Chapter 10
Adipocytes as Target Cells for Endocrine Disruption

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Abstract Throughout the first two decades of human development, growth of adipose tissue primarily results from an increase in adipocyte number (hyperplasia). Once established, the number of fat cells remains relatively constant, and adipose tissue grows larger primarily by filling the resident cells with more fat (hypertrophy). Obese children exhibit an augmented rate of increase in adipocyte number, and correspondingly, obese adults possess more fat cells. Hence, childhood and adolescence appear to be critical periods in establishing the number of fat cells. Endocrine-disrupting chemicals (EDCs) can predispose a child to obesity by influencing all aspects of adipose tissue growth, starting from multipotent stromal cells (MSCs) and ending with mature adipocytes. EDC exposure can increase the number of preadipocytes, enhance the differentiation of preadipocytes into adipocytes, and augment the uptake of fat into existing adipocytes. Unlike genetic mechanisms, which require a mutation event, EDCs have the capacity to quantitatively alter gene expression by modulating cellular-signaling pathways and by introducing epigenetic changes that also alter gene expression. Therefore, EDC exposure could foster a swift change in the metabolic profile of a population, which might provide at least a partial explanation for the rapid rise in obesity. This review focuses on the developmental origins of the adipocyte and its connection to early-onset obesity with the aim of providing a foundation for formulating hypotheses regarding how EDCs can interfere with adipogenesis and contribute to the obesity epidemic.
Keywords Adipocyte • Adipogenesis • Endocrine-disrupting chemical (EDC) • Endocrine disruption • Epigenetic reprogramming • Epigenetics • Multipotent stromal cell (MSC) • Nuclear receptor • Obesity • Obesogen • PPAR gamma • Stem cell • Transgenerational effects

Introduction

On April 20, 2010, a group of retired military leaders reported that 27% of all Americans aged 17–24 were too overweight to join the military [1]. Although current recruitment goals are satisfied, the concern is that this trajectory will continue until only a small proportion of America’s youth will be qualified to serve [2]. This is supported by a recent study projecting that by 2030, 86% of Americans will be overweight, contributing to upwards of 900 billion dollars yearly in additional health care costs [3]. Notwithstanding the national security implications, the major concern with childhood obesity is its strong link with and ability to predict adult obesity and metabolic disease [4–7]. Indeed, a recent longitudinal study showed that increased waist diameter and body mass index (BMI) in children and adolescents increased the risk for abdominal obesity, insulin resistance, thrombotic disorder, elevated low-density lipoproteins (“bad” cholesterol), and systemic inflammation, later in life [8, 9]. These are the signatures of metabolic syndrome, and while adults might rise above this outcome, prevention at earlier stages in life would be more effective.

Throughout the first two decades of human development, growth of adipose tissue primarily results from an increase in adipocyte number (hyperplasia) [10, 11]. After this, the number of fat cells remains relatively constant, and adipose tissue grows larger primarily by filling the resident cells with more fat (hypertrophy) [11]. Obese children exhibit an augmented rate of increase in adipocyte number, and correspondingly, obese adults possess more fat cells [10, 11]. Hence, researchers have hypothesized that childhood and adolescent periods are critical in establishing the number of fat cells [12, 13]. The inference is that a child who is overnourished will produce an excess of new fat cells and, in essence, be “stuck” with these cells later in life. In part, this explains why the military leaders suggest school nutrition intervention, and why celebrities like Chef Jamie Oliver champion the eradication of processed foods from school lunch programs [14]. While these are wise choices that will ultimately be beneficial, unfortunately, mounting evidence supports the idea that obesity is established before puberty [15] and even before birth [16]. Genetics is a popular mechanism to explain such a deterministic phenomenon, except that it cannot account for the rapid rise in obesity.

