Minireview: The Case for Obesogens

Felix Grün and Bruce Blumberg

Departments of Developmental and Cell Biology (B.B., F.G.) and Pharmaceutical Sciences (B.B.), University of California, Irvine, Irvine, California 92697-2300

Obesity and obesity-related disorders, such as type 2 diabetes, hypertension, and cardiovascular disease, are epidemic in Western countries, particularly the United States. The conventional wisdom holds that obesity is primarily the result of a positive energy balance, *i.e.* too many calories in and too few calories burned. Although it is self-evident that fat cannot be accumulated without a higher caloric intake than expenditure, recent research in a number of laboratories suggests the existence of chemicals that alter regulation of energy balance to favor weight gain and obesity. These obesogens derail the homeostatic mechanisms important for weight control, such that exposed individuals are predisposed to weight gain, despite normal diet and exercise. This review considers the evidence for obesogens, how they might act, and where future research is needed to clarify their relative contribution to the obesity epidemic. (***Molecular Endocrinology* 23: 1127–1134, 2009)**

Obesity and obesity-related disorders such as type 2 diabetes, hypertension, and cardiovascular disease are epidemic in Western countries, particularly the United States. The conventional wisdom holds that obesity is primarily driven by a prolonged positive energy balance, *i.e.* too many calories ingested and too few calories burned. Although this axiom explains the fundamental basis of obesity in its simplest terms, a complex set of physiological interactions are necessary to move body weight outside of its normal range. Obesity is not simply a product of overeating and lack of exercise. Instead, the accumulation of fat or mobilization of lipids from adipose storage depots is controlled by a variety of factors. These include the hormonal regulation of appetite and satiety, regulation of glucose levels, central control of basal metabolic rate, regulation of metabolic setpoints, and the number, size, and metabolic activity of adipocytes. Moreover, adipose tissue itself produces key components in the body's feedback systems that help to fine tune appetite and satiety.

Obesity is the result of a prolonged disturbance in the homeostatic regulation of energy metabolism that favors triglyceride storage and adipocyte hypertrophy. The number of adipocytes is also greater in obese individuals, implicating increased adipogenesis or hyperplasia as contributing to fat mass. Measurement and modeling of fat cell dynamics via radionuclide tracing suggest that increased adipocyte number is largely established by early adulthood. This is a consequence of an earlier onset and increased adipocyte expansion (1). There is some evidence to support hyperplasia as a result of extreme hypertrophy in some adults although adipocyte turnover appears to be balanced and tightly regulated in both lean and obese individuals (1). Increased adipose mass elevates the risk for the initiation or progression of a variety of pathological conditions, including metabolic syndrome-associated disorders and some cancers. A multitude of factors will influence whether or not an individual becomes obese, including the factors noted above, as well as single nucleotide polymorphisms in a variety of genes, viral exposure, chronic reductions in sleep, and stress. These have been reviewed elsewhere (2) and will not be considered here. Instead, this review will focus on an emerging new field: the influence of chemical exposure on obesity.

Obesogens can be defined functionally as chemicals that inappropriately alter lipid homeostasis to promote adipogenesis and lipid accumulation (2, 3). Evidence is accumulating from laboratories around the world supporting this general concept. Here we discuss a set of chemicals that interact with fat and weight-regulatory mechanisms resulting in obesogenic phenotypes. We discuss evidence supporting the existence of chemical obesogens and identify potential mechanisms of action (where they are known). Parallels between obesogen action and similar effects observed in genetic models, with dietary components or

Abbreviations: BPA, Bisphenol A; DEHP, (2-ethylhexyl) phthalate; DES, diethylstilbestrol; ER, estrogen receptor; HSD, hydroxysteroid dehydrogenase; MEHP, mono[2-ethyl-hexyl] phthalate; NR, nuclear hormone receptor; PFC, perfluoro alkyl compound; PFOA, perfluorooctanoic acid; PPAR, peroxisome proliferator-activated receptor; RXR, retinoic X receptor; TBT, tributyltin; TPT, triphenyltin; TZD, thiazolidinedione.

pharmaceutical drugs, are highlighted. We discuss areas in which future research will be needed to ascertain the degree to which obesogen exposure contributes to the obesity epidemic.

