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Obesity I: Overview and Molecular and Biochemical Mechanisms

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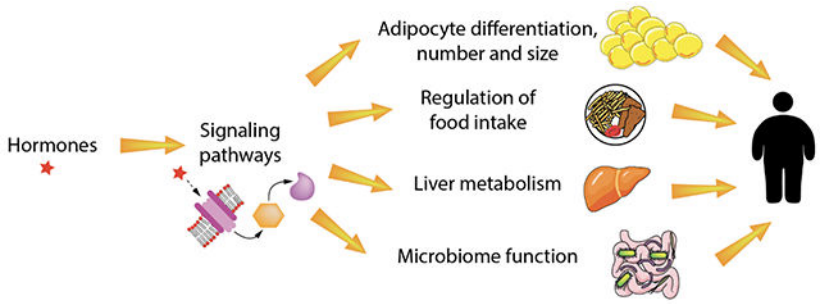
Abstract

Obesity is a chronic, relapsing condition characterized by excess body fat. Its prevalence has increased globally since the 1970s, and the number of obese and overweight people is now greater than those underweight. Obesity is a multifactorial condition, and as such, many components contribute to its development and pathogenesis. This is the first of three companion reviews that consider obesity. This review focuses on the genetics, viruses, insulin resistance, inflammation, gut microbiome, and circadian rhythms that promote obesity, along with hormones, growth factors, and organs and tissues that control its development. It shows that the regulation of energy balance (intake vs. expenditure) relies on the interplay of a variety of hormones from adipose tissue, gastrointestinal tract, pancreas, liver, and brain. It details how integrating central neurotransmitters and peripheral metabolic signals (e.g., leptin, insulin, ghrelin, peptide YY_{3-36}) is essential for controlling energy homeostasis and feeding behavior. It describes the distinct types of adipocytes and how fat cell development is controlled by hormones and growth factors acting via a variety of receptors, including peroxisome proliferator-activated receptor-gamma, retinoid X, insulin, estrogen, androgen, glucocorticoid, thyroid hormone, liver X, constitutive androstane, pregnane X, farnesoid, and aryl hydrocarbon receptors. Finally, it demonstrates that obesity likely has origins *in utero*. Understanding these biochemical drivers of adiposity and metabolic dysfunction throughout the life cycle lends plausibility and credence to the “obesogen hypothesis” (i.e., the importance of environmental chemicals that disrupt these receptors to promote adiposity or alter metabolism), elucidated more fully in the two companion reviews.

Graphical Abstract



1. Introduction and secular trends

Obesity is a chronic, relapsing condition characterized by excess body fat [1, 2]. It is among the most critical global health issues and a growing pandemic affecting adults, children, and infants [3–5]. Obesity rates have tripled since the 1970s, and the prevalence of adult obesity in the U.S. increased from 30.5% in 2000 to 42.4% in 2018, a 40% increase in frequency in less than two decades [6] . Currently, there are more obese individuals globally than those who are underweight [7–9].

However, this increase in the prevalence of obesity is not restricted to humans. In 2011, Klimentidis and colleagues [10] reported average mid-life body weights of many animals, including domestic dogs and cats, non-human primates, and rodents, regardless of living conditions (both feral and living in research colonies), have also increased. These changes in animal weights across numerous species suggest that similar environmental changes have impacted both animals and humans to promote obesity. Although changes in human behavior undoubtedly play a role in the manifestation of obesity, specific hormonal and biochemical mechanisms outside of their immediate control likely contribute.

This is the first of three companion reviews focusing on obesity and obesogens. This first review delineates the organs and mechanisms responsible for regulating metabolism and their tight control by hormones and their respective receptors. Disruption of this regulation by hormones or other environmental stimuli can lead to obesity anytime during the life cycle, including prenatally. The companion review will elucidate the chemistry and pathophysiological action of obesogens — environmental chemicals designed for a specific purpose, such as pesticides, flame retardants or plasticizers, but which have side-effects that interfere with hormone action — which can lead to altered metabolism and ultimately to obesity. This second review will also establish the causal link between obesogens and obesity, explicitly providing evidence supporting the “obesogen hypothesis,” and discuss research gaps that must be explored. The third review will focus on direct and indirect assays to detect obesogens.

2. Obesity and disease

2.1. The relationship between obesity and non-communicable disease

Obesity is thought to be unhealthy primarily because it is associated with what are known collectively as non-communicable diseases (NCDs), including hypertension [11] , type 2 diabetes (T2D) [12, 13], dyslipidemia, [14], nonalcoholic fatty liver disease (NAFLD) [15], and cardiovascular disease (CVD) [16]. Currently, 54% of adults greater than 60 years of age manifest one or more of these diseases [17]. Obesity is also associated with increased prevalence of and mortality from at least thirteen types of cancers, including stomach, colon, liver, pancreas, breast, prostate, and renal cancer [18]. Obesity is also associated with increased rates of dementia [19]. Corresponding with the increasing prevalence of obesity, the prevalence and severity of all these diseases have increased over a 50-year time frame [20], resulting in increased mortality [21] and healthcare costs [22]. Perhaps even more concerning is that these diseases are now noted in 19-35% of youth and increasing prevalence [23–25].

2.2. Relationship between obesity and communicable diseases

Obesity is also associated with increased susceptibility to nosocomial infections, wound infections, and influenza pandemics [26, 27]. The health effects of obesity include increased risk of COVID-19-related deaths, intensive care admission, and hospitalization of 48, 74, and 113%, respectively [28].

2.3. Is obesity always unhealthy?

Obesity, however, is not always associated with increased morbidity or mortality. Despite being obese, 20% of obese individuals appear metabolically healthy [29–32]. However, it is uncertain if these individuals are healthy or have fewer metabolic abnormalities than those with metabolically unhealthy obesity [33, 34]. Indeed, prospective studies suggest that some obese individuals characterized as metabolically healthy are at increased risk of developing metabolic disease [35]. Conversely, up to 40% of normal-weight adults harbor metabolic perturbations similar to those in obesity, including T2D, NAFLD, and CVD [36, 37]. 87.8% of adults exhibit metabolic dysfunction, while 73.6% are overweight or obese [38]; thus, a sizable portion of normal-weight individuals also show metabolic dysfunction. Abdominal computed tomography (CT) evidence demonstrates that normal-weight individuals can manifest increased visceral fat; that is, they are “thin on the outside, fat on the inside” [39].

The dissociation of obesity and metabolic dysfunction becomes readily apparent by contrasting two pathophysiologic hormonal conditions. The “Little Women of Loja” are a founder-effect cohort in Ecuador of patients with growth hormone insensitivity due to a growth hormone receptor mutation. They become markedly obese in adulthood yet are protected from chronic metabolic diseases such as T2D and CVD. Despite their obesity, they manifest low serum insulin and triglyceride concentrations, reflecting improved insulin sensitivity and metabolic health [40]. Conversely, patients with either genetic or acquired lipodystrophy have a paucity of subcutaneous and visceral fat due to the dysfunctional expression of adipose tissue. They are leptin-deficient yet manifest extreme hyperglycemia, hyperinsulinemia, fatty liver disease, and other aspects of metabolic disease [41]. These two disease entities suggest that the linkage between body fat and metabolic function is not linear but significantly more complex than previously conceived.

2.4. Body mass index (BMI) is not the best measure of metabolic perturbation

The most common metric of adiposity, BMI [42], highlights the problem in differentiating between obesity and metabolic disease. For instance, while obesity prevalence (based on BMI) and diabetes prevalence correlate, they are not concordant. There are countries that are obese without being diabetic, such as Iceland, Mongolia, and Micronesia. At the same time, there are countries that are diabetic without being obese, such as India, Pakistan, and China [43]. This is further elaborated looking at years of life lost from diabetes vs. obesity [44].

Furthermore, different populations manifest variations in types of adipose tissue, skeletal muscle (e.g., body-builders, elite athletes), other lean-body mass components (e.g., bone), as well as significant racial/ethnic differences in body composition that ultimately portend different health risks in different populations [45]. Individuals can have a normal BMI but still be metabolically unhealthy, e.g., South-East Asians [46]. Thus BMI, while helpful because it is easy to apply and correlates with morbidity and mortality in large population studies [47], is an inadequate measure of metabolic perturbation in individuals and some populations. For any given BMI individuals may be insulin sensitive or insulin resistant [48].

In contrast, waist circumference may be a better measure of adiposity as it considers the metabolically deleterious ectopic fat mass that correlates with metabolic disorders and insulin resistance [46] [13]. Another non-invasive approach to differentiating fat mass from lean mass is air displacement plethysmography [49]. Beyond these and other techniques [39], it may be helpful to identify and use biomarkers specific for metabolically unhealthy obesity.

2.5. Three fat depots

A possible key to the challenges imposed by using BMI as a clinical "vital sign" may be the existence of three separate fat depots within the body with divergent effects on the development of metabolic disease [50]. These fat depots respond differently to the various differentiation signals and therefore may be differentially vulnerable to the multiple stressors that can alter these signals.

2.5.1 Subcutaneous adipose tissue (SAT)—The largest fat depot is subcutaneous adipose tissue (SAT). SAT drains into the systemic circulation; therefore, increased SAT-derived cytokines reaching the liver will be diluted compared with cytokines derived from visceral fat depots that drain into the portal circulation. Excess SAT will increase cytokine levels [51] and predispose to metabolic disease; however, a relatively large pannus (approximately 10 kg) is necessary before metabolic dysfunction is apparent. This can be shown in four ways. First, patients with lipedema (excess subcutaneous fat in the abdomen and thighs, due to a lymphatic disorder) have increased subcutaneous fat yet maintain metabolic health [52]. Second, the paucity of SAT impairs glucose metabolism and increases the risk of heart disease, hypertension, stroke, and diabetes in patients with lipodystrophy [53]. Third, studies of liposuction of SAT manifest no metabolic improvement [54]. Fourth, thiazolidinediones (TZD's) improve insulin sensitivity and metabolic health at the expense of increasing SAT deposition and weight gain [55]. Thus, SAT tends to confer less metabolic morbidity and, in many cases, may even be protective against chronic metabolic disease [32].

2.5.2 Visceral adipose tissue (VAT)—In comparison, visceral adipose tissue (VAT), present mainly in the mesentery and omentum, is more metabolically active, more cellular, vascular, and innervated than subcutaneous fat, and it drains into the portal circulation [50, 56]. A mere two kg of excess VAT will increase portal vein cytokine levels, increasing hepatic insulin resistance leading to a higher risk of T2D [57]. One hypothesis to explain the insulin resistance caused by VAT is the "portal-visceral" paradigm [58] which states that increased adiposity leads to increased portal and systemic free fatty acid (FFA) flux. Recently an alternative theory has been proposed: "ectopic lipid deposition" [59], based on the fact that lipid content in the liver and/or muscle is a strong predictor of insulin resistance [60].

2.5.3 Ectopic (liver and muscle) fat—In contrast to lipid stored in WAT, which is, for the most part, adaptive, ectopic lipid in the liver and muscle is non-adaptive and associated with metabolic dysfunction. Liver fat is the most harmful to metabolic health [61]. It predicts whether people will develop T2D or CVD [62, 63]. It causes insulin resistance

locally and directly; only 0.25 kg of liver fat accumulation is required to increase hepatic insulin resistance in children [64], which can even occur in normal-weight people [15]. Excess ectopic fat can lead to NAFLD, leading to cirrhosis or liver cancer. Children with fatty liver disease (FLD) also have excess pancreatic fat, impairing insulin secretion [65]. Dietary sugar and branched-chain amino acids (arising from *de novo* lipogenesis (DNL)) increase liver fat. Therefore, liver fat and VAT, primarily determine insulin resistance, and better predict metabolic dysfunction than SAT or total body fat.

