Obesogens, stem cells and the developmental programming of obesity

A. Janesick* and B. Blumberg*,†

Departments of *Developmental and Cell Biology and †Pharmaceutical Sciences, University of California, Irvine, CA, USA

Introduction

We are in the midst of a worldwide obesity epidemic that is particularly apparent in the United States. Currently, 34% of American adults are obese (body mass index > 30) and an additional 68% are overweight (BMI > 25), double the worldwide average and 10 times the rates in Korea and Japan (Flegal et al., 2010). The fraction of overweight US adults is predicted to increase to 86% by 2020 (Flegal et al., 2010). BMI is a simple measurement that does not distinguish among increased subcutaneous adiposity, which is generally considered to be the preferred storage depot for excess calories (Ibrahim, 2010), increased visceral adiposity, which is a pathological condition that increases the risk of cardiovascular disease, metabolic syndrome and diabetes (Freedland, 2004) and increased muscularity, which is not a risk factor for metabolic diseases. However, the trend towards higher BMI in the population is largely accompanied by increased visceral adiposity and associated metabolic syndrome disorders (Lustig, 2006).

The most typical explanation given for the increased rate of obesity is that consumption of calorie dense food has increased and that physical activity has decreased, the thermodynamic or ‘calories in-calories out’ model. Obviously, to gain weight, calories consumed must exceed calories burned; however, the situation is not as simple as balancing one’s caloric checkbook. The biochemical nature of the calories consumed plays a very large role in how and where they are stored, as well as in the regulation of appetite and satiety (Lustig, 2006, 2010). In addition, there are considerable differences in how individuals accrue weight given the same amount of excess calories. Once an individual becomes obese, it is difficult to lose weight and sustain weight loss due to highly efficient homeostatic mechanisms regulating energy balance (Butte et al., 2007; Muhlhauser & Smith, 2009).

Keywords:
development, endocrine disrupters, environmental factors, epigenetics, fish < animal models, hormone receptors, mouse < animal models, obesity, phthalates, sex hormones

Correspondence:
Bruce Blumberg, Department of Developmental and Cell Biology, 2011 BioSci 3, University of California, Irvine, CA 92697-2300, USA. E-mail: blumberg@uci.edu

Received 1 September 2011; revised 28 December 2011; accepted 4 January 2012
doi:10.1111/j.1365-2605.2012.01247.x

Summary

Obesogens are chemicals that directly or indirectly lead to increased fat accumulation and obesity. Obesogens have the potential to disrupt multiple metabolic signalling pathways in the developing organism that can result in permanent changes in adult physiology. Prenatal or perinatal exposure to obesogenic endocrine disrupting chemicals has been shown to predispose an organism to store more fat from the beginning of its life. For example, excess oestrogen or cortisol exposure in the womb or during early life resulted in an increased susceptibility to obesity and metabolic syndrome later in life. This review focuses on the effects of environmental chemicals, such as the model obesogen, tributyltin (TBT), on the development of obesity. We discuss evidence linking the obesogenic effects of TBT with its ability to activate the peroxisome proliferator-activated receptor gamma and stimulate adipogenesis. We also discuss how TBT and other environmental obesogens may lead to epigenetic changes that predispose exposed individuals to subsequent weight gain and obesity. This suggests that humans, who have been exposed to obesogenic chemicals during sensitive windows of development, might be pre-programmed to store increased amounts of fat, resulting in a lifelong struggle to maintain a healthy weight and exacerbating the deleterious effects of poor diet and inadequate exercise.
The observation that people do not accrue weight equally given the same amount of caloric excess highlights the obvious point that individuals are different. Why is it that some apparently have the ability to eat prodigious quantities of food without becoming obese whereas others do not? Do individual differences result in altered metabolic responses to diet; i.e., do variations in personal metabolic set points contribute to obesity? Two lines of evidence suggest that the prenatal environment has a role in establishing such set point differences. First, babies born to mothers who smoked while pregnant exhibited low birth weight and had an increased risk of babies born to mothers who smoked while pregnant has a role in establishing such set point differences. First, babies born to mothers who smoked while pregnant exhibited low birth weight and had an increased risk of obesity and metabolic syndrome later in life (Power & Jeffers, 2002; Oken et al., 2005; Al Mamun et al., 2006). Second, babies who received inadequate nutrition in utero grew up to become adults with higher rates of cardiovascular disease (Barker & Osmond, 1986, 1988; Barker et al., 1989). The Developmental Origins of Health and Disease (DOHaD) model proposes that the prenatal and early life environment plays a key role in establishing life-long patterns of health and disease (Gluckman & Hanson, 2004). The DOHaD model holds that the development of chronic diseases (or the lack of chronic disease) is influenced by environmental factors (amount and quality of diet, chemical exposure, maternal stress, etc.) acting in early life that interact with genetic differences and factors associated with adult lifestyle. Simplistically, the prenatal environment elicits corresponding changes in the foetus that adjust metabolism to match the projected caloric environment. However, metabolic changes that favour the most effective use of scarce calories will not be adaptive when calories are in excess as in modern societies (Gluckman et al., 2008). There is some evidence to suggest that ‘catch-up growth’ in early life is a key factor predisposing individuals towards obesity, insulin resistance and cardiovascular disease (Ong et al., 2000; Ong & Dungan, 2002). Thus, while individuals appear outwardly normal, early life events occurring during critical developmental time windows (e.g., perinatally) may lead to permanent changes that are manifested at adulthood (Hanson & Gluckman, 2008). Although the bulk of evidence related to DOHaD comes from nutritional studies, there is no reason to suppose that other factors, such as prenatal stress (Entringer et al., 2008, 2009) and exposure to endocrine disrupting chemicals (EDCs) (Janesick & Blumberg, 2011a), will not elicit similar changes in metabolic programming. Adipogenesis, weight control and metabolism are under hormonal control and are thus susceptible to interference by EDCs. EDC exposure has been linked with diabetes and metabolic syndrome, which may be related to, or independent from their effects on obesity (Lee et al., 2010; Sergeev & Carpenter, 2010, 2011).