Pathways Susceptible to Obesogen Action

Obesogen action on metabolic sensors

Because obese individuals exhibit both increased adipocyte number and volume, one obvious place that obesogens could act is on metabolic sensors that control adipocyte function and differentiation. A number of transcriptional regulators control lipid flux, adipocyte differentiation, and proliferation. Nuclear hormone receptors (NRs), particularly the peroxisome proliferator-activated receptors (PPARα, -δ, and -γ) play key roles in these processes. NRs serve as metabolic sensors for a variety of lipophilic hormones, dietary fatty acids, and their metabolites. Activation of the retinoic X receptor (RXR)-PPARα heterodimer stimulates β-oxidation of fatty acids (4). In contrast, activation of RXR-PPARγ favors the differentiation of preadipocytes and adipocyte progenitors in adipose tissue and regulates lipid biosynthesis and storage (5). Human allelic variants of PPARγ that reduce activity, such as Pro12Ala, are associated with lower body mass and improved insulin sensitivity and serum lipid profiles in diabetics (6). Alleles that increase activity, such as Pro115Gln, are associated with obesity and insulin resistance (7). Pharmaceutical modulators of PPARγ activity similarly shift the balance in adipogenic programs. Treatment with PPARγ antagonists, such as SR-202, GW9662, or JTP-426467, prevents high-fat diet-induced weight gain in rodents (8–10). PPARγ agonists such as the antidiabetic thiazolidinediones (TZDs), rosiglitazone and pioglitazone, are potent insulin sensitizers used to improve glycemic control and serum triglycerides (11). However, TZDs lead to peripheral edema and persistent weight gain with prolonged use (12, 13). Therefore, TZDs can be considered to be pharmaceutical obesogens, and it follows that other PPARγ activators could have similar effects.

Obesogenic effects mediated by sex steroid dysregulation

In addition to nutrient-sensing NRs, such as PPARs, NRs for sex steroid hormones also impact adipose tissue development. The hormones help to integrate metabolic functions among major organs that are essential for metabolically intensive activities like reproduction. Knockouts (KOs) of sex steroid pathway components, *e.g.* FSH receptor (FORKO), aromatase (ArKO), estrogen receptor (ER) (αERKO), and androgen receptor (ARKO), show that sex steroids are required to regulate adipocyte hypertrophy and hyperplasia. Sex steroids also influence the sex-specific remodeling of specific adipose depots (14–17). Together with peptide hormones such as GH, sex steroids mobilize lipid stores and help to counteract the actions of insulin and cortisol that promote lipid accumulation in adults. In this way, they are antiobesogenic. Antiandrogenic therapies for prostrate cancer produce weight gain, whereas estrogenic hormone replacement therapy protects against many age- and menopause-related changes in adipose depot remodeling (18). Dietary soy phy-

toestrogens, such as genistein and daidzein, modulate ER signaling and reverse the truncal fat accumulation in postmenopausal women and in ovarectiomized rodent models (19, 20).

In contrast to the antiobesogenic effects of estrogen treatment in adults, fetal or neonatal estrogen exposure can lead to obesity later in life. Mice derived from dams maintained on diets with low phytoestrogen content during pregnancy and lactation experienced elevated serum estradiol levels and fetal estrogenization syndrome. Despite a lower than normal birth weight, both males and females developed obesity at puberty when maintained on soy-free chow (21). Interestingly, another study noted a gender-specific adipogenic effect in immature mice fed a low (or within the normal nutritional range) genistein diet. Adipogenic weight gain was only seen in male mice and this effect reversed at the highest pharmacological dose (22). Furthermore, neonatal exposure to the potent synthetic estrogen, diethylstilbesterol (DES), initially led to depressed body weight that was followed by long-term weight gain by adulthood in female mice (23, 24). Male mice exposed to DES in the same way did not become obese but rather showed a dose-dependent decrease in overall body weight (25). These disparate results underscore the important and potentially contrasting effects that the same chemical may have, depending on gender. Thus, differences in outcome elicited by treatment with various classes of ER agonists probably reflects the ability of the compounds to activate the ERs as well as their potential for targeting additional cellular signaling pathways and organ target sites.