These adipose tissue depots are sexually dimorphic; on average, men have more visceral fat, women have larger subcutaneous fat stores [66]. Given the relative impact of these fat depots on metabolic health, this sexual dimorphism may explain sex differences in metabolic disease risk until menopause, when the reduction in estrogen results in increasing LDL, triglycerides, visceral fat, and morbidity and mortality in females [67, 68].

3. Adipose tissue development and function

Adipose tissue grows by increased cell number and size during *in utero* life, childhood, and adolescence; after that, the number of adipocytes remains stable if weight remains stable. In humans, adipose tissue appears between the 14^{th} and 24^{th} week of gestation, and in mice, adipose tissue is apparent between postnatal days one and seven [69]. Adipose tissue depots are highly dynamic and plastic organs. Changes resulting from weight gain or loss involve coordinating multiple cell types, including immune cells, endothelial cells, fibroblasts, and neurons [69]. An increase in adipose cell number (hyperplasia) is protective against unhealthy obesity as it results in less inflammation. An increased adipocyte size (hypertrophy) is a marker of metabolic risk in obesity, with coordinated increases in inflammation [70]. A decrease in body weight will only change fat cell size, while weight gain can increase adipocyte size and number [71]. Adipocyte turnover rate is similar for all weight categories, with about 10% of adipocytes renewed annually, i.e., the average life of an adipocyte is about ten years [72].

Adipocytes derive from a common mesenchymal stem cell (MSC) precursor-like muscle and bone. Various transcription factors expressed during fetal life commit these precursors to alternative lineages. Myostatin and glucocorticoids (see below) are essential factors that inhibit muscle and promote adipocyte differentiation [73]. Furthermore, there are distinct types of adipocytes: white, brown, beige, and pink [74]. Specific cell surface markers distinguish between white, brown, and beige adipocytes [75], resulting in distinct functional roles. Pink adipocytes form during pregnancy, lactation and post-lactation from subcutaneous white adipocytes, which transform into milk-producing glands in breast tissue [76].

3.1. White adipose tissue (WAT)

White adipose tissue (WAT) is adapted explicitly for fat storage. White adipocytes have an expansive fat vacuole with a perilipin border and very few mitochondria, hence their white color. These cells are found in fat depots throughout the body; more white adipocytes provide greater fat storage and less likelihood of metabolic dysfunction, depending on their location. Liver and muscle cells can also store fat, but they do not

have fat vacuoles under normal physiological conditions. WAT is an endocrine organ that secretes over 50 different hormones, growth factors, enzymes (e.g., dipeptidyl peptidase 4), and cytokines, including adiponectin, leptin, resistin, visfatin, apelin, bone morphogenic protein 2, endotropin, angiopoietins, adipokines, and noncoding RNAs sometimes found in extracellular vesicles [77]. These endocrine signals play a critical role in mediating the role of WAT in metabolic regulation. The characteristics of healthy WAT include smaller, more numerous adipocytes, adiponectin secretion, insulin sensitivity, low basal lipolysis, high vascularity, normal oxidative capacity of mitochondria, low macrophage infiltration, macrophages with an anti-inflammatory profile and a subcutaneous location [78, 79]. The characteristics of WAT in unhealthy obesity include increased secretion of leptin and resistin, decreased secretion of adiponectin, adipocyte hypertrophy, decreased insulin sensitivity, increased basal lipolysis, decreased vascular density, increased macrophage infiltration, pro-inflammatory macrophage profile, and predominantly visceral location [80].

3.2. Brown adipose tissue (BAT)

Brown adipose tissue (BAT) is composed of adipocytes designed for thermogenesis [81]. They are enriched in the interscapular, axillary, cervical, perirenal and periaortic areas. In humans, they are especially abundant in newborns, protecting against cold exposure. Brown adipocytes have little capacity for fat deposition, are highly vascularized, and are filled with mitochondria, hence their brown color. BAT dissipates chemical energy to produce heat either as a defense against cold [82] or as energy expenditure to compensate for food intake. They express high uncoupling protein-1 (UCP-1) levels, which dissociates energy utilization from ATP production to generate heat to maintain body temperature in cold environments [83]. They are the primary site for sympathetic (adrenergic)-mediated adaptive thermogenesis through stimulation of β_3-adrenergic receptors. This leads to an increase in peroxisome proliferation activated receptor (PPARγ) coactivator-1α and thyroid hormone leading to mitochondrial biogenesis [84, 85]. In humans, BAT derives from a myogenic factor 5 (myf5) positive cell lineage, a muscle mesenchymal cell origin, the same as that of myocytes [86]. In animals, brown adipocytes derives from the mesodermal germ layer [87]. Thus far, efforts to transform WAT into BAT to improve insulin sensitivity have not been successful.

3.3. Beige adipose tissue

Beige adipocytes are distinguished from white adipocytes by their multicolor lipid droplets. They develop in subcutaneous adipose tissue from a distinct set of adipocyte precursor cells that are distinct from SAT [88] that emerge from a myf5 negative lineage or via the transdifferentiation of existing white adipocytes [89] and take up residence in SAT [90, 91]. In response to persistent sympathetic stimulation, e.g., prolonged cold exposure or exercise, white adipocytes can increase their mitochondria number and UCP-1 expression, thereby becoming beige adipocytes [92]. The appearance of beige adipocytes within WAT does appear to confer improvements in metabolic health [93].

4. Receptors involved in the control of energy metabolism

MSCs differentiate into mature white adipocytes (WAT) under the control of various cellular receptors, which act as transcription factors (Table 1) to control four physiological processes: proliferation, mitotic cloning, early differentiation, and terminal differentiation. Other liver-based receptors alter liver metabolism to direct energy disposition into adipose tissue for storage [94]. Lastly, systemic hormones that bind to their receptors in the liver, brain, and adipose tissue alter food intake versus energy expenditure or storage (Table 2). This section describes these receptors involved in controlling energy storage vs. expenditure and their role in obesity.

4.1. Adipose tissue transcription factors

4.1.1. Peroxisome Proliferator-Activated Receptors (PPARs)—Human adipose tissue differentiation is dependent on the actions of PPARγ [95], integral to adipose tissue differentiation and widely considered the master regulator of adipogenesis. Treatment of pre-adipocytes and/or MSCs with PPARγ agonists robustly promotes triglyceride accumulation [96, 97]. Adipogenesis is comprised of two phases: the determination phase and terminal differentiation. The determination phase of adipogenesis transitioning to the terminal differentiation phase is marked by changes in expression levels of the PPARγ isoforms PPARγ1 and PPARγ2 [98]. PPARγ operates as a physiological lipid sensor activated by the combined concentration of weakly activating fatty acids and eicosanoids. In its absence, adipose tissue is sparse and poorly regulated [99]. PPARγ has a large promiscuous ligand-binding pocket that creates a vulnerable access point for multiple obesogenic ligands to enter the adipocyte life cycle at various stages. To establish the necessity of this pathway to adipogenesis, Rosen et al. demonstrated that PPARγ-null cells do not generate adipocytes; cells lacking both copies of PPARγ could not be induced to differentiate, cells with one copy of PPARγ exhibited an intermediate degree of differentiation, and wild-type cells with both copies exhibited robust differentiation and efficacious expression of adipocyte-specific molecular markers [100].

The other PPAR isoforms, α and β/δ, have received less attention, though also have important roles in adipogenesis and obesity. Brun et al. reported that receptor isoform-specific activation failed to induce adipogenesis and triglyceride accumulation for PPARβ/δ, but did for PPARα, if with lower magnitude and potency than activation of PPARγ [101]. Activation of both α and β/δ isoforms in mice promotes anti-obesogenic effects, with improved lipids, triglycerides, and resistance to diet induced obesity [102–106]. In humans, treatment with PPARα agonists decreases serum triglycerides, LDL cholesterol, and increases HDL cholesterol [107, 108]. Human therapeutic testing in humans is limited, though treatment of monkeys with PPARβ/δ agonists lowered LDL cholesterol, triglycerides, insulin, and increased HDL cholesterol [109].

4.1.2. Retinoid X receptor (RXR)—RXR functions as a heterodimer with PPARγ, supporting a key role for RXR in adipogenesis [100]. Specific activation of RXR can promote both adipogenic differentiation and preadipocyte proliferation [110–112]. RXR heterodimers during the early stages of differentiation, transitioning to majority occupancy

by PPARγ: RXR heterodimers in the later stages of differentiation [113]. Recent research described RXR activation as an essential signal for adipocyte cell lineage commitment in MSCs and promoting subsequent differentiation [114]. Adipocyte differentiation induced via RXR activation appears to create a functionally distinct adipocyte from those generated via PPARγ [115]. These RXR-induced white adipocytes demonstrated decreased glucose uptake and adiponectin expression. They failed to induce adipocyte browning pathways, suggesting a dysfunctional white adipose that promotes or exacerbates obesity and/or diabetes risk [115]. RXR global knock-out mouse models are embryonic lethal [116], though tissue-specific knockouts provide some context for the role of the receptor in metabolic health. Mice with ablated adipocyte-specific RXR receptors are resistant to diet and chemical-induced obesity have inhibited pre-adipocyte differentiation and inhibited lipolysis during fasting [117]. Exposure of rodents to RXR agonists can sensitize diabetic and obese mice to insulin [118] and reduce hyperglycemia, hypertriglyceridemia, hyperinsulinemia, weight gain, and food intake [118–120]. In humans, treatment with RXR agonists increases plasma triglycerides and decreases thyroid hormone [121–123].

4.2. Liver transcription factors

4.2.1. Liver X receptor (LXR)—The liver X receptor (LXR) forms a permissive heterodimer with RXR, and ligands can activate either receptor [124]. The α-isoform of the receptor is primarily expressed in the adipose, liver, intestine, and kidney, while the β-isoform is ubiquitously expressed [124]. LXRs mediate cholesterol transport, degradation, uptake, and fatty acid and triglyceride synthesis [124–126]. LXR agonism has been reported to increase triglyceride accumulation, differentiation of adipocytes, stimulation of adipogenic gene expression, and pre-adipocyte proliferation in a variety of cell and animal models [110, 127, 128], mediated at least in part via PPARγ [127, 128]. Knockdown experiments in rodents have described a primary role for LXRα in lipolysis [129] and LXRβ in cholesterol regulation [130]. LXR-null mice (both isoforms) have inhibited lipid metabolism, elevated thyroid hormone production, and are resistant to diet-induced obesity [126]; while LXRβ-knockout mice have reduced adiposity, are glucose-intolerant and accumulate lipids in pancreatic islets [130]. Adipocytes are reduced in size in LXR-deficient mice [128], with increased energy expenditure and reduced lipid accumulation in the brown adipose [131]. Mice treated with LXR agonists decreased visceral adiposity and increased SAT [132], reduced energy expenditure, and increased triglyceride accumulation in BAT [131]. LXR expression is increased in obese humans, and receptor polymorphisms are associated with increased metabolic health risks [133]. Despite some beneficial effects on adipose distribution, treatment with LXR agonists in humans resulted in increased cholesterol, plasma and hepatic triglycerides, and other negative metabolic markers [134].

4.2.2. Pregnane X receptor ((PXR) and constitutive androstane receptor (CAR)—The pregnane X receptor (PXR) and the constitutive androstane receptor (CAR) are closely related liver-enriched receptors that regulate xenobiotic-metabolizing enzymes, glucose and energy homeostasis, immune function, and lipid metabolism [135, 136]. PXR appears to act indirectly via PPARγ [136], and CAR may promote effects via PPARα [137]. PXR knockouts exhibit inhibition of diet-induced obesity, insulin resistance, and fatty liver disease in rodent models [136, 138]. PXR agonists induce hepatic triglyceride

accumulation and promote fatty liver disease [139]. Treatment with CAR agonists enhances insulin sensitivity, improves glucose and lipid metabolism, and protects against diet-induced obesity [135, 140]. In humans, CAR activation via phenobarbital decreases glucose levels. It improves insulin sensitivity in diabetes and people with liver hyperplasia and cancer [135]. PXR activation via rifampicin, statins, and other pharmaceuticals appears to induce hyperglycemia and increase the risk of T2D [138].

