males and females and caused hepatic steatosis and altered hepatic gene expression in both males and females through the F3 generation. Skinner and colleagues have similarly shown that plastic components such as BPA, DEHP, dibutyl phthalate [355], a mixed hydrocarbon mixture (jet fuel JP-8) [355], and DDT [355] all lead to a transgenerational predisposition to obesity in the F3 generation. The molecular mechanisms remain unclear; however, many of the toxicants work through nuclear receptors [610] that are likely linked to epigenetic changes [612,613] that likely play a significant role in the transgenerational effects. Imprinting, altered DNA methylation, histone modifications and copy number variants have all been implicated in transgenerational phenotype transmission as a result of exposure to chemicals or altered nutrition [609,614–616]. Candidate sperm epimutations were also identified that could be involved in the etiology of the transgenerational obesity and other disease outcomes Guerrero-Bosagna, Weeks [617].

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6. Conclusions: a perfect storm for metabolic disease

Many of the studies discussed above highlight the importance of development as a sensitive time for programming all aspects of metabolism. Environmental chemicals with endocrine activity can alter programming of metabolism; this fact, along with the importance of diet during development and throughout life on metabolism, and the role for exercise in controlling weight and glucose metabolism, leads to the perfect storm for metabolic disease. *In utero*, and the first few years of life, are critical periods where the sensitivity or set point for obesity, diabetes and liver disease are established. We have herein shown that sensitivity or set points for the development of these diseases can be altered by MDCs that interfere with the normal developmental trajectories of adipose tissue, pancreas, muscle, liver, GI tract and the brain. These set points are also influenced by diet and nutrition *in utero* and early childhood years, thus nutrition and MDC exposures during development are the key along with genetic background for setting the stage for all metabolic diseases.

These metabolic diseases may not manifest until later in life when the system is challenged by over-nutrition and/or lack of exercise. MDCs can change the expression of genes involved in the control of adipogenesis as well as glucose and lipid metabolism. Exposure to MDCs, together with excess calories and lack of exercise, would increase the susceptibility to these disease epidemics. Thus, we propose that some individuals are more prone to gain weight due to both their genetic background and the effects of developmental exposures to MDCs that are critical for setting the sensitivity or susceptibility of the tissues for metabolic disruption later in life.

Some recent publications support increased susceptibility to obesity due to environmental exposures. Developmental exposure to BPA induced weight gain due to increased food intake, changes in brain satiety neurons [618] and decreased activity and energy expenditure in females Johnson, Painter [619]. Similarly, prenatal nicotine leads to increased body weight due to a marked hypertrophy of adipocytes and fat deposition along with decreased spontaneous physical activity later in life, cold intolerance, and also increased sensitivity to the effects of high fat diet [311]. In addition, there are many examples of the effects of developmental exposures to MDCs that are exacerbated by high fat diet later in life, again indicating that developmental exposures increase the susceptibility to obesity (and other metabolic diseases) but may need a "second hit" later in life for the effects to actually become apparent as disease. For example, developmental exposure to PAH results in obesity, insulin resistance and inflammation only after a high fat diet as adults [373,374]; the effect of atrazine on insulin resistance was exacerbated by high fat diet [528]; and BPA-induced insulin resistance may be additive with high fat diet [329]. Thus there are emerging data supporting a role for developmental exposures to MDCs in altering the set point of susceptibility for metabolic diseases later in life. The second hit of high fat diet and lack of exercise then results in onset of the metabolic diseases.

Of course, throughout life there are likely to be multiple exposures to MDCs that can also increase sensitivity to metabolic disruption leading to weight gain, altered glucose tolerance and lipid disorders. For example, young mice exposed to BPA for 30 days showed significantly increased body weight and fat mass on a chow diet [330] but not on HFD (45%) which could be due to the overwhelming effect of the HFD. If true, then it would be difficult to control or treat metabolic disorders with pharmaceuticals later in life, as they would need to be able to offset the increased sensitivity programmed during early development. Indeed, the current state of science and medicine focuses on losing weight, and restoring glucose homeostasis and liver lipids after they are disrupted; it is clear that this approach is not working as the incidence of these diseases continues to increase. Furthermore, it is well documented that while it is possible to lose weight and keep it off for an extended time, the vast majority of people will gain the weight back, perhaps indicating they are fighting against a set point or sensitivity to develop these metabolic problems that favors calorie storage over the long term [434,435,620,621].

For this reason, a consequence of the MDC hypothesis is that a focus should be on prevention instead of intervention. If indeed a set point for body weight, diabetes and/or METS is developed in early life, then a better approach would be to focus on limiting factors that can alter programming during these sensitive times; for example, addressing these metabolic epidemics will require reducing MDC exposures and improving early-life nutrition. In this way, the MDC hypothesis offers the ability to actually prevent these diseases, which is more cost effective and public health protective than the current focus on interventions after the diseases are apparent. Primary prevention measures must include up-to-date regulation of chemicals: robust tools are needed in order to identify MDCs among existing as well as new chemicals.