Obesogens and central integration of energy balance

Drugs and chemicals that target NRs with direct relevance to adipocyte biology are obvious candidates for obesogen action. Another class of targets would be components of the central mechanisms that coordinate the whole-body response to daily nutritional fluctuations. The hypothalamic-pituitary-adrenal axis plays an important role in regulating appetite to prevent hyperphagia and normalize energy homeostasis. Appetite and satiety are regulated by a variety of monoaminoergic, peptidergic, and endocannabinoid signals that are generated in the digestive tract, adipose tissue, and brain. Any of these signals could be potential obesogen targets. Indeed, body weight disruption is observed in various neurological disorders (schizophrenia, bipolar disorder, and depression), and as a result of some pharmaceutical treatments (atypical antipsychotics, tricyclic antidepressants, selective serotonin reuptake inhibitor antidepressants) intended to treat them (26–28). For example, patients undergoing olanzapine therapy experience a dose-dependent weight gain of 5–10 kg/yr (27) compared with patients on therapy with typical antipsychotic drugs (29, 30). This topic has been recently reviewed elsewhere (2) and, for brevity, will not be considered further here.

Obesogens and programming of metabolic setpoints

The activity of metabolic sensors, sex steroid regulation, or the perception of hunger and satiety are all important potential obesogen targets. Hyperphagia resulting from disruption of hypothalamic appetite centers provides one plausible way to unbalance the energy equation. Hypothalamic output plays an

important role in implementing adaptive responses that establish metabolic setpoints and regulate overall metabolic efficiency. Much of the control over these adaptive processes resides in the hypothalamus-pituitary-thyroid axis that determines systemic thyroid hormone output. Thyroid hormone exerts widespread effects on metabolism and sets the basal metabolic rate. Local conversion of T_4 (which is inactive on the thyroid hormone receptor) to the receptor agonist T_3 by type 2 deiodinase increases thyroid hormone receptor signaling in a tissue-specific manner. Combined with sympathetic adrenergic activity, elevated thyroid hormone receptor signaling regulates expression of a number of respiratory components, including uncoupling protein-1 in brown adipose tissue and muscle that reduces metabolic efficiency and increases energy expenditure (31). An interesting recent report links the ability of the PPARγ agonist rosiglitazone to 1) reduce sympathetic activity to brown adipose tissue and white adipose tissue; 2) down-regulate hypothalamus-pituitary-thyroid signaling by reducing expression of type 2 and type 1 deiodinases; and 3) decrease expression of the proenergy expenditure peptides CRH and cocaine and amphetamine-regulated transcript in the hypothalamus with positive energy balance (32). Depression of circulating T_4 levels, localized decreases in peripheral T_3 synthesis or reduced input from the sympathetic nervous system would be expected to blunt adaptive responses and promote a propensity for metabolic syndrome and obesity.