4.2,3. Farnesoid X receptor (FXR)—The farnesoid X receptor (FXR) regulates bile acid synthesis, enterohepatic circulation, lipid metabolism, and other bile acid-associated receptors [141, 142]. It is expressed in mature adipocytes and differentiated 3T3-L1 cells [143]. FXR agonists increase adipocyte differentiation and enhance insulin-associated signaling, whereas FXR antagonists inhibit these processes [143, 144]. FXR antagonists have also been described as anti-adipogenic and pro-apoptotic [145]. FXR-knockout mice have decreased adiposity, reduced leptin, elevated free fatty acids, increased energy expenditure [144, 146–148]. These animals also have impaired insulin resistance and glucose tolerance [144, 149]. FXR agonist treatment in diet-induced obese mice exacerbated weight gain and glucose intolerance [150]. However, other researchers have reported beneficial metabolic effects of agonist treatment [142, 151]. In humans, FXR expression is downregulated in obese individuals [141, 152]. Treatment with FXR agonists reduces hepatic lipid accumulation, increases glucose uptake, reduces high-density lipoprotein (HDL), increases low-density lipoprotein (LDL) cholesterol, and reduces insulin resistance [141, 142, 151].

4.2.4. Aryl hydrocarbon receptor (AhR)—The aryl hydrocarbon receptor (AhR) is a member of the basic-helix-loop-helix (bHLH)–PER-ARNT-SIM (PAS) superfamily of transcriptional factors [153]. Like other members of the PAS superfamily, the AhR transduces signals in response to the environment, including changes in oxygen levels, altered redox potential, and changes in circadian rhythm, by binding various small-molecule ligands [153]. AhR signaling in metabolism deregulation is exemplified in diet- and obesogen-induced obesity. AhR inhibition prevented and reversed obesity, making it an attractive target for the control of obesity. Indeed, MSCs contain AhR receptors and their activation by kynurenine (Kyn) or benzo[a] pyrene (BaP) (AhR agonists) inhibit terminal adipogenic differentiation [154]. AhR levels and activity are most significant in the liver's hepatocytes [155, 156]. The majority of fat metabolism and cholesterol biosynthesis occurs in the liver [157], much of which is dependent on AhR signaling [158, 159]. Thus, the contention that the liver is the site where AhR signaling operates in the manifestation of obesity is not surprising and is supported by recent studies showing that the conditional/inducible knockout of the AhR gene in hepatocytes caused obesity resistance in female mice fed a HFD [160].

4.3. Systemic hormone receptors

4.3.1. Insulin receptor (IR)—The insulin receptor (IR) and signaling cascade are essential to fat cell differentiation. For instance, lack of fetal pancreatic insulin secretion during the third trimester results in Transient Diabetes Mellitus of the Newborn, characterized by a lack of adipose tissue in all fat depots [161]. Similarly, leprechaunism, a

genetic defect of the IR, leads to a virtual absence of neonatal adipose tissue and extreme insulin resistance [162]. Insulin can stimulate both the insulin receptor and the insulin growth factor-1 receptor (IGF-1R) to induce adipogenesis; however, knockout of IGF-1R only lost 25% of its WAT, while knockout of the insulin receptor resulted in a 95% loss of WAT, with a concomitant 50% increase in BAT [163]. These effects are enacted through insulin's mediation of Forkhead Box O (FOXO) transcription factors in various fat-specific depots [164].

4.3.2. Estrogen receptor (ER)—Estrogen acts via both membrane and nuclear (ERα and ERβ) receptors [165, 166] Signaling through the nuclear estrogen receptor (ER) is an important factor in SAT development, particularly at times when CNS leptin signaling for reproductive competency becomes necessary (e.g., puberty, pregnancy) [167]. Indeed, estrogen deficiency during gestation, as seen in aromatase deficiency, results in reduced SAT and the appearance of liver fat [155, 156], both of which can be abrogated by estrogen replacement [157] suggesting that these two fat depots are malleable postnatally. Furthermore, estrogen is positively associated with obesity in children across the sexes [168], starting at puberty. In humans, decreased estrogen levels at menopause are associated with increased abdominal obesity. Estrogen replacement therapy may reduce this weight gain [169]. Estrogens act on adipocytes to inhibit lipogenesis and help modulate energy expenditure and food consumption [170]. Studies have described a role for estrogens in promoting preadipocyte proliferation and regulating adipocyte number in various depots [171, 172], presumably mediated by IGF-1R and PPARγ [171]. Some additional insight can be gained through examination of estrogen receptor knock-out (ERKO) mice, which supports differential roles for estrogen receptors alpha and beta. αERKO mice exhibit increased adipose tissue, fat pad weights, adipocyte size, adipocyte numbers, and dysregulated lipoprotein profiles relative to wild type control animals [173, 174], and over time develop both impaired glucose tolerance and insulin resistance [173]. This is mirrored by studies demonstrating that ovariectomized female mice also exhibit increased adiposity, primarily in the abdominal depot [175], and aromatase deficient (ArKO) mice have significantly elevated adipose and fat pad weights as well as hyperplasia and hypertrophy of adipocytes, reduced physical activity levels, reduced glucose oxidation, and decreased lean body mass [176–178]. There are also data describing inhibitory effects of estrogens on adipocyte differentiation [179], possibly mediated through the G-protein-coupled ER (GPER) rather than the nuclear ER [180].

4.3.3. Androgen receptor (AR)—Androgens also play a crucial role in adipogenesis and adipose tissue development. Androgens are generally considered anti-obesogenic, with decreased androgens associated with increased adiposity [181, 182]. Dihydrotestosterone inhibits triglyceride accumulation and adipogenic gene expression in human MSCs and preadipocytes from various adipose depots [183]; co-treatment with anti-androgens inhibited these effects. Neither had any apparent impact on preadipocyte proliferation [183]. Treatment with flutamide, a non-steroidal anti-androgen, has been demonstrated to promote triglyceride accumulation in 3T3-L1 and OP9 preadipocytes [110], again without impacting preadipocyte proliferation. Other research has suggested that some of these effects may occur through inhibition of adipocyte lineage commitment [184, 185]. In

agreement with the data indicating that androgens are anti-obesogenic, androgen receptor knock-out (ARKO) mice have increased adiponectin secretion, increased adiposity and body weights, increased triglycerides, and decreased insulin sensitivity [186–190]. Androgen replacement, as expected, protects against these metabolic effects, including obesity [188]. Androgen treatment inhibits adipogenesis in adipose tissue samples collected from both sexes [191] and reduces human fat mass [192]. Anti-androgens such as flutamide can improve lipid profiles in women [193, 194]. In men, they are generally associated with a favorable metabolic phenotype and reduced adiposity [195]. There are sex-specific effects of androgens [196], as demonstrated by elevated androgens and excess adiposity in women with polycystic ovary syndrome (characterized by excess androgens) and increased obesity, hypertension, dyslipidemia, insulin resistance, and metabolic dysfunction in men with hypogonadism, e.g., low testosterone [192, 196].

4.3.4. Glucocorticoid receptor (GR)—The glucocorticoid receptor (GR), and its related signaling cascade, are primary drivers of visceral fat differentiation [197] and metabolic dysfunction [198]. VAT is differentially responsive to glucocorticoids compared to SAT [199]). Cushing's syndrome, a disease characterized by high glucocorticoid levels, exhibits excessive visceral fat [200]. Furthermore, VAT possesses high levels of 11β-hydroxysteroid dehydrogenase type 1, which converts inactive cortisone to active cortisol, increasing visceral fat differentiation and growth [201]. Extensive evidence supports the role of GR in lipid metabolism, adipose formation, and maintenance [202]. GR agonist treatments (typically dexamethasone) promote triglyceride (TG) accumulation and pre-adipocyte proliferation in diverse mesenchymal and pre-adipocyte models [110, 203], while GR antagonists inhibit differentiation [204]. Some studies have reported mediation of effects of GR on adipocyte differentiation in part through PPARγ [205]; however, other studies have not confirmed these results [206]. Silencing GR inhibits cortisol's adipogenic effects and decreases leptin and adiponectin [207], suggesting specificity to GR. GR activation may be necessary for an intermediate commitment state before differentiation of preadipocytes [208], though it could also be due to varied receptor expression in this model [110]. Although tissue-specific knockouts have been developed, GR knock-out (GRKO) mice are perinatally lethal due to respiratory failure [209]. Local GR knock-out promoted a favorable metabolic profile via 11(-hydroxysteroid dehydrogenase overexpression. It reduced fat accumulation and food intake, improved insulin sensitivity and glucose tolerance, and increased energy expenditure [210].

4.3.5. Thyroid hormone receptor (TR)—The thyroid hormone receptor (TR) is essential for metabolic health regulation [211], mainly via maintaining lipid and carbohydrate metabolism, blood pressure, and muscle mass [124, 212]. Receptor isoforms (α, β1, β2) play distinct roles in metabolic health. TRα primarily regulates thermogenesis, while TRβ primarily regulates cholesterol metabolism and lipogenesis [212]. TRβ also governs several genes and enzymes essential for pre-adipocyte proliferation and adipocyte differentiation, either directly or via PPARγ [212]. TR agonist treatments are pro-adipogenic [110, 213, 214]. TRα-null mice are leaner than wild-type counterparts, with reduced adiposity, higher energy expenditure, increased oxidative capacity of fat, and resistance to diet-induced obesity [215]. Mice with a point mutation in TRα showed increased visceral

adiposity, serum leptin, fasting insulin, fasting glucose, and an inhibited cold-induced adaptive thermogenesis [216]. TRβ-null mice demonstrated an increased energy expenditure [217], with no reported effects on adiposity. Conversely, synthetic TRβ agonists cause a reduction in cholesterol, triglycerides, and adiposity [218, 219], suggesting a potential therapeutic mechanism. In humans, low thyroxine (T_4) and triiodothyronine (T_3) along with high thyroid-stimulating hormone (TSH) levels result in hypothyroidism that is characterized by weight gain, that can be treated successfully with supplementation [220–222]. High T_3 and T_4 and low TSH characterizing hyperthyroidism are associated with reduced weight, fat-free mass, and adiposity [223, 224].

These cellular systems, which play a critical role in the differentiation and growth of fat cells and weight control, can be targets of various exogenous obesogens, as delineated in the companion review. They can promote energy deposition and either primary (via liver dysfunction) or secondary (via obesity) chronic metabolic disease when activated or inhibited.

5. Neuroendocrinology of obesity

5.1. Homeostatic mechanisms

Regulation of energy balance, and hence weight status, relies on integrating peripheral hunger and satiety signals by the central nervous system (CNS) controlling feeding behavior and activity [225, 226]. Feeding behavior is often dichotomized as homeostatic or hedonic [227]. Homeostatic feeding is defined as that which is required to meet physiological/survival needs and is based on increasing the motivation to eat when energy stores are depleted. In contrast, hedonic feeding is driven by sensory perception or pleasure. The hedonic drive may override homeostatic regulation even in the face of abundant energy stores via increased desire to consume highly palatable foods [227, 228].