Endocrine-disrupting chemicals (EDCs) have the strong potential to predispose a child to obesity by influencing all aspects of adipose tissue growth, starting from multipotent stromal cells (MSCs) and ending with mature adipocytes [17]. Certain EDCs can create an immutable adipocyte landscape characterized by increased proliferation and differentiation of adipose progenitors, coupled with an inherent
alteration in the MSC compartment that biases stem cells toward the adipose lineage [18]. Unlike genetic mechanisms, which require a mutation event, EDCs have the capacity to quantitatively alter gene expression by modulating cellular-signaling pathways and by introducing epigenetic changes that also alter gene expression. Epigenetic marks in chromatin are programmed during times of developmental plasticity (in the womb or during childhood and adolescence) [19]. Therefore, EDC exposure could foster a swift change in the metabolic profile of a population, which might provide at least a partial explanation for the rapid rise in obesity. This also vindicates the common experience that adipose tissue is often unyielding to shrinkage through improved diet and exercise. Many of the early events in adipogenesis remain unclear, thus, the processes targeted by EDCs may not be fully understood until fundamental mechanisms of adipose development have been resolved. This review focuses on the developmental origins of the adipocyte and its connection to early-onset obesity with the aim of providing a foundation for formulating hypotheses regarding how EDCs can interfere with adipogenesis and contribute to the obesity epidemic.

The Morphology of Adipose Tissue in Early-Onset Obesity

Humans are the fattest of all mammals at birth, typically possessing ~ 15% body fat, of which most is white adipose tissue (WAT) [20]. This is predicted to be the result of high encephalization [21] because our large brains consume an enormous amount of energy. During infancy, body fat composition nearly doubles (to 28%), but then declines during early childhood [22]. After about 8 years of age and throughout adolescence, adipose tissue grows, although the body distribution becomes sexually dimorphic. Males decrease their fat composition as a percentage of total body mass, whereas females increase their fat composition [23]. Under normal circumstances, body fat functions in the proper timing of puberty, again with a sexual dimorphism. A high-percent body fat delays puberty in males, but initiates early menarche in females [24]. Recent research, using 14C labeling, highlighted the childhood and adolescent periods as the main time of adipose hyperplastic growth [11]. In early adulthood, the total number of fat cells stabilizes; the number only increases when existing cells have reached full capacity through hypertrophic growth [11].

While more sophisticated, the 14C-labeling studies actually confirmed long-standing results. Nearly 40 years ago, obesity, particularly early-onset obesity, was linked to hypercellularity of adipose tissue [25–27]. Ten years later, researchers charted the steady increase in adipocytes during the first two decades of life and showed that obese children possessed more fat cells which multiplied at a faster rate than non-obese children [10]. Further studies demonstrated that once established, a person’s adipocyte population is resistant to changes in number. For example, obese adolescent girls who were put on a strict diet and advised to engage in physical activity surprisingly showed increased hyperplastic adipocyte growth after 1.5 years, compared to the reference group [28]. Those girls that were most resistant to the
treatment had the greatest increase in adipocyte number. This is supported by the 14C-labeled adipose studies, mentioned above, which also showed that the number of adipocytes remains relatively constant throughout adulthood, is higher in obese individuals, and cannot readily be reduced even after bariatric surgery (although adipocyte volume decreases) [11].

The body’s resistance to changes in adipocyte number correlates well with the observation that the body resists major alterations in weight gain or loss. In the 1930s and 1940s, the general belief was that obesity was induced by a lack of will-power [29], perhaps due to some hypothalamic disruption that influenced satiety [30]. However, when obese patients were forced to follow a severe liquid diet, they reached a more normal weight, but this was, by no means, a homeostatic state [31–33]. They exhibited signs of starvation, and a preoccupation with the craving for food, stronger than addiction, an urge akin to an extreme thirst for water or the desire to breathe. In the opposite scenario, lean volunteers from the Vermont State Prison were asked to eat 2–3 times more than usual [34]. The authors of the study stated, “achieving a serious gain in weight cannot be undertaken as a secondary occupation.” Although the prisoners gained weight at different rates, they were all able to return to their former weight. Importantly, the prisoners’ weight gain was hypertrophic in nature, whereas the starving obese subjects’ weight loss was hypotrophic. In each case, the individuals were struggling against their basic biology, their metabolic set point, defined by the number of cells in adipose depots.