Regulation of glucocorticoid hormone levels is another critical component of the hypothalamic-pituitary-adrenal axis that regulates metabolism in peripheral tissues (including fat) and the stress responses. Glucocorticoids play an important role in adipocyte differentiation, and altered glucocorticoid levels can affect long-term metabolic programming and the response to physiological challenges (33, 34). Increased glucocorticoid production or inhibited local inactivation via modulation of 11β-hydroxysteroid dehydrogenase type 1 (reactivating) or type 2 (inactivating) enzymes will inappropriately activate the nuclear glucocorticoid receptor, contributing to the development of obesity (35). For example, transgenic overexpression of 11β-hydroxysteroid dehydrogenase (HSD)1 in adipose tissue increases intracellular corticosterone levels, resulting in visceral obesity, glucose intolerance, and insulin resistance. In contrast, targeted overexpression of the inactivating enzyme, 11β-HSD2, protects against diet-induced obesity (36). A number of dietary agents with the ability to elevate or depress glucocorticoid signaling have now been described (37). Notably, the minor component of licorice, glycyrrhetinic acid, or a synthetic derivative carbenoxolone, inhibits 11β-HSD2 activity, raising active glucocorticoid levels (38). Prenatal exposure to carbenoxolone in rats reduces birth weight, raises basal corticosterone, alters hypothalamic expression of GR, and induces hyperglycemia (39, 40). Thus, environmental chemicals that can inhibit 11β-HSD2 would be expected to have similar effects (41).

Endocrine Disrupters as Obesogens

The discussion above illustrates several examples of pharmaceutical obesogens that target a variety of cellular pathways to promote adipogenesis and obesity. In light of these observations, it is reasonable to expect that dietary or environmental chemicals that target the same pathways would produce comparable effects. We will point out several classes of potential environmental endocrine-disrupting chemicals that also have the potential to act as obesogens. Cellular targets are indicated where they are known.

Bisphenol A (BPA) and xenoestrogens

Several prominent xenoestrogenic pollutants exhibit obesogenic properties. BPA and nonylphenols are essentially ubiquitous in human populations through their wide use in industrial and consumer products (e.g. leachates from polycarbonate plastics for BPA or alkylphenol polyethoxylate detergents as a source of nonylphenol). BPA is routinely detected in human serum within the range of 0.3–4.4 ng/ml (1.3–19 nM) (42, 43), and a positive association has been made between human serum BPA levels and obesity and polycystic ovary syndrome (44). Cell culture studies in the murine 3T3-L1 model demonstrate that such compounds can promote adipogenesis (45–48). Treatment with BPA in the presence of insulin enhances the differentiation of 3T3-L1 preadipocytes by up-regulating genes required for adipocyte differentiation (46, 49). However, it is not clear whether these effects are mediated exclusively by activation of the nuclear ER or through some other mechanism, because different xenoestrogens have varying effects on adipocyte differentiation (49). In addition to its ability to bind to ERs, BPA has been shown to activate the membrane ER at low doses (50) via the insulin-dependent phosphatidylinositol 3-kinase/Akt kinase pathway, enhancing glucose uptake (45, 48). Therefore, it is possible that BPA acts in a nongenomic manner to stimulate adipocyte differentiation, and future studies will be required to sort out the mechanism of action. Consistent with the DES results noted above, prenatal and neonatal exposure of rodents to levels of BPA (equivalent to serum concentrations observed in humans) resulted in increased body weight and hyperlipidemia (51, 52). Trends toward increased food intake and decreased activity levels were also noted in these experiments, although the results did not reach statistical significance. It will be important to determine the relative contributions of altered developmental metabolic programming, effects on physical activity, and excess caloric intake on obesity in this model. Taken together, these data suggest that xenoestrogens can exert proadipogenic effects through a number of plausible mechanisms and that more detailed analysis of how xenoestrogens affect weight is warranted.

Organotins

Organotins are a class of persistent organic pollutants that are widely used in polyvinylchloride plastics, as fungicides and pesticides on crops, as slimicides in industrial water systems, as wood preservatives, and as marine antifouling agents. We and others showed that tributyltin (TBT) and triphenyltin (TPT) are highly selective and potent activators of two different types of NRs: the RXRs (RXRα, -β, and -γ) and PPARγ (53, 54). PPARγ and RXRs function as obligate heterodimers and, as noted above, act as metabolic sensors that regulate adipocyte number, size, and function. The ability to target both halves of the RXR-PPARγ heterodimer, or of RXR homodimers simultaneously

would be predicted to be particularly effective in eliciting obesogenic effects because adipogenic signaling can be mediated by ligand activation of either type of dimer.