The MDC hypothesis proposes both a mechanism for the increased epidemic of obesity, diabetes and MetS and a solution. If indeed these diseases are due in part to developmental exposures to MDCs, as proposed, then for the first time there is a path to actually preventing them. The MDC hypothesis changes the focus from genetics to environmental exposures and from intervention to prevention.

Peripheral signals reach the central nervous system through two main routes:

Adiposity Signals (leptin, insulin and others) and hunger (Ghrelin, Orexin A, and others) signals bypass the blood brain barrier and target the hypothalamus (transparent blue circle), in particular the arcuate nucleus (ARC).

b) Peripheral hunger and satiety signals that control meal processing, gastrointestinal activity and changes in energy stores reach the brainstem (nucleus of the solitary tract, NST) through vagal and other sensory nerve fibers.

NPY and MSH neurons located within the ARC (stimulated or inhibited by adiposity and hunger signals) project to other hypothalamic nuclei (paraventricular nucleus, PVN, lateral hypothalamic nucleus, LH, and others). In particular, within the PVN they control CRH and TRH neurons, regulating (via the adenohypophysis) the hypophysis-adrenal and hypophysis-thyroid axes.

From the hypothalamus, catabolic and anabolic pathways reach the brainstem where their data are integrated with the peripheral signals carried by the sensory system. There are also ascending projections from the NST that may reach the hypothalamus, through the lemniscus visceralis, contributing to adaptative changes in food intake and energy expenditure.

1. Mesenchymal stem cells commit to the adipogenic lineage and become preadipocytes. Commitment to the adipocyte lineage is mediated by transcription factors Zfp423, Zfp467, Schnurri2, Tcf7l1 and the mTORC1 effector S6K1. 2. Adipocyte differentiation is primarily controlled by PPARγ and CCAAT-enchancer binding proteins (C/EBP)α, β and δ which establish a sustained feedback loop. Numerous chemicals are capable of differentiating pre-adipocytes into mature adipocytes. Adipocyte number and size can be increased in vivo under hormonal control and can also be influenced by chemical exposure. 3. Adipocyte hyperplasia has been shown in rodents to be caused by perinatal exposure to a variety of chemicals. 4. Adipocyte hypertrophy in rodents due to permanent upregulation of genes involved in lipid uptake

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is also caused by exposure during perinatal life to a number of chemicals.

Glucose enters pancreatic beta-cells through glucose transporters (GLUT2 in mice and GLUT1 in humans) where it is metabolized in mitochondria resulting in an increase in the ATP/ADP ratio; this results in closure of membrane ATP-sensitive K^+ channels (K_{ATP}) that are responsible for the resting membrane potential. K_{ATP} channel closure results in cellular depolarization that opens voltage-gated calcium channels, triggering Ca^{2+} signals that induce insulin granule exocytosis and a subsequent rise in circulating insulin levels. This secretory pathway is disrupted by EDCs at different points: 1) Bisphenol-A, nonylphenol, octylphenol and triphenyltin impair mitochondrial function. 2) Bisphenol-A blocks K_{ATP} channels after binding ERbeta. 3) Calcium signaling is altered by Bisphenol-A, Arsenic, PCBs and Triphenyltin. 4) disruption of insulin secretion has been described for Bisphenol-A, dioxins, PCBs, DDT, Arsenic, and Cadmium. Beta-cells have a low antioxidant capacity and are very sensitive to oxidative stress mediated by reactive oxygen and nitrogen species that impair their function by altering metabolism and/or K_{ATP} activity while inducing apoptosis. Mercury and Cadmium (5) are EDCs that produce oxidative stress in beta-cells. 6) Insulin gene expression is regulated by BPA via ERα, while DEHP and Cadmium provoke cell death and decrease in beta-cell mass.

Hepatic steatosis occurs due to a combination of increased fatty acid (FA) synthesis or uptake and decrease FA oxidation or efflux. FA synthesis occurs as a consequence of liver X receptor (LXR) target gene activation which may occur following receptor activation by myriad environmental chemicals or via nuclear receptor cross talk. FA synthesis is upregulated by BPA, metals, PFCs, POPs, and tributyltin. BPA and POPs also upregulate scavenger receptors (e.g. CD36) to increase FA uptake into hepatocytes. Decreased FA oxidation is a consequence of mitochondrial dysfunction which may be mediated by BPA, chlorinated solvents POPs and metals. Liver also mediates xenobiotic metabolism which may increase oxidative stress. Endoplasmic reticulum (ER) stress is a consequence of exposures to aldehydes and metals. ER stress, in turn, impacts FA metabolism. Steatohepatitis occurs due to increased hepatic inflammation and cytokines. Proinflammatory cytokines are induced by many exposures including POPs, vinyl chloride, VOCs, and metals. More data are needed on the impact of MDCs on FA efflux in hepatic steatosis.

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