Obesogens

‘Obesogens’ are chemical compounds that can promote obesity by increasing the number of fat cells (and fat storage into existing fat cells), by changing the amount of calories burned at rest, by altering energy balance to favour storage of calories and by altering the mechanisms through which the body regulates appetite and satiety. Our environmental obesogen hypothesis proposes that a subset of EDCs could promote the development of obesity. Although initially controversial, the obesogen hypothesis has gained momentum in recent years with the identification of obesogenic chemicals that promote adipogenesis and obesity in animals and humans (Newbold et al., 2009; Janesick & Blumberg, 2011a,b,c; La Merrill & Birnbaum, 2011; Tang-Peronard et al., 2011). Perhaps most significantly, several classes of pharmaceutical drugs have been linked with weight gain and obesity in humans. Among these are thiazolidinedione anti-diabetic drugs (Larsen et al., 2003; Rubenstrunk et al., 2007), tricyclic antidepressants (Berken et al., 1984), selective serotonin reuptake inhibitors (Fava, 2000) and atypical anti-psychotic drugs, such as olanzapine (Nemeroff, 1997). Considering that exposure to these drugs has been linked with obesity in humans, it is reasonable to suppose that exposure to EDCs targeting the same pathways will produce similar outcomes. For example, thiazolidinediones activate the peroxisome proliferator-activated receptor gamma (PPARγ), a ligand-dependent transcription factor that is a key regulator of adipogenesis (Evans et al., 2004; Tontonoz & Spiegelman, 2008). Chemicals that activate PPARγ should have the same effect.