Key CNS regions involved in the homeostatic pathway include the neuroendocrine hypothalamus and the nucleus of the solitary tract (NST) in the lower brainstem (Figure 1). There are two distinct populations of neurons within the arcuate nucleus (ARC) of the hypothalamus. One population expresses the anorexigenic neuropeptide precursor pro-opiomelanocortin (POMC), while the other population expresses the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related protein (AgRP). These neurons, in turn, project to other hypothalamic nuclei, including the paraventricular nucleus (PVN), which integrate emotional and stress responses as well as exert physiological control over metabolism via the release of thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH) [229]. Serotonergic neurons from the dorsal raphe nucleus (DRN), which receive afferent input from the spinal column and many parts of the brainstem, project to the ARC, NTS and paraventricular nucleus (PVN). Depleting CNS serotonin results in hyperphagia and obesity, while elevated CNS serotonin resulted in anorexia and decreased energy intake [230, 231].

The integration of central neurotransmitters and peripheral metabolic signals to control energy homeostasis are well known [232] and they exert central effects that alter food-seeking behavior and, ultimately obesity. Key peripheral hormones involved in energy

homeostasis include but are not limited to leptin, ghrelin, insulin, peptide YY (PYY_{3-36}) and cholecystokinin (CCK) [231, 233]. Leptin is synthesized by adipose tissue and is secreted in proportion to fat mass; insulin is secreted by pancreatic β-cells in response to elevated blood glucose levels, and PYY_{3-36} is produced by enteroendocrine L-cells of the gut and released into the circulation postprandially. Hence increased leptin, insulin and PYY_{3-36} levels represent the fed state and/or a surfeit of stored energy. These three hormones bind receptors in POMC neurons, stimulating POMC release and bind receptors in NPY neurons that suppress NPY/AgRP signaling with a resultant decrease in orexigenic tone. The gonadal hormone estradiol also targets POMC neurons in the ARC, indirectly repressing the synthesis of NPY and AgRP and thereby reducing caloric intake [234]. Oxyntomodulin (OXM) and glucagon-like peptide-1 (GLP-1) are also produced by enteroendocrine L-cells of the gut and are released postprandially. GLP-1 and OXM inhibit appetite: OXM may also influence energy balance via increased activity-related energy expenditure. CCK released post-prandially from the small intestine reduces food intake via binding CCK1 receptors on the afferent vagal nerve, resulting in POMC in the NST [235].

Ghrelin, dubbed “the hunger hormone,” is a 28 amino acid peptide hormone produced by the stomach [236]. Acylation of ghrelin with an octanoyl group at serine 3 is necessary for this hormone to cross the blood-brain barrier. Ghrelin production rises in response to fasting and falls post-prandially [236]. In contrast to leptin, insulin and PYY_{3-36}, ghrelin stimulates the production of NPY/AgRP neuronal activity leading to inhibition of POMC neuronal signaling, resulting in increased food intake.

5.2. Hedonic mechanisms

The neurological substrates and circuits involved in binge eating and food addiction have been previously reviewed [237]. It has been proposed that binge eating and addiction interplay between the dopaminergic reward centers (nucleus accumbens (NA), amygdala, ventral tegmental area (VTA)) and the prefrontal impulsivity-control networks (prefrontal cortex, the anterior cingulate cortex, and the insular cortex). Binge eating disorders are thought to be due to a transition from reward- or goal-directed drive to consume food to an impulsive drive to consume food that involves changes in how the ventral and dorsal striatum communicate. This change may be due to the expression of two different receptors for the neurotransmitter dopamine in the striatum. Eventually, this change decreases reward sensitivity (less dopamine release) and is associated with decreased inhibition of reward from the impulsivity network (prefrontal cortex, etc.).

Highly palatable foods increase the release of dopamine in the NA [238]. The mesolimbic dopamine pathway, which demonstrates increased dopamine signaling from nuclei in the VTA onto neurons in the NA in response to common drugs of abuse, is thought to drive hedonic feeding [239]. Cellular and molecular changes like those associated with prolonged limbic system activation by drugs of abuse are also seen in rodents chronically exposed to highly palatable foods [240, 241]. Compared to lean women, obese women have increased activation of several limbic areas when presented with pictures of highly palatable foods [228]. Hence alterations in reward pathways may promote obesity when exposed to highly palatable foods, and/or chronic exposure to highly palatable foods may result in alterations

in reward pathways that activate the hedonic feeding drive. Both the homeostatic and hedonic pathways control obesity. The hormones and neurotransmitters that control them are subject to modifications that can lead to obesity via exposures to obesogens.

5.3. Importance of the leptin setpoint

In most humans, bodyweight remains relatively stable over long periods. It is autoregulated, without conscious control, similar to that of body temperature and blood pressure by leptin signal transduction, which functions as a “servomechanism” for bodyweight [242]. An acute change of 5-10 pounds of weight gain or loss quickly returns to normal when factors perturbing weight are removed. This ability to maintain weight results from a metabolic body weight setpoint [243], a physiological value around which the normal weight range fluctuates. The actual location of the body’s weight setpoint is not known. It is thought to have a genetic basis. Still, it may also be modified by epigenetic changes due to outside stressors such as environmental chemicals or changes in nutrition, especially during development. The concept of the leptin setpoint concept and its regulation [244] argues that “homeostatic obesity” may occur due to an environmental stressor promoting defective leptin signaling (e.g., leptin resistance) at the ARC, resulting in “brain starvation”; and thus altering the threshold for leptin signaling resulting in both reduced energy expenditure and increased food intake [245]. Similarly, “hedonic obesity” can result from defective leptin signaling at the VTA, resulting in failure to extinguish the food reward signal, resulting in continued consumption [246]. In each case, obesity results from overriding the setpoint due to interference with the leptin signal, both at the ARC and VTA [244].

Although still debated, the likely culprit that promotes leptin resistance at both nuclei is hyperinsulinemia [247] and resultant CNS insulin resistance (Figure 2). Neurons in both CNS nuclei co-localize insulin and leptin receptors on their cell surface [248]. POMC neurons, exposed to a high insulin concentration *in vitro*, silence their firing in response to leptin administration, resulting in leptin resistance [249]. Hyperinsulinemia blocks leptin receptor signaling in the hypothalamus through three separate mechanisms; at insulin receptor substrate-2 (IRS-2) [250], at protein tyrosine phosphatase-1B (PTP-1B) [251], and finally at phosphoinositol-3-kinase (PI3-kinase) [252]. Thus, insulin resistance and hyperinsulinemia can lead to central alterations of CNS leptin signaling, resulting in “brain starvation,” which stimulates appetite and persistent weight gain [253].

6. Heterogeneous nature of control of weight and adiposity

As noted above, energy metabolism, and thus weight as a secondary metric, is tightly controlled by an integrated system of organs and hormones dependent on genetics and the environment. The complex changes in metabolism that result in obesity account for the difficulty in understanding, controlling, and treating obesity: no two patients have the same genetic backgrounds and environmental stimuli. It also illustrates that the pathogenesis of obesity involves more than just overeating and lack of exercise. Below we will discuss each of these factors and their role in obesity.

6.1. Genetics of obesity

Twin studies indicate that 40-70% of obesity may be due to genetics [254]. This figure is misleading because twins have genetic, epigenetic, and environmental similarities. The most common form of obesity is polygenic obesity. Genome-wide association studies (GWAS) of obesity have identified over 300 gene variants associated with obesity, including *MCR4, BDNF, and PC1*. These genes only account for about 3-5% of individual variation in the genetic risk for obesity [42]. However, GWAS evaluation of metabolic syndrome suggests that only 15% can be explained by genetics alone; the other 85% is explained by the environment [255].

While genes certainly play a role in obesity pathogenesis, genetics alone cannot explain the increase in obesity rates over the last 40 years, as genetics have not changed significantly over that short time frame. Thus, the focus must turn to environmental factors as the cause of the current obesity pandemic.

6.2. Environment and obesity

Environmental factors that promote obesity include a host of alterations, including nutrition, overeating and binge eating disorders/food addiction, time of eating, physical inactivity, drugs, viruses, and the gut microbiome. Various obesogens exert their actions within one or more of these pathways, and their actions will be discussed in the review following this one. We recognize that there are other environmental factors involved in obesity, such as the built environment, social disparities, and economic policies; however, they will not be covered here.

6.3. Nutrition and obesity

The traditional explanation for obesity has been that it results from an imbalance between calorie intake and energy expenditure. Therefore, excess caloric intake accumulates fat whenever calorie intake is greater than energy expenditure. However, this explanation is overly simplistic. Increased caloric intake correlates with weight gain but does not explain the mechanism for the increased calorie intake. In addition, obesity has multifactorial origins and, nutrition is more complicated than just counting calories. Indeed, all calories are not equivalent. An attractive alternative hypothesis is that hyperinsulinemia is the primary factor driving energy storage and weight gain [252, 256]. According to this model, increasing fat deposition resulting from an exaggerated insulin response to specific foods (e.g., refined carbohydrate and sugar), which foments positive energy balance, leads to obesity [256]. Indeed, the typical Western diet promotes obesity by increasing calorically dense (high fat and high sugar) diets, which promote insulin secretion, insulin resistance, and resultant weight gain. Furthermore, hyperinsulinemia interferes with leptin signal transduction to increase food intake [252].

6.3.1. Calories.—While it is true that all calories possess the same capacity for heat generation, equivalent to 4,184 joules of energy, this is not equivalent to how much energy is needed to store it. The efficiency of capturing calories and transforming them into chemical energy in the human body is highly uneven. Understanding these various phenomena show

that, in fact, “a calorie is not a calorie,” and there is an actual difference between eating a handful of almonds and a donut, even if their calorie count is identical [257].

6.3.2. Fiber.—Of the 160 calories in a handful of almonds, the body only absorbs 130. The other 30 are prevented from absorption because the fiber in the almonds prevents early absorption in the duodenum allowing the bacteria in the jejunum and ileum to utilize the remaining 30 for their purposes. Thus, even though 160 calories were ingested, not all of them reach the systemic circulation because the microbiome metabolizes it.

There are two types of fiber — soluble (e.g., pectin, inulin) and insoluble (e.g., cellulose, chitin). Together they form a gel on the inside of the duodenum, reducing intestinal absorption by 25-30%. Thus, the two fibers reduce the absorption of mono- and disaccharides and slow the catabolism of starches. Reduced absorption means reduced transport to the liver, preventing the liver from turning excess energy into fat and, thus, preventing hepatic insulin resistance [258]. A sizeable portion of what is eaten stays in the intestine for bacteria to metabolize it. When the gut bacteria are starved of nutrients, they will hydrolyze the protective mucin layer that overlays intestinal epithelial cells, denuding the intestine resulting in “leaky gut” and inflammation while increasing the risk of autoimmune disease and food allergy [259]. Fiber also helps food transit the intestine faster, thereby generating the “satiety signal” (the gut hormone peptide $YY_{3\text{-}36}$, which is transmitted to the brain) sooner, reducing consumption of second portions.

Gut bacteria metabolize soluble fiber into short-chain fatty acids such as butyrate. These feed the colon’s microbiome and are absorbed into the bloodstream, where they are anti-inflammatory and suppress pancreatic insulin secretion, lowering insulin levels [260].

6.3.3. Protein.—Suppose a branched-chain amino acid is is metabolized for energy metabolism. In that case, the amino group is removed in the liver by branched-chain amino-acyl transferase (BCAAT) to convert it into an organic acid (e.g., aspartate to oxaloacetate). Instead of phosphorylating carbohydrates , which costs only one ATP, it costs two ATPs to metabolize amino acids. The amount of energy required for digestion and absorption of food is known as the *thermic effect of food* (TEF). Fats generate about 2–3% of TEF, carbohydrates about 6–8%, and protein about 25–30% of TEF [261]. In other words, it takes more energy to burn a protein than carbohydrate.