TBT can drive the differentiation of murine 3T3-L1 adipocytes in vitro and activates RXR-PPARγ-dependent proadipogenic gene networks in liver, adipose tissue, and bone marrow (53–56). Prenatal exposure to TBT results in precocious lipid accumulation in adipose tissues and hepatic steatosis of newborn mice (53). Long-term effects of prenatal exposure include an increase in epididymal fat mass and a trend toward body weight gain with age (Ref. 53 and our unpublished data). Developmental exposure to TBT leads to ectopic adipocyte formation in the frog *Xenopus laevis* (53), revealing a conservation of mechanism in vertebrates. Intriguingly, TBT perturbs fatty acid homeostasis and enhances lipid accumulation in ramshorn snails, which implicates RXR as a key player in this process, because snails lack a PPARγ ortholog (57). Taken together, these studies reveal both acute and long-term adipogenic effects of organotin exposure, particularly if such exposure occurs within sensitive developmental windows.

In addition to their ability to activate RXR and PPARγ, organotins such as TBT and dibutyltin inhibit 11β-HSD2 activity by targeting cysteine residues necessary for enzymatic activity (58). Maternal dosing of TBT leads to significant transfer and accumulation of organotins in the fetal placenta, liver, and brain (59). This suggests another mechanism through which organotins can affect obesity, i.e. by causing hypercortisolism as a result of inhibiting the protective actions of 11β-HSD2 in fetal tissues.

It is reasonable to question the doses at which these effects occur and to compare them with actual or inferred human exposure. Both the receptor binding affinity (K_d) and potency (EC_{50}) values for TBT and TPT are in the range of 5–20 nM for both RXRs and PPARγ (53). Organotin levels in marine mammals that bioaccumulate persistent organic pollutants routinely reach levels of several micrograms/g wt (~7 μm) (60). There are relatively few data from human tissues and blood currently available. Documented organotin levels in Europe and Asia are in the range of 2 ng/g wet weight (~7 nM) (61); although a more recent study of Finnish fishermen shows TPT as the major organotin in the range of 0.09 and 0.67 ng/ml (~ 0.5–2 nM) (62). There is only a single study documenting total organotins in human blood from the United States; this study showed average TBT levels of approximately 8 ng/ml (~27 nM) (63). These geographical and historical variations likely reflect the sparse nature of the data available, but they also illustrate the general principle that human exposure to obesogenic organotins is in the range required to activate RXR-PPARγ.

Perfluorooctanoic acid (PFOA) and phthalates

Other classes of commonly encountered chemicals can negatively impact lipid and adipose homeostasis. These include phthalate plasticizers (some of which are also xenoestrogens) used to soften PVC plastics and various perfluoro alkyl compounds (PFCs) that are widely used surfactants and surface repellents in consumer products. Work in several laboratories has established that phthalates and PFCs are agonists for one or more of the PPARs (with many exhibiting a preference for

PPARα activation). This activation provides a mechanistic basis for disturbed lipid and steroid metabolism (64–69). For example, exposure to (2-ethylhexyl) phthalate (DEHP) or PFOA increases PPARα-dependent lipid mobilization and fatty acid oxidation and leads to adipose tissue atrophy (70, 71). Consequently, exposure to DEHP or PFCs might be expected to result in reduced body weight and decreased adipose mass. As expected, prenatal exposure to low to moderate levels (>5 mg/kg body weight) of PFOA in rodents led to decreased adipose mass and body weight (72). Paradoxically, chronic low-level exposure to PFOA (>5 mg/kg body weight) depressed birth weight, as previously reported, but increased adipose tissue mass and body weight gain after puberty (73). This suggests that PFOA is acting through a non-PPARα-mediated pathway to induce obesity. One candidate is PPARγ, but this is somewhat controversial because PFOA has been reported to activate PPARγ by some investigators (69, 74) but not others (75).