Of course, this is not to say that adipocytes are static entities, or that only a fixed number of cells are allocated to each person. Although adipocytes are postmitotic, they do regenerate about once every 10 years [11] through the processes of apoptosis, autophagy, dedifferentiation, or necrosis, and subsequent renewal [35–37]. The adipocyte pool size can fluctuate; a high-fat diet, for example, will encourage hyperplastic growth of subcutaneous fat depots in adult mice [38]. Moreover, when cells have reached their lipid capacity, they will generate paracrine signals that result in the generation of more fat cells in rodents [39–41]. Not all fat tissue is equally capable of hyperplastic growth; in particular, visceral abdominal fat (VAT) does not readily increase its cell number [38, 42]. A very popular hypothesis is that many pathological consequences of obesity are due to excessive adipocyte hypertrophy (as a result of nutrient excess, or an inherent imbalance in fatty acid synthesis and oxidation [43]) coupled with an impaired ability to compensate with adipose tissue expansion [44–48]. The result is adiposopathy [49], which is often characterized by lipotoxicity, where lipid essentially “leaks” into other tissues generating proinflammatory signals and oxidative stress, leading to chronic hyperglycemia and increased circulation of triglycerides [50, 51]. One reason that thiazolidinedione antidiabetic medications are effective is because they protect against this ectopic fat “leakage” by encouraging the birth of new adipocytes in depots other than the VAT, thereby preventing adipocytes from bursting or leaking into the surrounding tissue [52].

Notwithstanding these results, increased adipocyte number, rather than increased size, is the morphology commonly shared among obese individuals who developed the disease early or during adolescence. Furthermore, adipose depot hypercellularity is also the morphology associated with resistance to weight loss. This review
highlights programming events early in life that augment the proliferation and differentiation capacity of adipose precursors resulting in an increased number of fat cells. This is important because the obesity epidemic is now recognized as a crisis trending toward the very young [53]. Hence, there is a strong impetus to understand the mechanisms underlying early fat cell development, and how EDCs can influence the differentiation of preadipocytes to adipocytes and the commitment of stem cells to preadipocytes.

Endocrine Disruption During the Differentiation Phase

In the field of adipose biology, a heightened number of fat cells is simply an end point, and it becomes important to investigate the mechanistic basis. The mature adipocyte is generated from a white adipocyte precursor (often called a “preadipocyte”) which is committed to the adipocyte fate and cannot differentiate into any other lineage (like bone, cartilage, muscle, or even brown fat) [54–57]. This precursor is derived from multipotent stromal cells (MSCs) found in almost all fetal and adult tissues [58], but most commonly cultured from adipose tissue or bone marrow. Most evidence supports the theory that MSCs are the progeny of perivascular cells that surround blood vessel walls [59, 60]. In support of this hypothesis, it was recently shown that the white adipose precursor exists within the adipose vascular network [61]. This is not surprising because adipose is a highly vascularized tissue and antiangiogenic agents reduce adipose mass [62, 63]. The differentiation of white adipocyte precursors into mature adipocytes (adipogenesis) is well characterized in the literature. The central regulator in this process is the peroxisome proliferator–activated receptor gamma (PPARγ), which associates with the retinoid X receptor (RXR) and binds DNA targets as a heterodimer [64]. Figure 10.1 depicts the many of the known events in adipocyte differentiation, focusing on their origin from multipotent precursors, the other main pathways that these precursors can differentiate along, commitment to preadipocytes, differentiation, and apoptosis.