6.3.4. Fat.—All dietary fats would liberate nine calories per gram if burned in a bomb calorimeter. But omega-3 fatty acids are required for cell membrane maintenance and therefore are not burned. Conversely, mitochondria cannot burn trans-fats; humans do not have the enzyme to cleave the trans-double bond. Over the past 50 years, dietary advice has been predicated on the idea that dietary fat is intimately involved in the pathogenesis of obesity and metabolic syndrome. The implication was that the removal of dietary fat should improve health. One restriction study and two substitution studies assessed the effects of removing saturated fat from the diet. The restriction study was the Women’s Health Initiative which studied women who reduced their consumption of saturated fat from 30% to 10% of calories and showed no effect on either weight loss or CVD [262, 263]. In the Sydney Diet Heart Study, men who had experienced a heart attack had the saturated fat

removed from their diet and replaced with linoleic acid, an omega-6 fatty acid, which can be pro-inflammatory. All subjects experienced a decline in their low-density lipoprotein (LDL) levels, yet their risk for heart attack increased by 62%, and their mortality risk increased by 70% [264]. Finally, the Minnesota Coronary Study followed 9,000 patients over five years at state mental hospitals and nursing homes, where meals were controlled by removing saturated fat and substituting linoleic acid. The study found similar findings as in Sydney, LDL declined, but heart attacks and deaths increased [265]. These data show that the focus on "a calorie is a calorie" in obesity and obesity-associated comorbidities are incorrect. The nature of the calories consumed is likely much more important than the actual number of calories.

6.3.5. Sugar.—Added sugar (sucrose) consists of equal amounts of glucose and fructose. Both provide the same number of calories, but they are metabolized differently in the liver and the brain. All body tissues can metabolize glucose. Only 20% of a glucose load goes to the liver, and insulin turns it into glycogen (liver starch). All fructose is metabolized in the liver and is unaffected by insulin. An excess of fructose overwhelms the capacity of hepatic mitochondria to utilize it, and the excess is converted into liver fat, driving insulin resistance. Fructose does not shut off the hunger hormone ghrelin, so the brain does not respond appropriately to satiety signals. Fructose is also addictive. Indeed, data show that the adverse effect of sugar on obesity is driven by fructose and not glucose. Fructose, especially when consumed during development and early childhood, causes weight gain [266].

6.3.6. Other carbohydrates.—There are three inherent issues about carbohydrates that play a role in whether they are causative or protective against obesity and metabolic syndrome.

6.3.6.1. Sugar vs. starch.: Sugars are mono- and disaccharides (1 or 2 linked molecules, glucose and fructose), while starches are complex carbohydrates composed of many linked molecules (glucose only). Sugars have one or no bonds to break. They are digested and absorbed quickly in the duodenum, especially when outside a food matrix (e.g., soda, fruit juice), and rapidly move to the liver. Starch has more bonds to break and is digested and absorbed more slowly. Fructose is only found in dietary sugar, not in dietary starch.

6.3.6.2. Type of starch.: There are two basic types of starch: amylose (e.g., beans, lentils, legumes — linked together by alpha-1,4-glucosidyl bonds, which are digested and absorbed slowly) and amylopectin (e.g., wheat, pasta, rice, potatoes — linked together by both alpha-1,4-glucosidyl and alpha-1,6-glucosidyl bonds, which are digested and absorbed rapidly). Amylose is healthier because it is a string of glucose with two ends; therefore, only two enzymes at a time can digest it, resulting in slow digestion and absorption. The longer it stays in the intestine, the greater the chance for gut bacteria to utilize it. Amylopectin is more like a tree of glucoses, with many branch points. Various enzymes can hydrolyze it simultaneously, releasing glucose more rapidly, which is more likely to be absorbed early, flood the liver and pancreas, and generate a more significant insulin response.

6.3.6.3. Glycemic index vs. glycemic load.: A primary goal of improving metabolic health is to lower insulin levels. One way to do so is to eat foods that produce a reduced

postprandial glucose excursion (an indirect proxy for insulin), such as with amylose. Higher glucose spikes upon eating are associated with more inflammation [267] and higher mortality [268]. Tables of specific foods and their inherent GI are readily available [269]. Some propose that a low-GI diet will keep blood glucose down and help weight loss [270]. However, the real reason that GI works is that it reduces insulin spikes. Indeed, the glycemic load of carbohydrates consumed is a more important predictor of weight gain than the actual number of calories [271].

6.4. Exercise and obesity

Management of obesity is generally related to interventions in terms of lifestyle, mainly through changes in diet directed at caloric restriction and adherence to exercise programs. Indeed, such interventions, especially when recommended together, are well known to lead to beneficial health effects, e.g., improved mitochondrial function, decreased muscle and liver fat, decreased insulin resistance, reduced inflammation, decreased level of serum triglycerides, weight loss, and reduction in waist circumference [272]. Accordingly, other metabolic diseases such as NAFLD or T2D also benefit from such recommendations [273–275].

Mechanistically, physical activity can counteract insulin resistance [276, 277], notably by interfering with the metabolism of bioactive lipids such as ceramide diacylglycerols [278]. Other possible mechanisms to improve insulin sensitivity might relate to a positive impact of exercise on mitochondria-associated ER membranes (MAMs) that play critical roles in calcium homeostasis, lipid transport, and metabolism [279]. Exercise can also mitigate immunemetabolic disturbances [280–282] due to the production of soluble factors (myokines, hepatokines, osteokines) as well as cytokines and adipokines [280, 283]. It is noteworthy that myokines can crosstalk with metabolic organs (adipose tissue, liver, pancreas), favoring thermogenic activity, glucose production, and insulin secretion [283, 284]. Similarly, extracellular vesicles produced by skeletal muscle might be involved in crosstalk, possibly due to their role as transporters of myokines [285] and for micro-RNAs (miRNAs) [286]. Physical exercise can modulate miRNA expression [287] [288]. Such epigenetic effects of exercise might explain why maternal exercise can have a beneficial action on the metabolic health of offspring [289, 290]. Lastly, an emerging role for lactate, known to be produced by glycolysis upon physical activity, has recently been reported as an appetite-regulatory molecule, thereby controlling energy intake [290, 291].

6.5. Viruses and obesity

Surprisingly, infection with seven different viruses and a scrapie agent has been associated with obesity in animals and humans [292]. Lyons first described the development of massive obesity in a high percentage of Swiss albino mice that survived infection with the canine distemper virus [293]. Subsequent mechanistic studies suggest that obesity resulted from damage to and altered neurochemistry in the hypothalamus of affected mice [292]. Chickens infected with Rous-associated virus type 7 developed obesity accompanied by stunting, dyslipidemia characterized by high serum triglyceride levels, enlarged fatty livers, anemia, and immunosuppression. Of particular interest, obesity develops despite no significant increase in caloric intake. Although this phenotype is associated with depressed thyroid

hormone levels [294], damage to the CNS may also develop this obesity phenotype [292]. SMAM-1 is an avian adenovirus that causes increased accumulation of fat and fatty liver along with a paradoxical decrease in serum lipids in infected chickens. Neither canine distemper virus nor Rous-associated virus seven nor SMAM-1 virus is thought to infect humans.

Three additional viruses that are known to infect humans can also cause obesity in animals: human Adenovirus 5 (Ad-5) in mice, Adenovirus 36 (Ad-36) in chickens, mice, rats, and marmosets, and Adenovirus 37 (Ad-37) in chickens [292]. A role for Ad-36 (but not Ad-5 or Ad-37) in promoting human obesity was first suggested by the observation that the prevalence of serum neutralizing antibodies for Ad-36 was significantly higher in obese individuals than non-obese individuals (30% vs. 11%, respectively). Furthermore, the average BMI of seropositive individuals was substantially higher than that of seronegative individuals. Twin pairs discordant for Ad-36 seropositivity had significantly higher BMIs and body fat than seronegative twins. Both serum cholesterol levels and serum triglyceride levels were paradoxically lower in seropositive subjects [295]. Most, but not all, subsequent studies corroborate the relationship between Ad-36 and obesity. A meta-analysis of 11 case-controlled studies found that compared with non-obese controls, Ad-36 infection increased obesity risk by a pooled OR of 1.60. A subgroup analysis revealed exceptionally high risk in children (OR = 1.95) [296].

Mammals infected with Ad-36 have increased body weights and reduced serum levels of cholesterol and triglycerides, and infected rats also show an increase in insulin sensitivity and glucose uptake. Upregulation of C/EBPβ, C/EBPα, PPARγ and glycerol-3-phosphate dehydrogenase expression in infected animals stimulates preadipocyte differentiation. *In vitro* studies show that Ad-36 accelerates differentiation and proliferation of 3T3-L1 preadipocytes and primary human adipose-derived stem/stromal cells from human volunteers, with enhanced accumulation of lipid. Consistent with increased glucose uptake in rats, human skeletal muscle infected with Ad-36 demonstrates higher gene expression and glucose transporter GLUT1/GLUT4 receptor abundance independent of insulin [297]. Ad-36 infection also suppressed the expression of leptin mRNA and leptin release in 3T3-LI cells and rat primary adipocytes. Adipose tissue of infected rats showed two to five-fold lower levels of leptin mRNA and several-fold higher levels of acetyl Co-A carboxylase-1 and fatty acid synthase expression compared to weight and adiposity matched controls [298]. Finally, glucose, insulin, insulin resistance (HOMA-IR), and leptin levels were all found to be significantly lower in obese human subjects seropositive for Ad-36 compared to obese seronegative subjects [299].

Hence Ad-36 infection is associated with obesity in humans via virally induced hyperplasia and hypertrophy of SAT paired with an alteration of key peripherally and centrally acting adipokines. It is unlikely that this association is simply due to increased susceptibility to adenovirus infection associated with obesity because the rates of seropositivity for Ad-2 and Ad-37 do not differ between weight classes. However, reverse causality cannot yet be ruled out. The obesity phenotype associated with Ad-36 infection appears to be that of “healthy obesity” with paradoxically lower lipids, glucose, insulin, and insulin resistance. This is reminiscent of changes induced by thiazolidinediones, a class of anti-diabetic drugs

that act as PPARγ agonists and paradoxically promote weight gain) and improve insulin sensitivity via selective adipogenesis and fatty acid uptake SAT rather than VAT. Further work is needed to characterize the Ad-36 associated obesity phenotype, including risks, responses to interventions, and interaction with behaviors and obesogens.

7. Pathophysiologic mechanisms that promote obesity and/or NCDs

7.1. Insulin resistance and obesity

Insulin resistance is defined as the decreased tissue response to insulin-mediated cellular actions. It has been proposed that insulin resistance results from reduced glucose transport, particularly impairment of GLUT4, which may be due to increased reactive oxygen species (ROS) from fatty acid oxidation via an unknown mechanism [300]. As stated earlier, while obesity and insulin resistance overlap, they are not the same, as some patients are obese without being insulin resistant, and some are insulin resistant without being obese [301]. This is because not all tissues are equally insulin resistant; only liver, muscle and brain insulin resistance lead to hyperinsulinemia and obesity [302], while adipose tissue insulin resistance prevents further fat accumulation.

7.1.1. Hepatic insulin resistance.—The liver is the primary target of insulin action. Following a glucose load, insulin travels directly to the liver via the portal vein, where it binds to the insulin receptor recruiting and activating the PI3K pathway, eliciting two key actions at the level of gene transcription. First, insulin stimulates the phosphorylation of the forkhead protein FoxO1, which prevents it from entering the nucleus [303, 304]. This diminishes the expression of two genes required for gluconeogenesis (phosphoenolpyruvate carboxykinase and glucose 6-phosphatase), thereby shutting down glucose synthesis leading to diminished hepatic glucose output. Second, insulin induces sterol regulatory element-binding protein (SREBP)-1c, which increases transcription of genes required for fatty acid and triglyceride biosynthesis (ATP-citrate lyase, acetyl-coenzyme A carboxylase, and fatty acid synthase, which constitute the process of *de novo* lipogenesis (DNL)). Excess fat synthesized by DNL that is not exported out of the liver as VLDL is instead stored as triglyceride (TG) droplets within the hepatocyte [305], contributing to fatty liver disease, increasing the enzyme *c-jun* N-terminal kinase-1 (JNK-1), altering the phosphorylation status of insulin receptor substrate-1 (IRS-1) [306] and inducing hepatic insulin resistance [307].