Human exposure to phthalates and PFCs is primarily the result of these chemicals leaching from plastics containing nonbonded phthalates and PFCs from treated surfaces. Transfer of primary phthalates, such as DEHP, to food during processing results in an estimated average daily intake of about 160 μg/d (76). Urinary phthalate metabolites and serum levels of major PFC species are in excess of several micrograms/liter in more than 75% of the US population (77), well within the range of concern for endocrine disruption. A recent epidemiological study revealed a positive association between the presence of urinary DEHP metabolites and increased waist circumference and insulin resistance in men (78). Among the metabolites noted, mono[2-ethyl-hexyl] phthalate (MEHP) is a known potent and selective activator of PPARγ (66) that promotes differentiation of 3T3-L1 cells into adipocytes (79). This suggests that, although many phthalates are more active on PPARα than they are on PPARγ, phthalate metabolites may be more selective for PPARγ. Moreover, if the parent phthalates exert their effects on PPARα in the liver whereas their metabolites act on PPARγ in fat, this could also explain the net weight gain observed in exposed individuals.

Obesogens and Animal Models

There is growing interest in the effects of chemicals on obesity. Considering the potential complexity of obesogen action, it is worthwhile considering what types of experiments in animal models could be most useful. We need to know whether obesogens are truly causative and to establish the range of possible effects to discriminate among possible physiological mechanisms and understand the relative contribution of obesogens to the obesity epidemic. An important experimental parameter is to define appropriate regimens for dosing and timing of exposures. It is well established that effects of exposure to endocrine-disrupting chemicals may not always reflect expected monotonic dose-response relationships. Many, if not most, of the known and suspected obesogens have multiple modes of action or may elicit compensatory mechanisms. Obesogens affecting adipogenesis, *per se* (i.e. recruitment, differentiation, and hyperplasia) likely exert their maximal effects when adipose tissues

differentiate during discrete windows of sensitivity (*e.g.* fetal development, perinatal nursing, or adolescence). Those that promote hypertrophy, via misregulation of metabolic fluxes, may be active throughout life if exposures are chronic.

It is becoming increasingly apparent that the relative distribution of fat mass among the various adipose depots has disproportionate consequences for metabolic physiology. For example, abdominal adiposity is highly correlated with metabolic syndrome disorders whereas sc fat in other areas is not (80). Thus, reliance on weight gain, by itself, may not adequately reflect the effects of obesogen exposure. High-resolution live imaging technologies for fat-water analysis, *e.g.* dual energy x-ray absorptiometry (DXA) or improved Dixon MRI protocols (81), should allow a more comprehensive evaluation of changes in adipose depots and any potential association with disease risk factors. It would also be valuable to complement such data with information on dynamic responses at the tissue level, such as changes in adipose tissue cellularity, adipocyte size distribution, and altered adipokine profiles.

Another important area where information is lacking concerns whether and how obesogen exposure alters energy intake and expenditure. Effects of exposure on appetite, physical activity, resting metabolic rate, adaptive thermogenesis, and growth rates should all be quantified to identify any alterations in the balance among these physiological pathways. Sensitive infrared thermographic techniques can now be applied to adipocyte cell cultures and to whole adipose depots, in live animal studies to measure changes in thermogenesis. Such data would be particularly valuable for extrapolating cellular outcomes of obesogen exposure to site-specific effects on metabolic efficiency *in vivo* (82–84).