PPARγ is first induced at the transcriptional level by CCAAT/enhancer-binding protein (C/EBP) β and δ [65, 66], and then engages in a feed-forward loop with C/EBPα, amplifying the adipogenic signal [67]. However, C/EBPα also induces Sirtuin-1 [68] which curbs adipogenesis via inhibition of PPARγ target genes [69]. The induction of adipogenesis is typically initiated in cell culture by differentiating agents [70] such as insulin, glucocorticoids, and methylisobutylxanthine, which act through the PI3K/AKT (phosphoinositide 3-kinase/AKT), glucocorticoid receptor, and cAMP protein kinase pathways, respectively. This induction cocktail primarily functions to increase the expression level of C/EBPα or PPARγ, not to activate PPARγ via the production of ligand. An exception to this is the insulin-induced transcription factor, sterol regulatory element–binding protein 1c (SREBP1c), which synthesizes fatty acids that can bind PPARγ [71]. Indeed, the fatty acid derivative, 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), is the strongest candidate for an endogenous ligand for PPARγ [72, 73], although 15d-PGJ2 primarily functions
EDCs have the potential to affect multiple aspects of adipocyte development. MSCs reside within the vasculature of adipose depots; however, EDCs could increase homing of circulating MSCs to adipose tissues. EDCs could also alter the epigenetic program of MSCs by turning on the expression of adipogenic genes and turning off osteogenic, chondrogenic, and myogenic genes. These changes, in addition to the possible involvement of EDCs in the modulation of cellular-signaling pathways (BMP, WNT), increase the commitment of MSCs to the adipogenic lineage at the expense of other lineages. EDCs also play a direct role in the differentiation phase by binding PPARγ, promoting the proliferation and differentiation of preadipocytes. Finally, EDCs could exert effects on the mature adipocyte by inhibiting apoptosis, or enhancing the storage of fat, stimulating hypertrophic growth.
in angiogenesis [74]. It was recently suggested that PPARγ may function in adipogenesis without requiring the ability to be activated by ligand [75]. However, the ligand-binding domain itself is required. When the ligand-binding domain of PPARγ was mutated, the receptor was unresponsive to known agonists, but the ability of preadipocytes to differentiate into adipocytes was unaffected in cell culture [75]. In contrast, deletion of the activation function 2 region of the ligand-binding domain rendered the receptor unable to support adipogenesis [75].

Several EDCs affect PPARγ activity during adipogenesis. The most well-known synthetic agonists of PPARγ are the thiazolidinedione class of antidiabetic agents including rosiglitazone (ROSI) and pioglitazone (PIO) [76]. In addition to increasing insulin sensitivity, these drugs encourage new fat-cell growth and relieve inflammatory stress from hypertrophic cells, but promote hyperplastic obesity. Environmental chemicals such as certain phthalates [77–79] and organotins [80–82] are agonistic ligands for PPARγ. Perfluoroalkyl acids either activate PPARγ weakly [83] or not at all, [84] despite activating PPARα or PPARδ. In cell culture models, phthalates and organotins have the expected effect of promoting preadipocyte differentiation [78, 80]. Importantly, prenatal exposure to tributyltin (TBT) in mice caused substantial storage of triglycerides in newborn tissues that normally have little to no fat at all [80]. The experiments did not distinguish between increased lipid accumulation inexisting cells and an increased number of fat cells. However, given the fact that TBT exposure in Xenopus laevis tadpoles caused the entire testes to essentially turn into fat, it was concluded that TBT primarily functions to promote new adipocyte development at the expense of other cell types. Further studies (outlined in the next section) were undertaken to understand how TBT biases progenitor cells toward the adipocyte lineage.

To date, TBT is the only EDC known to cause in utero effects on adipocytes via PPARγ. Prenatal exposure to phthalates has not yet been linked to adiposity later in life; although high levels of urinary phthalate metabolites were positively correlated with waist diameter in men [85]. Other EDCs also promote adipogenesis, but do not act through PPARγ. Coplanar PCBs (e.g., PCB-77) bind the aryl hydrocarbon receptor in adipocytes and increase adipogenesis [86]. Bisphenol A (BPA) and BPA-related chemicals including alklyphenols stimulate adipogenesis in cell culture [87]. There are a variety of other nuclear receptors and their cofactors that are activated during adipogenesis [88, 89] including those known to be involved in energy metabolism such as the liver X receptor (LXR), the glucocorticoid receptor (GR) and the thyroid receptor (TR), and those more well known in other non-metabolic pathways such as nuclear receptor–related 1 (NURR-1) and the germ cell nuclear factor (GCNF) [88]. Any of these receptors could potentially be targeted by chemicals. Furthermore, RXR is also upregulated during adipogenesis and is activated by TBT [80, 90]. RXR is an obligate heterodimeric partner for PPARγ, as well as TR, NURR-1, LXR, and PPAR (among many other nuclear receptors). RXR itself can be activated in a subset of these heterodimers.