7.1.2. Brain insulin resistance.—There are several postulated mechanisms for the development of CNS insulin resistance. As stated earlier, hyperinsulinemia can drive CNS insulin resistance by down-regulating the insulin receptor at the level of the ARC, resulting in defective leptin signal transduction resulting in “brain starvation” and in a lack of attenuation of reward in the NA, both leading to increased food intake and weight gain [252]. Another proposal for the mechanism of CNS insulin resistance is the production of ceramide due to fatty liver disease, which can induce brain oxidative stress and inflammation leading to CNS insulin resistance [308]. Lastly, as seen in systemic insulin resistance, increased peripheral free fatty acids may be taken up by microglia in the ARC to induce hypothalamic neuroinflammation and CNS insulin resistance [309].

7.1.3. Adipose tissue insulin resistance.—If any given adipocyte (subcutaneous or visceral) remains insulin sensitive, insulin-induced lipoprotein lipase will drive fatty acids from circulating VLDL and chylomicrons to promote fat storage in vesicles insulin-induced GLUT4 will increase glucose uptake to make glycerol, and triacylglycerol deposition can continue [310–312]. Increases in glucose uptake also increase branched-chain hydroxy-fatty acid esters, which protect GLUT4 levels and reduce inflammation to increase insulin sensitivity in adipose tissue [70]. However, continued expansion of adipose tissue causes cells to become hypoxic and die and secrete inflammatory mediators that promote insulin resistance by releasing TNF-alpha and other cytokines [313] [314]. Adipocyte insulin resistance disinhibits hormone-sensitive lipase (HSL), leading to free fatty acid release into the systemic circulation, which leads to hepatic inflammation and hepatic insulin resistance [315, 316]. Cell death also reduces adiponectin production, promoting hepatic insulin resistance [317].

7.2. Inflammation and obesity

A state of low-grade inflammation and immune dysfunction may account for some of the links between obesity and chronic metabolic diseases [46]. Obese humans and rodents show increased production of pro-inflammatory cytokines and adipokines such as monocyte chemotactic protein 1 (MCP1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), IL-1β, and leptin, along with infiltration of macrophages with pro-inflammatory M1-like phenotype in adipose tissue [318], [319]. Resistin secretion from macrophages occurs during inflammation and enhances the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12 [320]. Resistin also plays a role in the upregulation of the expression of chemokines and adhesion molecules.

Both adaptive and innate immunity are also disturbed in obesity. There are reports of a decrease in naive CD4+ T cells and regulatory T cells (T regs), an increase in CD4+ Th17 and Th22 pro-inflammatory subsets, CD8 cytotoxic T cells, and natural killer (NK) cells [27]. Inflammation also makes obese patients more prone to develop infectious and non-infectious diseases. In addition to immune mechanisms, endothelial and adipose dysfunction coupled with viral receptor expression and insulin resistance can account for these harmful effects [28].

The immune system plays both a homeostatic and pathologic role in diseases of metabolic organs. The balance between pro-and anti-inflammatory processes is critical to achieving metabolic homeostasis. Immune system imbalance is observed in metabolic diseases; however, many pathways connecting obesogens, inflammation, and metabolic disease(s) remain unknown[321]. There is a close relationship between nutrient excess and activation of innate immunity, which is seen in the pancreas, liver, skeletal muscle, adipose tissue, gut, and blood vessels, i.e., the organs playing critical roles in the maintenance of energy homeostasis [317]. Adipose tissue inflammation, linked with the processes governing fibrosis and insufficient angiogenesis within adipose tissue, contributes to adipocyte expansion and systemic inflammation [322, 323].

Resident M2-like macrophages in adipose tissue promote the health of normal adipose tissue and influence energy metabolism and mitochondrial function in adipocytes [324]. Adipose

tissue inflammation is associated with a perturbation of the homeostatic role of adipose tissue-resident macrophages [325]. Obesity leads to an altered immune state in adipose tissue where enlarged adipocytes produce chemokines and chemotactic adipokines such as MCP1 and leukotriene B4 (LTB4) that attract monocytes [326]. Adipocytes also can secrete other chemokines that attract eosinophils, invariant natural killer T cells (iNKTs) and T-cells to adipose tissue [327, 328]. Upon recruitment of pro-inflammatory cells, cytokines such as TNF-α, IFN-γ, and IL-17 promote M1 polarization of adipose tissue macrophages [328, 329]. T-helper cells are polarized to Th1 cells *via* M1 macrophages and adipocytes secreted leptin [327]. Through the production of TNF-α and IFN-γ by Th1 cells, the vicious cycle of macrophage activation is invoked, subsequently remodeling the adipose tissue [328–330]. This shift towards pro-inflammation in adipose tissue was also observed in obese mice [328, 329]. The crosstalk between adipocytes and immune cells progressively creates a pro-inflammatory environment in adipose tissue. Additionally, pro-inflammatory cytokines cause insulin resistance through direct serine phosphorylation of the insulin receptor substrate-1 or 2 [326]. Together these studies point to an association of enhanced pro-inflammatory and reduced anti-inflammatory state with obesity and metabolic dysfunction.

7.3. Gut microbiome and obesity

Research in the last decade has unraveled a significant role of the host gut microbiome in defining the development of obesity and its promotion of metabolic consequences in organ systems such as liver, lung, kidney, reproductive organs, and the heart [331]. Diseases such as NAFLD, chronic hypertension, polycystic ovarian syndrome, CVD, and chronic kidney disease (CKD) have all been associated with obesity [332, 333]. Importantly, in all the complications associated with an obese phenotype, the host gut microbiome has been found to play a profound role in disease progression leading to poor outcomes [334].

The gut microbiome is a large body of bacteria, viruses, and fungi that reside in a complete symbiotic environment in the small intestine, the large intestine and the colon [335], [336]. Host microbiomes play a crucial role in physiological homeostasis, forming a critical part of the gut, brain, metabolic, and immune health. These resident bacteria and viruses are intertwined with the host's metabolism and often contribute to small molecule intermediates that help the host maintain normal metabolic processes, e.g., short-chain fatty acids [337]. Conversely, defined as a change in the relative abundance of the millions of bacteria, viruses, and fungi needed for the symbiotic environment, a modified microbiome is associated with obesity [338, 339]. The development of genetic sequencing methods and adoption of more sophisticated bioinformatics tools have led to significant progress to identify abundance among phyla, order, family, genus and species of the host microbiome, empowering studies to examine the linkage of dysregulated microbiota to metabolic dysfunction.

Some of the first studies of an altered microbiome accurately identified an increase in *Firmicutes* abundance over the more common *Bacteroidetes* in obesity [340, 341]. Later, this altered microbiome signature was also found in FLD, confirming that diet and accumulation of free fatty acids play a role in the altered diversity and abundance of the host bacteriome [342]. Several studies have identified the role of specific phyla such

as *Porphyromonadaceae, Enterococcaceae* and *Lactobacillaceae* in obesity [343]. More importantly, obesity is associated with low-level inflammation primarily from elevated levels of TNF-α, IL1β and MCP-1[344]. An altered microbial diversity and increases in the abundance of *Firmicutes* or *Porphyromonadaceae* species may be responsible for a "leaky gut" and increased levels of these cytokines in the circulation [345]. Obesity is often associated with a low inflammatory trigger and fat accumulation that skew the healthy microbiome towards an increased abundance of the gut bacteria known to decrease gut and immune health. Transplant studies showed proof of concept; for example, cohousing mice harboring microbiota from an obese twin with mice containing microbiota from a lean twin prevented increased body mass and metabolic phenotypes in the obese cage mates [346].

Disruptions of the gut microbiome may lead to altered production of important bacteria (and host)-derived molecules, including short-chain fatty acids (fermentation products), tryptophan metabolites including indole-3-carboxylic acid, 10-oxo-12-ocadecenoic acid (from lactate), bile acids (mediators of thermogenesis) with a known impact on obesity and metabolism [347–350]. The altered bacterial composition may also disrupt intestinal barrier functions and affect distant organs, including adipose tissue, pancreas, brain, and liver, thus promoting metabolic inflammation and obesity [351]. Gut microbiota dysbiosis can promote white adipose tissue inflammation and expansion [352]. Alterations in the gut microbiome strongly impact NAFLD development [353]. The gut is also a critical organ in developing metabolic syndrome [354].

7.4. Circadian rhythms and obesity

In mammals, the circadian clock is responsible for regulating 24-hour rhythms of behavior and physiology. A central clock controls this timing system in the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral clocks in peripheral tissues (liver, adipose tissue, skeletal muscle, etc.), playing a pivotal role in many biological processes. The circadian clock regulates several metabolic processes, including lipid and glucose metabolism and mitochondrial oxidative phosphorylation [355–359]. Interestingly, gut microbiota may also regulate their host circadian rhythms *via* the metabolites they produce, such as short-chain fatty acids [360]. In this context, any change in circadian rhythms can impact metabolic health, resulting in pathologies such as obesity, T2D, metabolic syndrome, or NAFLD [361–364].

As will be discussed in detail in the companion review, all of these tissues, organs and mechanisms that control metabolism and weight gain are possible sites of obesogen action.

8. Fetal origins of obesity

Excessive weight gain can start at any time across the lifespan. Still, the prenatal and neonatal environment has long been considered a critical period for the origins of obesity and cardio-metabolic disease in humans, as described in the Developmental Origins of Health and Disease (DOHaD) hypothesis [365]. For example, undernutrition during pregnancy leads to a low birth weight linked to an increased incidence of obesity, CVD and T2D later in life [366]. Substantial evidence from animal and human studies indicates that the conditions of the *in utero* environment can contribute to the risk of obesity and metabolic

disease in childhood and adulthood [367, 368] by increasing the sensitivity or susceptibility to gain weight. The DOHaD paradigm applies to nutrition during development and stress and environmental chemical exposures, including obesogens. Developmental exposure to obesogens also leads to obesity later in life and even across generations (discussed in detail in the companion review).

8.1. Birth status and future obesity

Birth weight appears to have a U-shaped association with later cardio-metabolic risk. Both low and high birth weights have been associated with a greater risk of obesity and metabolic disease [369–372]. Restricted fetal growth may be followed by rapid or aberrant growth in infancy, and early-life “catch-up growth” has been linked to a greater risk of obesity and greater abdominal fat mass in childhood [373, 374]. Consistent with this pattern, specific prenatal environmental exposures have been associated with lower infant birth weight (236,237) but greater adiposity later in childhood or adulthood [375–378]. Conversely, excessive prenatal somatic growth, independent of maternal type 2 diabetes, leads to obesity and metabolic syndrome in the offspring [379].

8.2. Small for gestational age (SGA), developmental programming, and future obesity

Documentation of the relationship of SGA with adult obesity and cardiovascular disease started with studies of the Dutch famine during World War II and its aftermath [380]. Several studies of newborns born SGA demonstrate that they are hyperinsulinemic and insulin resistant at birth, exhibit rapid catch-up growth in the early post-natal period, and develop obesity in childhood, with persistent insulin resistance and late development of the metabolic syndrome. An analysis of Indian newborns born in India vs. the U.K. [381] demonstrates that despite weighing 700 gm less at birth, their glucose and insulin levels are markedly elevated. They show increased adiposity and become insulin resistant and obese during early childhood [382].