Indeed, we and others identified the organotin tributyltin (TBT) as a xenobiotic obesogen (Kanayama et al., 2005; Grun et al., 2006). TBT and the related chemical, triphenyltin (TPT), are nanomolar affinity ligands for PPARγ and its heterodimeric partner, the retinoid X receptor (RXR) that were shown to induce adipogenesis in preadipocyte cell lines, such as 3T3-L1 cells (Kanayama et al., 2005; Grun et al., 2006). Currently, organotins are prevalent used in industry, as fungicides, wood preservatives and heat stabilizers in polyolefin plastics (Piver, 1973; Nath, 2008). Organotins, including TBT have been documented in house dust, suggesting that exposure from sources other than food may be widespread (Kannan et al., 2010). Although TBT has largely been phased out of agricultural use, TPT remains in use as a fungicide and miticide. Organotins are lipophilic and have been shown to bioaccumulate in bacteria, algae and aquatic invertebrates (Hoch, 2001). Although TBT is most famous for its sex altering effects on gastropod mollusks (Blaber, 1970; Gibbs & Bryan, 1986) and fish (Shimasaki et al., 2003), we unexpectedly found that Xenopus laevis
tadpoles exposed to low levels of TBT exhibited ectopic fat cell production (Grun et al., 2006). In mice, prenatal exposure to TBT during gestation resulted in premature accumulation of fat in adipose tissues at birth and increased fat depot size at 10 weeks of age, although, the exposed mice were slightly smaller (Grun et al., 2006). The main conclusion from these studies was that the tendency to store excess fat was programmed before birth due to TBT exposure. Subsequent experiments aimed at understanding the mechanisms underlying the effects of prenatal TBT exposure revealed that a single prenatal treatment with TBT or with the pharmaceutical obesogen, rosiglitazone (ROSI), altered the fate of multipotent mesenchymal stromal stem cells (MSCs). MSCs normally give rise to several tissue types in vivo, including bone, adipose and cartilage (Pittenger et al., 1999). In offspring of pregnant dams treated with a single dose of TBT or ROSI, MSCs derived from white adipose tissue were predisposed to become adipocytes. MSCs derived from obesogen treated animals were about as likely to differentiate into adipocytes in culture as control cells and this frequency was further increased by subsequent in vitro treatment with TBT or ROSI (Kirchner et al., 2010). The ability of these cells to differentiate into bone was correspondingly inhibited (Kirchner et al., 2010). The ability of TBT or ROSI to induce adipogenesis in MSCs (Kirchner et al., 2010) or in 3T3-L1 preadipocytes (Li et al., 2011) was completely dependent on activation of PPARγ, suggesting that the in vivo effects of these compounds similarly depend on PPARγ. However, this remains to be demonstrated.

The topic of obesogens and obesogen action has been extensively reviewed in recent years (Grun & Blumberg, 2009a,b; Grun, 2010; Newbold, 2010, 2011; Blumberg, 2011; Heindel, 2011; Janesick & Blumberg, 2011a,b,c; Tang-Peronard et al., 2011) as have the effects of EDCs on metabolism (Diamanti-Kandarakis et al., 2009; Casals-Casas & Desvergne, 2011). In this review, we highlight likely mechanisms for obesogen action and summarize recent studies linking EDC exposure with obesity in humans.

**Obesogens acting on sex steroid receptors**

Estrogens in the adult are protective against abdominal obesity and metabolic disease whereas perinatal oestrogen exposure has the opposite effect (see below). Ovariectomized rats (a model for menopause in women) developed abdominal obesity, which was reversed upon treatment with oestrogen (Laudenslager et al., 1980; Wade et al., 1985). Consistent with this observation, loss-of-function in the oestrogen receptor alpha (ERα) resulted in increased white adipose depot size, central weight gain and impaired glucose metabolism (Heine et al., 2000; Cooke et al., 2001). Knockout of P450 aromatase in mice inhibited the conversion of testosterone to estradiol, producing obese animals (Jones et al., 2000); loss of the human CYP19A1 (aromatase) gene produced metabolic disease, fatty liver and abdominal obesity (Maffei et al., 2007).

In contrast to its effects in adults, perinatal exposure to excess oestrogen promoted weight gain. Mice treated neonatally with the potent synthetic oestrogen diethylstilbestrol (DES) gave birth to pups that were initially smaller, but became heavier later in life (Newbold et al., 2005, 2008, 2009; Newbold, 2010, 2011). Similarly, treatment of pregnant mouse (Cagampang et al., 2007) or rat (Rubin et al., 2001) dams with the environmental oestrogen bisphenol-A (BPA) resulted in smaller offspring that exhibited ‘catch-up’ growth and were significantly heavier as adults. Dichlorodiphenyl-dichloroethylene (DDE), the major metabolite of the pesticide DDT, is both an oestrogen receptor activator and an anti-androgen (Kupfer & Bulger, 1976; Kelce et al., 1995). Mothers who lived along the Lake Michigan shoreline where they were exposed to high levels of DDT, were more likely to have a child that exhibited elevated BMI in adulthood (Karmaus et al., 2009). More recently, Mendez and colleagues showed that prenatal exposure to DDE was associated with rapid weight gain in human infants and elevated BMI later in infancy (Mendez et al., 2011). Despite a large number of available studies, the effects of BPA on health remain controversial. Recent human studies have revealed a link between BPA levels and obesity in humans (Carwile & Michaels, 2011) and animal studies showed low dose effects of BPA on obesity and diabetes (Rubin, 2011). A recent study tested the effects of prenatal BPA exposure and concluded that while the animals were larger and males had significantly more fat stored at 7 weeks, the animals were neither obese nor did they have increased susceptibility to the effects of high fat diet at adulthood (Ryan et al., 2010). The prevailing view at the moment is that low dose gestational BPA exposure is likely to be causally linked with the development of obesity. Although it appears likely that BPA exerts its obesogenic effects by acting as a developmental oestrogen, the mechanism(s) through which BPA acts to exert its deleterious effects on health need to be more fully elucidated. Ongoing studies in a number of laboratories should shed further light onto this important issue in the near future.