Despite the fact that many EDCs accumulate in adipose tissue and contribute to local effects, most studies have explored the broader metabolic consequences of EDCs, and then addressed the secondary effects on the adipocyte. For example,
polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) reduce thyroid function [91] possibly by competing for thyroid transport proteins [92]. High levels of maternal PCBs and PBDEs are correlated with reduced total and free $T_4$ levels in infant cord blood [93]. Thyroid hormone stimulates lipolysis in adipocytes by downregulating phosphodiesterase activity which normally functions to inhibit catecholamine-induced lipolysis [94, 95]. Thyroid hormone also down-regulates SREBP1c, resulting in the inhibition of lipogenesis [96]. The inference is that exposure to EDCs like PCBs and PBDEs will reduce thyroid hormone levels and cause a concomitant increase in lipid accumulation in adipocytes. Another large class of EDCs that globally affect energy metabolism is the synthetic estrogens, like diethylstilbestrol (DES) and bisphenol A (BPA) [97]. In adults, estrogens protect against adiposity through exergonic, energy-consuming reactions in glycolysis, fatty acid oxidation, and electron transport [97]. At the level of the adipocyte, estrogen receptor beta (ER$\beta$) blocks the transcriptional activity of PPAR$\gamma$ and, hence, is antiadipogenic but prodiabetogenic [98]. In contrast to their effects in adults, low doses of estrogens given pre- or perinatally strikingly promote obesity in exposed animals [99]. Similarly, nicotine, which promotes weight loss in adults, increases adipose hypertrophy in young rats [100]. The overall conclusion from these studies is that EDCs can impact the differentiation of adipocytes in a variety of ways.

Endocrine Disruption During the Commitment Phase

Recent research has been directed toward understanding the commitment phase of adipocyte development, that is, how MSCs become preadipocytes. Recently, progenitor cells (which later matured into adipocytes) were purified and found to have the following phenotype: lin$^-$, CD29$^+$, CD34$^+$, Sca-1$^+$, CD24$^+$ [101]. These cells could generate an entire adipose depot in lipodystrophic mice, suggesting that they are bona fide adipocyte precursors [101]. What remains largely unknown is the transcriptional program that turns stem cells into preadipocytes. Bone morphogenic protein (BMP) signaling is not only important in skeletal development but appears to be a vital component in stem cell commitment to the adipocyte lineage [102]. Recently, Zfp423, a downstream target of BMP signaling, was found to be upregulated in fibroblast clones with high adipogenic potential compared with cells having a low adipogenic potential [103]. However, Zfp423 expression remained unchanged during the preadipocyte to adipocyte transition, suggesting that it is involved in the commitment of stem cells to the preadipocyte lineage, but perhaps not in preadipocyte maintenance [103]. In addition to active BMP signaling, repression of noncanonical WNT5a signaling is required for MSCs to evade the osteogenic lineage and proceed toward the adipogenic lineage [104]. This aligns well with the observation that preadipocytes do not differentiate in the presence of WNT signaling [105].

There are very few studies that investigate how EDCs could bias the MSC population toward the adipogenic lineage. In cell culture, organophosphates and
4-tertoctylphenol thwarted the bone differentiation capacity of MSCs [106]. When MSCs were cultured from adipose tissue, then treated with TBT or ROSI plus induction cocktail, their proliferation capacity decreased, and up to 60–80% of the cells differentiated into mature fat cells [18]. Cells treated with induction cocktail, but without TBT or ROSI, maintained higher proliferative levels, and only 25–40% of cells became adipocytes [18]. Interestingly, this effect was also seen after in utero exposure. Pregnant dams were treated with a single dose of TBT or ROSI, and the MSCs (cultured from the adipose tissue of embryos) were already predisposed to become fat cells, even without further treatment with TBT or ROSI [18]. In addition, the MSCs harvested from the TBT- or ROSI-exposed pups were preprogrammed to prefer the adipogenic fate because, when induced with bone differentiating cocktail, many cells still differentiated into adipocytes [18]. This suggests that the MSC population in prenatally TBT- or ROSI-treated animals is enriched in adipocyte precursors at the expense of osteoblasts [18]. This mutually exclusivity ability of a subset of MSCs to differentiate into bone or fat is why osteoporosis has been called “obesity of bone” [107, 108]. MSCs cultured from postmenopausal women with low bone density accumulate twofold more lipid and twofold less type I collagen (part of the bone extracellular matrix) compared to women with healthy bones [109]. Not surprisingly, diabetes medications that activate PPARγ increase the risk for bone fractures [110]. The results with TBT suggest that obesogen exposure may have a similar effect on osteoporosis.