Animal models of gestational caloric restriction recapitulate the human condition and lead to SGA and insulin resistance at the birth of the offspring [383, 384]. Several investigators have postulated that prenatal metabolic perturbation alters the normal ontogeny and organization of the hypothalamus and, ultimately, post-natal regulation of energy balance, mediated through changes in leptin action *in utero*. Leptin-deficient mice (*ob/ob*) exhibit maldevelopment of hypothalamic architecture, with aberrant projections of neurons from the arcuate nucleus (the site of leptin receptors) to the paraventricular nucleus (the site of the melanocortin-4 receptors) [385]. However, a single leptin injection at birth can restore normal hypothalamic development and neurotransmission [386]. This effect of neonatal leptin is also seen in a rat model of maternal undernutrition. Offspring of pregnant rats placed on food restriction during gestation are SGA, insulin resistant, and leptin-deficient at birth. However, with adequate nutrition after the neonatal period, these animals become obese as adults, particularly when placed on high-fat chow after weaning [387], suggesting that the neonatal leptin overrode a developmental programming signal for future obesity.

8.3. Large for gestational age (LGA), epigenetics, and future obesity

Overnutrition during pregnancy, as experienced with maternal obesity, gestational diabetes, and excess weight gain, is also associated with greater adiposity and risk of obesity in the offspring [388–391]. Babies born LGA are hyperinsulinemic at birth [392], demonstrating a doubling of the prevalence of insulin resistance and metabolic syndrome [393]. In contrast, obese women who underwent bariatric surgery reduced the incidence of LGA offspring and their future risk for obesity [394]. Offspring of mothers with obesity and hyperglycemia during pregnancy demonstrate epigenetic changes at birth [395], which may link the early life environment to later obesity phenotype [396–398]. Overnutrition during this sensitive period may produce lasting changes in offspring body composition, either via direct influences on organ and adipose development or via epigenetic regulation of gene expression [397, 399, 400].

8.4. Prematurity, prenatal stress, glucocorticoids, epigenetics, and future obesity

Although there are no studies documenting hyperinsulinemia at birth in premature infants due to blood drawing issues, follow-up of these babies into early childhood also demonstrates increased weight gain and insulin resistance with compensatory insulin secretion that is inappropriately high for their degree of weight gain [401]. Thus, some aspect of prematurity leads to alteration in developmental programming and obesity and insulin resistance in later life.

Prenatal stress may alter the newborn through glucocorticoid effects or autonomic CRH effects [401]. For instance, glucocorticoid exposure during pregnancy results in lower birth weight [402, 403] and predisposition to obesity in later life. Similarly, offspring born of prenatal stress demonstrate altered glucose and insulin homeostasis upon reaching adulthood [404] and are more vulnerable to a high fat diet in later life [405].

Prenatal stress, likely working through CRH manufactured in the placenta, or possibly through maternal cortisol, which overwhelms placental 11bHSD2 (which normally protects the fetus), may alter fetal metabolism in several ways. Prenatal stress may also cause epigenetic changes in the methylation status of the CpG island in the NR3C1 gene, coding for the glucocorticoid receptor, which predicts altered neonatal stress reactivity [406].

Thus, the high glucocorticoid levels associated with chronic stress may act as a feedforward system, recruiting a major chronic stress response network [407] that alters the normal output of autonomic, neuroendocrine and behavioral systems, biasing the usual responses toward increased HPA axis activity as well as accentuating fear-like behavior. Increased activity of this system increases ingestion of high energy-density foods [408] with subsequent increased VAT stores and the metabolic syndrome.

9. Conclusions

This review focused on the tissues/organs, hormones, pathways, and mechanisms that play key roles in metabolism to induce adipose tissue, resulting in obesity. Obesity is a multifunctional, multi-tissue, multi-hormone, multi-receptor, and multi-mechanism disease. When obesity results from increased VAT or liver fat with large fat cells, inflammation,

and insulin and leptin resistance, it is also associated with several metabolic disorders, including T2D, NAFLD, CVD and some cancers. On the other hand, when the obesity results from increased SAT with small adipocytes, limited inflammation, and normal insulin and leptin activity, there is, in some cases, a lack of corresponding metabolic perturbation, at least initially. The multifunctional nature of obesity results from the many highly coordinated interacting factors that play a role in obesity, including genetics and environmental factors. The environment includes nutrition, exercise, viruses, microbiome, circadian rhythms (this review), and environmental chemicals (discussed in the companion review). Environmental factors act on the complex interacting organ systems that control metabolism, including adipose tissue, the gastrointestinal tract, muscle, pancreas, liver, and various parts of the brain, that integrate the control of feeding behavior, including homeostatic hedonic eating. Control of adipose tissue development, as well as the number and size of adipocytes, depends on the activity and interaction of a variety of transcription factors, including the two master regulators of adipogenesis: PPARγ; and RXR, which can activate adipogenesis either alone or as a heterodimer with PPARγ. The hormones insulin, estrogen, androgen, glucocorticoid, and thyroid hormone also play important roles in metabolism and adipogenesis by binding to their receptors. Other liver transcription factors modulate specific metabolic signals, which can lead to disease when dysfunctional. LXR, although not activated by specific hormones, regulates adipocyte differentiation, cholesterol transport, and triglyceride accumulation. PXR and CAR appear to act in conjunction with PPARγ and regulate glucose and energy homeostasis and immune and lipid metabolism. FXR regulates bile acid synthesis and lipid metabolism, and AhR can result in hepatic insulin resistance. Activation of these receptors can result in hyperinsulinemia, leptin resistance, and weight gain.

The tissues and organs controlling metabolism, and therefore weight gain, communicate via a network of hormones and neurotransmitters. For example, leptin, resistin, and adiponectin are elicited from adipocytes; ghrelin and GIP from the stomach; CCK, GLP-1, OXM, and $PYY_{3\text{-}36}$ from the gastrointestinal tract; insulin and glucagon from the pancreas; NPY-AgRP and POMC from hypothalamic neurons; dopamine from the VTA and NA; as well as estrogen, androgen, thyroid hormone, and cortisol from their respective endocrine glands.

While obesity can occur throughout the lifespan, it can have its origins during fetal development and infancy and is thus regulated by changes in epigenetic regulation or developmental programming of gene expression. These perturbations are particularly susceptible to environmental influences.

This review of metabolism highlights the organs and mechanisms responsible for regulating adiposity. It also sets the hypothesis that environmental chemicals capable of disrupting these mechanisms, termed obesogens, can lead to obesity. Numerous compounds, some nutritional and some endocrine-disrupting chemicals (EDCs), can affect the hormonal control of adipose tissue differentiation, development, growth, and/or maintenance. These changes subsequently result in differential effects on fat depots that can ultimately affect metabolic dysfunction. Thus, we proffer that the change in prevalence and severity of obesity is, at least in part, due to the occurrence and accumulation of various environmental alterations — in the form of either poor nutrition or obesogenic EDCs — in an otherwise

genetically susceptible population, the most susceptible of which is the fetus. The second companion article will review the plausibility, mechanism, and evidence for these obesogens — *in vitro*, animals, and humans.

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Abbreviations

Ad	Adenovirus
AgRP	agouti-related protein
AhR	aryl hydrocarbon receptor
Akt	AKR Thymoma, protein kinase B
AR	androgen receptor
ARC	arcuate nucleus
ARKO	Androgen receptor knock-out
ATP	adenosine triphosphate
BAT	brown adipose tissue
BaP	benzo[a]pyrene
BCAAT	branched-chain amino-acyl transferase
bHLH	basic-helix-loop-helix
BMI	body mass index
CAR	constitutive androstane receptor

CCK	cholecystokinin
CKD	chronic kidney disease
CNS	central nervous system
CRH	corticotropin-releasing hormone
CT	computed tomography
CVD	cardiovascular disease
DNL	*de novo* lipogenesis
DOHaD	Developmental Origins of Health and Disease
DRN	dorsal raphe nucleus
EDC	endocrine disrupting chemical
eIF-4E	Eukaryotic translation Initiation Factor 4E
ER	estrogen receptor
ERK	extracellular signal-regulated Kinase
ERKO	estrogen receptor knock-out
FFA	free fatty acid
FLD	fatty liver disease
FOXO	Forkhead box O
FXR	farnesoid X receptor
GI	glycemic index
GIP	gastric inhibitory polypeptide
GLP	glucagon-like peptide
GLUT	glucose transporter
GPER	G-protein-coupled estrogen receptor
GR	glucocorticoid receptor
Grb2	Growth factor receptor-Bound protein 2
GRKO	glucocorticoid receptor knock-out
GSK3b	Glycogen Synthase Kinase 3-beta
GWAS	genome-wide association studies
HDL	high-density lipoprotein

HFD	high-fat diet
HOMA-IR	homeostatic model assessment of insulin resistance
IFN-γ	interferon gamma
IGF	insulin growth factor
IGF1R	insulin growth factor-1 receptor
IL	interleukin
iNKT	invariant natural killer T cells
IR	insulin receptor
IRS	insulin receptor substrate
JAK2	Janus Kinase 2
JNK-1	*c-jun* N-terminal kinase-1
Kyn	kynurenine
LDL	low-density lipoprotein
LTB4	leukotriene B4
LXR	liver X receptor
MAM	mitochondria-associated endoplasmic reticulum membranes
MCP1	monocyte chemotactic protein-1
MEK	MAPK/ERK Kinase
miRNA	micro-RNA
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
mTOR	mammalian Target Of Rapamycin
myf5	myogenic factor 5
NA	nucleus accumbens
NAFLD	non-alcoholic fatty liver disease
NK	natural killer cells
NPY	neuropeptide Y
NST	nucleus of the solitary tract
OXM	oxyntomodulin

PAS	PER-ARNT-SIM
PDE	phosphodiesterase
PI3K	phosphoinositol-3-kinase
POMC	pro-opiomelanocortin
PPAR	peroxisome proliferation activated receptor
PTP-1B	protein tyrosine phosphatase-1B
PVN	paraventricular nucleus
PXR	pregnane X receptor
PYY_{3-36}	peptide YY_{3-36}
RAF	Rapidly Accelerated Fibrosarcoma kinase
RAS	Rat Sarcoma virus protein
ROS	reactive oxygen species
RXR	retinoid X receptor
S6	S6 ribosomal protein
SAT	subcutaneous adipose tissue
SCD	stearoyl-CoA desaturase
SCN	suprachiasmatic nucleus
Shc	Src homology 2 domain-containing protein
SHP2	Src Homology region 2-containing Protein tyrosine phosphatase 2
SOCS3	Suppressor Of Cytokine Signaling 3
SREBP	sterol regulatory element-binding protein
STAT3	Signal Transducer and Activator of Transcription 3
T2D	type 2 diabetes
T_3	triiodothyronine
T_4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEF	thermic effect of food
TG	triglyceride
TNF-α	tumor necrosis factor-alpha

TR	thyroid hormone receptor
TRH	thyrotropin releasing hormone
TSH	thyroid-stimulating hormone
TZDs	thiazolidinediones
UCP-1	uncoupling protein-1
VAT	visceral adipose tissue
VLDL	very-low-density lipoproteins
VTA	ventral tegmental area
WAT	white adipose tissue

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Essential Points

- There is an expanding global obesity and non-communicable disease pandemic.
- Obesity is a multifactorial, multi-organ, multi-hormone, and multi-mechanism disease.
- Genetic and environmental influences control adiposity and weight gain.
- Understanding the tissues/organs, hormones, and mechanisms involved in obesity set the stage for understanding the evidence for the obesogen hypothesis.