**Obesogens and glucocorticoid metabolism**

In addition to the sex steroid receptors, disruption of another nuclear hormone receptor regulated signalling pathway, the glucocorticoid receptor, is known to
contribute to obesity. Obesity is linked to a general increase of positive feedback within the hypothalamic-pituitary-adrenocortical (HPA) axis, leading to an over-secretion of cortisol from the adrenal gland (Marin et al., 1992; Björntorp, 1993; Chalew et al., 1995; Björntorp, 1997; Björntorp & Rosmond, 2000). However, rather than causing higher circulating glucocorticoid levels, obesity-related hypercortisolism is generally peripheral, local and characterized by an impaired ability to clear cortisol in adipose tissue, especially visceral adipose tissue (Rask et al., 2001). Glucocorticoids increased both the differentiation of adipocytes from MSCs and the proliferation of adipocytes. Therefore, excess glucocorticoid levels in adipose depots are likely to stimulate local adipogenesis (Hauner et al., 1989; Björntorp, 1991; Bujalska et al., 1999).

One possible mechanism underlying peripheral hypercortisolism is dysregulation of 11β-hydroxysteroid dehydrogenase type-1 (11βHSD1), a ubiquitously expressed enzyme that primarily functions to convert inactive glucocorticoids, such as cortisone (humans) and 11-dehydrocorticoestosterone (rodents) into their active relatives cortisol and corticosterone (Seckl et al., 2004). Elevated 11βHSD1 has been linked with obesity and metabolic syndrome in humans (Rask et al., 2001; Wake et al., 2003; Valsamakis et al., 2004) and in obese Zucker rats, (Livingstone et al., 2000). Excess glucocorticoid exposure during pregnancy was often associated with lower birth weights, but increased risk of cardiovascular disease, diabetes and hypertension in the adult offspring (Seckl, 2001). Maternal stress has been linked with increased levels of corticotropin-releasing hormone, increased cortisol secretion and reduced birth weight in the offspring (Weinstock, 2005; Entringer et al., 2009, 2010). Monkeys treated with the synthetic glucocorticoid dexamethasone during pregnancy produced offspring that were normal at birth, but exhibited significant weight gain at 2 months of age, subsequently became obese and developed metabolic syndrome (increased blood pressure, high total cholesterol, decreased HDL and insulin resistance) (Schlumb-ohm et al., 2007).

Activity of the hypothalamic–pituitary–adrenocortical (HPA) axis that regulates glucocorticoid homeostasis is tightly regulated; therefore, it is possible that any EDC that perturbs the set point of this axis in early life could contribute to subsequent obesity. Such a mechanism could account, at least in part, for why many people cannot lose weight effectively. There are many possible mechanisms through which EDCs could modulate glucocorticoid homeostasis to disrupt energy balance, appetite and the stress response (Odermatt & Gumy, 2008). As 11βHSD1 catalyzes the conversion of inactive to active glucocorticoids, increasing the activity of 11βHSD1 could readily disrupt the HPA axis. This is generally prevented in the foetus because placental 11βHSD2, which catalyzes the conversion of active to inactive glucocorticoids, is highly expressed throughout pregnancy to reduce foetal cortisol exposure (Edwards et al., 1993). Prenatal inhibition of 11βHSD2 by carbenoxolone administration resulted in reduced birth weight, increased anxious behaviour and increased secretion of corticotropin-releasing hormone in rats (Welberg et al., 2000). Therefore, increased glucocorticoid transport to the foetus by hyperactivating 11βHSD1, or inhibiting 11βHSD2 in the placenta are potential mechanisms through which EDCs might disrupt the HPA axis. Dithiocarbamates decreased 11βHSD2 activity in vitro (Atanasov et al., 2003) as did organotins (Atanasov et al., 2005). Moreover, dibutyltin inhibited the binding of ligands to the glucocorticoid receptor and the ability of this receptor to inhibit cytokine activity and inflammation (Gumy et al., 2008). Another potential mechanism for altered glucocorticoid homeostasis could be alterations in the levels of corticosteroid-binding globulin (CBG) (Fernandez-Real et al., 2002). Adipose tissue that is deficient in CBG cannot evacuate excess cortisol to the blood; moreover, CBG deficiency in humans leads to increased proliferation and differentiation of preadipocytes into adipocytes (Joyner et al., 2003). Therefore, exposure to EDCs that decrease CBG activity might also lead to obesity in the adult. Disruption of glucocorticoid action, stress and obesity are fertile areas for future studies because very little research has addressed EDCs and the HPA axis.