The most recent evidence supports the idea that fat cells are regenerated from an existing population of MSCs that are found in the vasculature of adipose depots [61, 101]. However, it is also possible that circulating MSCs derived from bone marrow can be recruited to the depots. The relative contribution of resident and circulating MSCs to the obesogenic phenotype of TBT- or ROSI-treated animals is currently unknown. Most studies of MSC migration have been devoted to how MSCs escape from bone marrow and flood an injury site [111, 112]. MSCs are predicted to move by chemotaxis, losing adherence to their origin, rolling along blood vessels, and moving through the extracellular matrix to the tissue that is injured [113]. By a similar mechanism, these cells could migrate to adipose tissue upon receiving an appropriate signal. This idea was recently tested by transplanting GFP-labeled bone marrow–derived MSCs into irradiated wild-type mice, and determining whether these cells could populate fat pads in response to adipogenic signals [114]. ROSI or a high-fat diet increased migration of circulating bone marrow cells to omental or dorsal intrascapular fat depots [114]. However, this view has been challenged in a subsequent paper, which states that bone marrow–derived circulating progenitor cells fail to differentiate into adipocytes [115]. Whether or not MSCs can be recruited to adipose depots from bone marrow is probably a moot point since it now appears that MSCs are pericytes that are found in close proximity with vasculature. Whether they are solely localized in the bone marrow and adipose vasculature [61, 101] or instead are found throughout the body [59] is currently controversial. More studies will be required to determine where adipogenic MSCs are located, whether or not they migrate to adipose depots in response to dietary stimuli, and what effects EDCs such as TBT and phthalates have on these processes.
Epigenetic Modifications During Puberty

Although ordinary genetic variability can account for why some people have the propensity to become obese, the rapid increase in obesity argues against a genetic explanation. Epigenetic phenomena occur much faster than gradual genetic mutation and can easily become established in a population within a single generation [116]. For this reason, epigenetics is a more likely explanation for the “epidemic” of obesity. Moreover, epigenetics can also underlie the rapid metabolic adaptations that occur in the womb under dietary stress, and perhaps during other developmental time windows, such as adolescence. While EDCs such as TBT can act on adipose tissue directly (e.g., by binding to PPARγ and inducing adipocyte differentiation), they can also target adipose development via more subtle, epigenetic modifications.

EDC exposure has been linked with alterations in the expression of proteins that remodel the chromatin landscape, such as DNA methyltransferases, histone acetyltransferases, deacetylases, and methyltransferases. For example, in the uteri of animals that were prenatally exposed to DES, there was a significant increase in the mRNA expression of DNA methyltransferase 1 (Dnmt1) and DNA methyltransferase 3b (Dnmt3b) [117]. In another example, exposure to the commonly used fungicide vinclozolin caused a decrease in the expression of Dnmt1, Dnmt3a, Dnmt3L, and euchromatic histone methyltransferase (Ehmt1) in the testes of male rats, and some of these genes remained inhibited in subsequent generations [118].