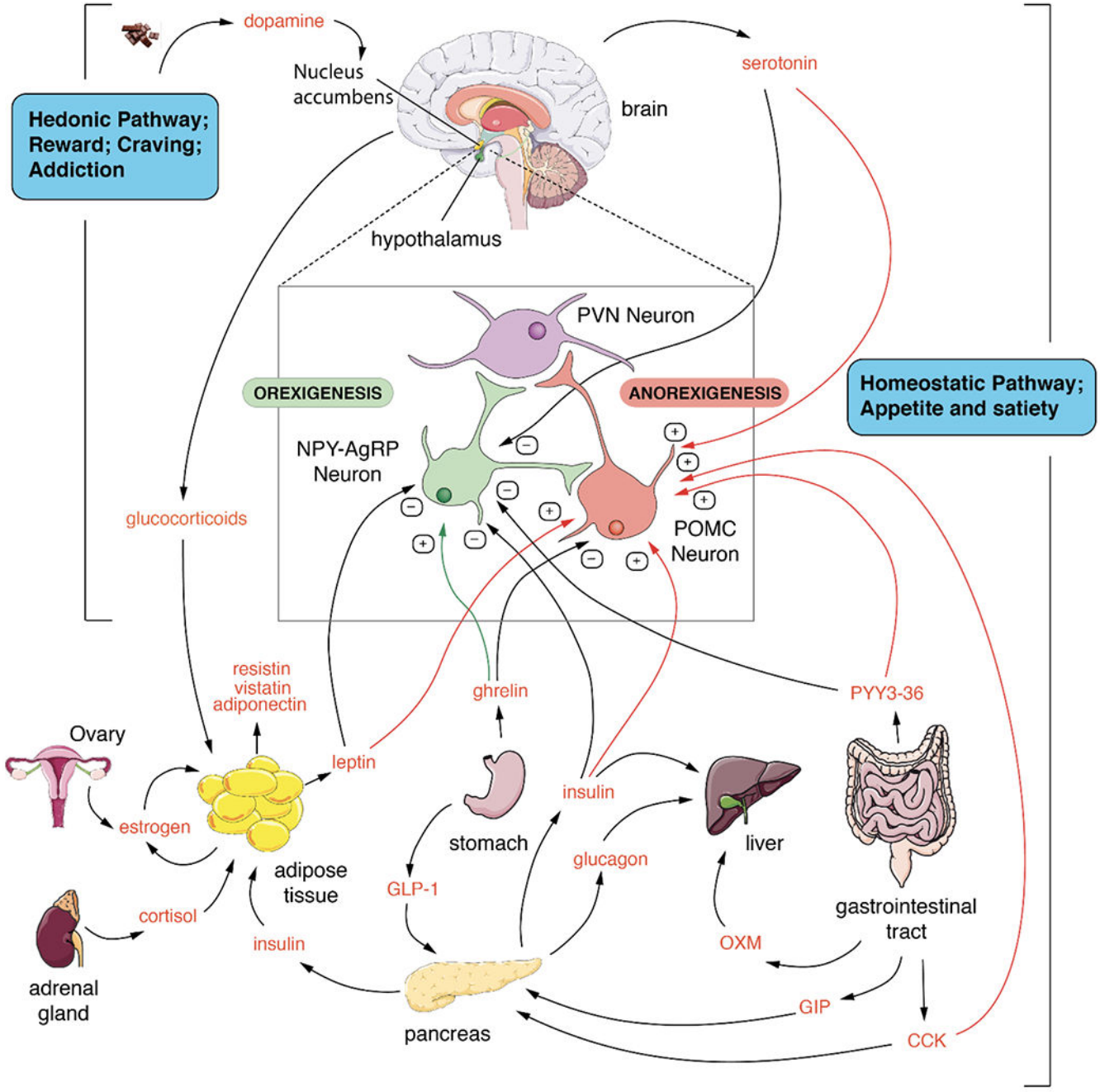

Figure 1. Endocrine control of Metabolism

The main tissues involved in controlling metabolism are shown along with the main endocrine and paracrine modulators of metabolic function. Many positive and negative control points in the tissues and the brain are integrated to control metabolism and body weight. The homeostatic pathway is the largest and most complex and likely regulates the set point for metabolism via control of the appetite and satiety centers in the brain. The hedonic center controls emotional eating and food addiction which can override the homeostatic system.

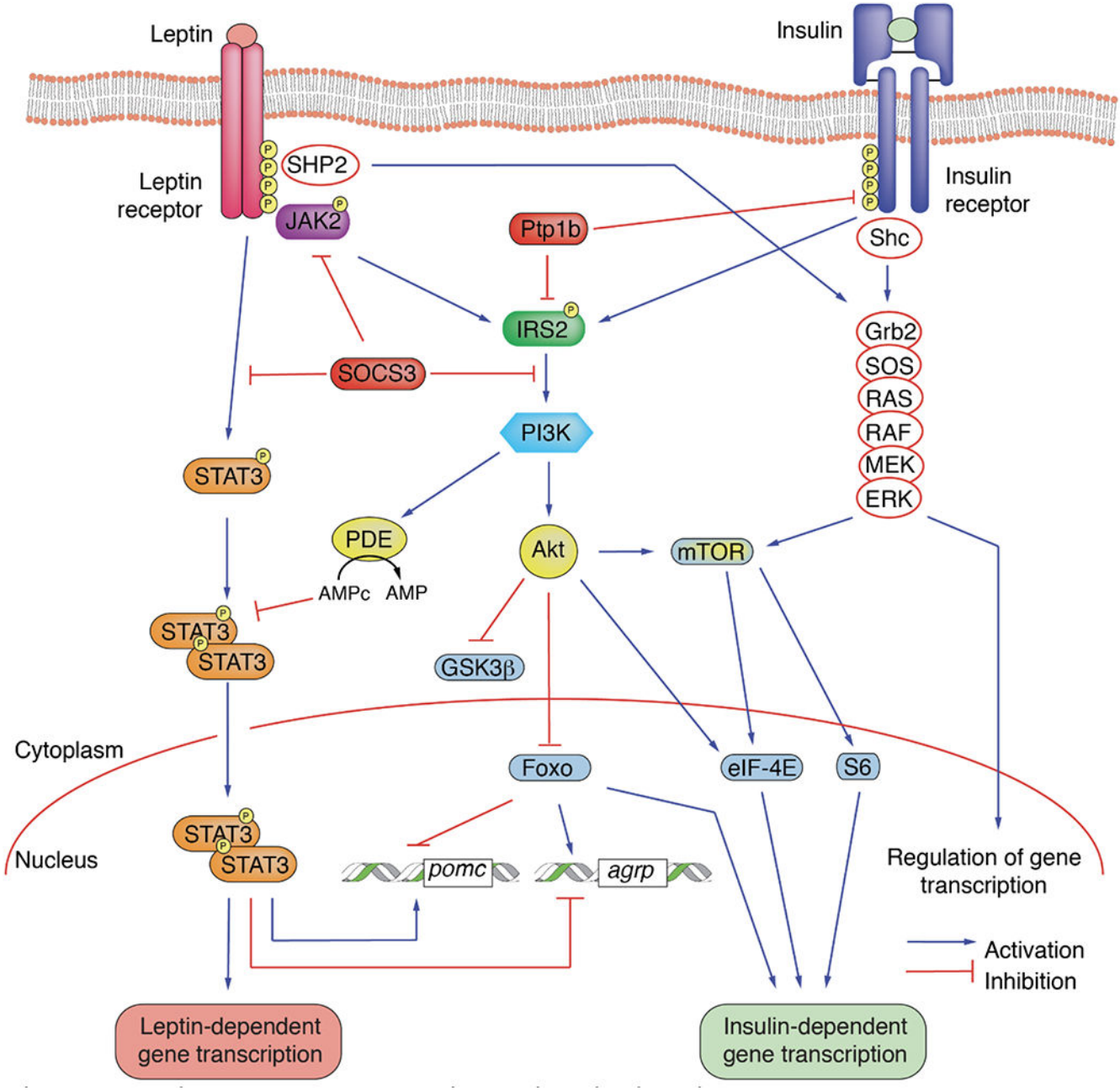

Figure 2. The interplay between leptin and insulin signaling pathways.

The insulin receptor and the leptin receptor recruit the low-abundance-message insulin receptor substrate-2. Lack of available insulin receptor substrate 2 for the leptin receptor due to hyperinsulinemia could result in defective leptin signal transduction. Alternatively, insulin induction of suppressor of cytokine signaling-3 could inactivate the leptin receptor through alterations in tyrosine phosphorylation.

Abbreviations, Agrp: Agouti-Related Neuropeptide; Akt: AKR Thymoma, protein kinase B; eIF-4E: Eukaryotic translation Initiation Factor 4E; ERK: Extracellular signal-regulated Kinase; Foxo: Forkhead box; Grb2: Growth factor receptor-Bound protein 2; GSK3β:

Glycogen Synthase Kinase 3-beta; IRS2: Insulin Receptor Substrate 2; JAK2: Janus Kinase 2; MEK: MAPK/ERK Kinase; mTOR: mammalian Target Of Rapamycin; PDE Phosphodiesterase; PI3K: PhosphatidylInositol 3-Kinase; pomc: Proopiomelanocortin; Ptp1b: Protein-Tyrosine Phosphatase 1B; RAF: Rapidly Accelerated Fibrosarcoma kinase; RAS: Rat Sarcoma virus protein; S6: S6 ribosomal protein; Shc: Src homology 2 domain-containing; SHP2: Src Homology region 2-containing Protein tyrosine phosphatase 2; SOCS3: Suppressor Of Cytokine Signaling 3; STAT3: Signal Transducer and Activator of Transcription 3

Table 1:

Transcription factors involved in obesity and obesogen action

Adipose Tissue Transcription Factors	**Abbreviation**	**Agonists promote:**
Peroxisome proliferator-activated receptor gamma (heterodimer with RXR)	PPARγ	Increased adiposity, improved insulin sensitivity
Peroxisome proliferator-activated receptor alpha	PPARα	Decreased serum triglycerides, LDL cholesterol, increased HDL cholesterol, protection against diet-induced obesity
Peroxisome proliferator-activated receptor beta/delta	PPARβ/δ	Decreased LDL cholesterol, insulin, increased HDL cholesterol, protection against diet-induced obesity
Retinoid X receptor (heterodimer with PPARγ)	RXR	Improved insulin sensitivity, reduced hyperglycemia, hypertriglyceridemia, hyperinsulinemia, reduced weight gain and food intake
Liver Transcription Factors		
Liver X receptor	LXR	Decreased visceral adiposity, increased subcutaneous adiposity, increased cholesterol, increased plasma and hepatic triglycerides
Pregnane X receptor	PXR	Enhanced hepatic lipid accumulation, fatty liver disease, increased hyperglycemia
Constitutive androstane receptor	CAR	Improved insulin sensitivity, glucose and lipid metabolism, protection against diet-induced obesity, decreased glyuose levels
Farnesoid X receptor	FXR	Increased adiposity, improved insulin resistance, increased glucose intolerance, reduced hepatic lipid accumulation
Aryl hydrocarbon receptor	AhR	Hepatic lipid accumulation, insulin resistance

Table 2:

Systemic hormone receptors and their role in obesity and obesogen action

Hormone receptor	Abbreviation	Agonists promote:
Insulin receptor	IR	Increased adiposity
Estrogen receptors	ER (α, β)	Increased adiposity
Androgen receptor	AR	Decreased adiposity, lipid accumulation
Glucocorticoid receptor	GR	Increased adiposity
Thyroid hormone receptors	TR (α, β)	α- increased adiposity, increased cholesterol, triglycerides β- reduction in cholesterol, triglycerides, and adiposity