Peroxisome proliferator-activated receptors as obesogen targets

The peroxisome proliferator activated receptors (PPARs) are a family of nuclear hormone receptors that respond to fatty acids and related ligands (Casals-Casas et al., 2008; Casals-Casas & Desvergne, 2011). There are three PPARs, PPARα, PPARβ/δ and PPARγ that all form obligate heterodimers with RXR to regulate the expression of target genes at the transcriptional level (Tontonoz & Spiegelman, 2008). PPARγ is considered to be the master regulator of adipogenesis (Evans et al., 2004) and plays key roles in nearly all aspects of adipocyte biology (Tontonoz & Spiegelman, 2008). Thiazolidinediones, which combat type 2 diabetes, are potent activators of PPARγ (Lehmann et al., 1995) and stimulation of PPARγ-regulated transcription is obesogenic, per se (Janesick & Blumberg, 2011b). Therefore, PPARγ has become a focus of many recent obesity-related studies. The ligand-binding pocket of PPARγ is large (Nolte et al., 1998) and can accommodate various chemical structures (Maloney & Waxman, 1999). The mechanistic basis for TBT-promoted
adipogenesis was most strongly supported by evidence that TBT is an agonist for both PPARγ and RXR (Kanayama et al., 2005; Grun et al., 2006). Competitive binding assays showed that TBT has comparable affinity to synthetic RXR agonists for RXR (Grun et al., 2006). The crystal structure of TBT along with the RXRα ligand binding domain, plus a coactivator fragment, showed that TBT binds covalently to RXR (le Maire et al., 2009), which means that it will not readily dissociate once attached. It has been proposed that TBT acts through RXR to promote adipogenesis and obesity (le Maire et al., 2009). However, treatment with the potent PPARγ antagonist T0070907 (Lee et al., 2002), inhibited TBT- or ROSI-stimulated adipogenesis in mouse and human MSCs (Kirchner et al., 2010), whereas treatment with the related PPARγ antagonist GW9662 blocked adipogenesis in 3T3-L1 preadipocytes (Li et al., 2011). The conclusion from these studies was that the stimulation of adipogenesis in MSCs and cell lines by ROSI or TBT required activation of PPARγ.

Because PPARγ is the master regulator of adipogenesis, it is clear that activation of PPARγ by EDCs is a potential risk factor for obesity. However, TBT is not the most common EDC to which humans are exposed. Phthalates are ubiquitous organic chemicals that give plastics, such as polyvinyl chloride (PVC), more flexibility and durability and readily leach into food, from medical devices and materials used in construction and manufacturing. Some phthalates were shown to be PPARγ agonists (Hurst & Waxman, 2003) and stimulated the proliferation of adipocytes in the 3T3-L1 cell culture model (Feige et al., 2007). Phthalate metabolites were associated with increased waist circumference in men (Stahlhut et al., 2007), and therefore, are predicted to be obesogenic. It is quite likely that other xenobiotic chemicals activate PPARγ and may contribute to the aetiology of obesity (Janesick & Blumberg, 2011b). Screening efforts such as the EPA’s Toxcast (Dix et al., 2007; Knudsen et al., 2011) and the joint NEHS/EPA/FDA Tox21 (Shukla et al., 2010) are likely sources for the identification of new obesogens that act on PPARγ and other biological targets.