Since EDCs typically have targeted effects on a particular metabolic pathway, the question of specificity arises. It was shown that Dnmt1 and Dnmt3 can be recruited to individual genes simply by being escorted by transcription factors to specific sequences of DNA, suggesting that the specificity of the EDC effect is conferred by the active transcriptional programs in individual cells [119, 120]. Of course, identification of bona fide DNA sequences (often CpG islands) modulated by EDCs is a challenge and requires a genomic approach. Over 6,000 genes have been predicted to affect body mass, and there are ten times more genes that foster an increase in weight, rather than a decrease [121]. It is likely that epigenetic changes related to adipogenesis and obesity originate within the stem cell compartment. The reason that diet and exercise primarily alter adipocyte volume rather than adipocyte number is because the stem cells are already biased, through changes in gene regulation, to replenish the adipocyte pool to its “set point,” if for any reason the number of adipocytes declines. In support of this model, MSCs from mice exposed to TBT in utero exhibited alterations in the methylation status of the CpG islands of adipogenic genes such as AP2 and PPARγ which led to an increase in the number of preadipocytes at birth and an increased propensity to differentiate into adipocytes upon stimulation [18].

Even more profound is the possibility that epigenetic changes caused by environmental exposures are accumulated or inherited across generations. Vinclozolin, for example, is linked to infertility throughout multiple generations, [122] due to a “memory” maintained within the male germ cells [123]. While there are currently no data regarding transgenerational effects of obesogens, it is reasonable to hypothesize
that obesogenic compounds such as TBT, BPA, or phthalates could also influence the propensity to be obese for some generations after the initial exposure. An example in humans serves to illustrate this point. In the Overkalix region of Sweden, it was demonstrated that food availability during the prepubescent period affected the longevity and mortality from cardiovascular disease of a boy’s grandchildren. A single winter of overeating could lead to a 6-year decrease in longevity of a boy’s grandsons, but not granddaughters [124]. While this is a nutritional study, it is quite possible that chemical exposure during development could have similar transgenerational effects. The human prepubescent period is especially susceptible to epigenetic changes because the testes or ovaries are developing, and the primordial germ cells incorporate sex-specific imprinting patterns in mice [125]. One hypothesis proposed to explain the Overkalix phenomenon is that stress caused by improper nutrition affects downstream proteins involved in imprinting [126]. One such protein candidate is BORIS (Brother of the Regulator of Imprinted Sites) which is expressed in the male testes only in germ cells undergoing genome remethylation [127].

During the prepubescent period, an exogenous chemical could regulate BORIS and permanently impact the methylation status of DNA. Hence, while it is debatable whether adolescence is the most critical period in establishing obesity, it is likely to be a period when epigenetic changes can be “locked in” for the future.

**Conclusion**

A somewhat vestigial function of the adipocyte, especially in Western societies, is its incredibly efficient storage capacity for fat. Hence, a resounding presumption is that unhealthy eating and a convenience food-driven society are enabling agents that contribute to self-induced corpulence. However, babies, children, and adolescents seem destined, almost programmed, to keep their “baby fat” throughout life. We have argued that the morphology of adipose tissue associated with early-onset obesity provides a basis for why weight loss in obese people (the state of being “reduced obese”) is not often a homeostatic state of normalcy and weight gain is observed in more than 90% of cases. We argued that EDCs could exacerbate this problem by increasing the differentiation capacity of preadipocytes, or biasing the MSC pool toward the adipocyte lineage. Moreover, we discussed how EDCs have the potential to affect epigenetic reprogramming events that might cause irreversible modifications that create transgenerational inheritance of obesity.

The concept of early disruption in adipocyte development explains why each person seems to possess a metabolic set point, which is regulated like a thermostat. The thermostat will resist change in temperature, no matter if a window is opened or a hot oven is turned on. If the set point is altered, the new temperature will be maintained. Early nutrition and chemical exposure could alter an individual’s set point, making the fight against weight gain that much more difficult. Obesity is difficult to reverse once established; therefore, it makes sense to shift the focus toward preventative measures. On May 11, 2010, First Lady Michelle Obama launched a
campaign called Let’s Move! As a result of strong communication between science and politics, Mrs. Obama drew attention to EDCs, calling for increased research in this area, reformulation of plastics, and screening for chemicals that are obesogenic [128]. With national attention to this problem, the hope is that the contribution of EDCs to the obesity epidemic will finally be recognized so that appropriate action can be taken to reduce exposure at critical periods during life.

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