Lastly, obesogen-induced increases in adipose mass should be placed in context relative to indices of metabolic syndrome. The physiological process of diverting excess calories toward lipid storage may be benign or pathological depending on the mechanism and site. For instance, the thiazolidinediones promote adipose weight gain, but help normalize deleterious blood glucose levels in diabetics. Alternatively, if adipose hypertrophy or hyperplasia is driven by chronic dysfunction (*e.g.* through inflammatory dysregulation of adipokine secretion or sensitivity) the obesity itself may actively advance associated disease states. Therefore, understanding how an obesogen challenge tilts the balance from benign to pathological patterns of weight gain will be an area of great interest, particularly in relation to early prognostic indicators of obesity-related disorders, such as insulin resistance and inflammatory cytokine and adipokine production.

Future Directions

It is perhaps paradoxical in the current economic climate that obesity is one of the greatest threats to worldwide public health. It is likely that the progressive increase in worldwide obesity rates across demographically diverse economies reflects a shift in how our bodies respond to dietary and environmental variations. Conventional medical wisdom holds that obesity can be prevented or treated by simply reducing caloric input and increasing physical activity. However, it is also quite clear that, despite unprecedented public awareness of the obesity epidemic, relatively little progress has been made in combating obesity in the Western world. The modern Western lifestyle with an abundance of energy-rich foods and decreased physical activity may be exposing underlying genetic and environmental factors that alter our ability to correctly regulate weight. The environmental obesogen hypothesis proposes that perturbations in metabolic signaling, resulting from exposure to dietary and environmental chemicals, may further exacerbate the effects of imbalances in diet and exercise, resulting in an increased susceptibility to obesity and obesity-related disorders.

The obesogens, for which the best data exist, share some common features. Many are mimics of NR ligands (TBT, MEHP, BPA, and PFOA) that can directly regulate genetic networks relevant to adipogenesis and obesity. Further complicating the picture, some of the compounds can have multiple modes of action (*e.g.* TBT regulation of RXR-PPARγ activity, expression of aromatase mRNA, aromatase enzymatic activity and glucocorticoid homeostasis; activation of PPARα by phthalates but the activation of PPARγ by phthalate metabolites). Prenatal and early postnatal exposures have been shown to result in lasting changes, suggesting additional epigenetic mechanisms of action. Epigenetic changes resulting from obesogenic exposures are currently poorly understood. This area will be important for future research, insofar as these changes may influence the stem cell compartment to modulate the size of the preadipocyte pool and/or the number of multipotent stem cells that enter the adipocyte lineage.

Whereas the action of obesogens in animal models is largely well established, the connection to human epidemiology is less so, and many questions remain to be answered. We currently know relatively little about overall burdens of the known (TBT, MEHP, BPA) and suspected (PFOA) obesogens in the population at large. We need to know when the exposures occur, compared with the windows of sensitivity for obesogen effects. Very little is known about the adult outcomes of prenatal, early postnatal, or later exposures. Do the effects differ depending on when the individuals are exposed, as is the case with estrogens? Are the effects of obesogens limited to altering developmental programming or are obesogens effective at increasing fat cell size and number at any time in life? Clinical experience with TZDs and atypical antipsychotics suggest that adult exposure is also effective at inducing weight gain. What factors might modify the effects of obesogen exposure? Are the effects of obesogen exposure on metabolic programming permanent or can they be overcome and, if so, how? Although exposure to obesogenic chemicals is presumed to be widespread, there are obviously differences in individual responses. Current studies such as the National Health and Nutrition Examination Survey are limited to measuring obesogens and their metabolites in blood and urine. Biomarkers of prior exposure, particularly during sensitive developmental windows, will be important to identify exposures that may have been transient, yet might have caused enduring effects.

In conclusion, although there is abundant evidence that diet and exercise are key factors in the obesity epidemic, it is equally clear that a variety of environmental factors play an

important role in this process. These include such factors as composition of the diet, gut flora, insufficient sleep, stress, social environment, the built environment, maternal influences, viruses, and polymorphisms in key genes. Environmental obesogens that target key hormonal signaling pathways involved in adipogenesis, fat cell function, metabolic setpoints, energy balance, and the regulation of appetite and satiety are also likely to play important roles in obesity and are therefore worthy of further study.

Acknowledgments

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