Intriguingly, it has recently been shown that in addition to its known effects in adipocytes and MSCs, PPARγ plays an important role in the brain by controlling appetite and metabolism in response to a high fat diet (Lu et al., 2011; Myers & Burant, 2011; Ryan et al., 2011). Specifically activating PPARγ in the brain lead to increased feeding and accrued body weight whereas blockade of PPARγ or PPARγ loss-of-function lead to decreased consumption of high fat, but not normal diet. The conclusion from these studies was that tissue-specific regulation of PPARγ action may play an important role in the outcome of exposure to chemicals that regulate PPARγ and in the body’s response to dietary excesses. The identification of other PPARγ disruptors, as well as the molecular pathways targeted by EDC-PPARγ action that reprogram stem cell fate to favour obesity will be important areas for future research.

**Epigenetics connects environmental exposures with gene expression**

Obesogens are predicted to act prenatally by eliciting epigenetic modifications that alter the expression of key genes in adipogenic pathways. Epigenetic modifications in genes responsible for regulating metabolism, body weight and fat deposition could result in developmental plasticity that allow an organism to make rapid adaptations to changing environments, typically by altering levels of gene expression via DNA methylation or modification of histone proteins (Gluckman & Hanson, 2004; Godfrey et al., 2007, 2011; Gluckman et al., 2008; Hanson & Gluckman, 2008; Hanson et al., 2011). Epigenetic changes that occur during germ cell development can potentially lead to transgenerational effects that may persist for many generations after the initial exposure (Skinner, 2010; Skinner et al., 2011).

Numerous studies have shown that changes in the nutritional environment lead to alterations in the methyl status of genes (Burdge & Lillycrop, 2010a,b; Jackson et al., 2010; Lillycrop & Burdge, 2011; Godfrey et al., 2011; Hochberg et al., 2011; Lillycrop, 2011). Foetal liver derived from rats fed a low-protein diet showed promoter hypermethylation in the liver X-receptor (LXR) (van Straten et al., 2010) and hypomethylation of PPARα (Lillycrop et al., 2008). The methylation-deficient status of PPARα was rescued by supplementing the low-protein diet with the methyl donor, folic acid (Lillycrop et al., 2008). Increased methylation of the RXRα promoter in humans was associated with increased fat mass at 9 years of age (Godfrey et al., 2011). Considered together, it is reasonable to infer that such epigenetic changes could lead to disturbances in metabolism and lipid homeostasis that might be causally linked to obesity. Further studies will be illuminating in this regard.

If changes in prenatal nutrition can lead to epigenetic changes, does exposure to EDCs elicit the same effects? Consistent with this possibility, chemical-induced alterations in DNA methylation status were observed for diethylstilbestrol (DES) (Li et al., 1997), TCDD (Wu et al., 2004), vinclozolin (Anway et al., 2005), BPA (Bernal & Jirtle, 2010) and TBT (Kirchner et al., 2010). DNA methyltransferase activity was altered in rat embryos, depending on whether the embryo was exposed to TCDD, DES or polychlorinated biphenyl-153 (PCB153) (Wu et al., 2006). Thus, although the evidence is still emerging, EDCs can affect the expression levels of
DNA and histone methyltransferases that might lead to subsequent broad impacts on gene expression, including genes that are important for metabolism and obesity.

Although the potential for EDCs to alter epigenetic programming to favour altered gene expression definitely exists (Jackson et al., 2010; Lillycrop & Burdge, 2011; Hochberg et al., 2011; Lillycrop, 2011) evidence supporting specific mechanisms of action is scant. One mechanism that has been described concerns epigenetic modifications that alter stem cell fate (Kirchner et al., 2010; Janesick & Blumberg, 2011a). Adipogenesis is a differentiation event in the mesodermal lineage in which MSCs or more lineage-restricted derivatives give rise to adipocytes. MSCs harvested from epididymal or ovarian fat pads of mice exposed to TBT in utero differentiated into significantly more fat cells, compared with controls, whereas fewer MSCs could differentiate into osteocytes (Kirchner et al., 2010). TBT likely induced epigenetic changes within the MSC compartment that promoted demethylation of adipogenic genes, thereby biasing the MSC compartment to favour the adipocyte lineage (Kirchner et al., 2010). Uninduced MSCs harvested from mice exposed to TBT in utero showed decreased methylation in the gene encoding fatty acid binding protein 4 (FABP4), a marker of adipocytes; suggesting that the MSC population had already been epigenetically modified to favour adipogenesis (Kirchner et al., 2010). Future studies will be needed to identify which regulatory genes have had their expression altered by prenatal exposure to TBT and other obesogens, whether these are the result of epigenetic changes and if the changes elicited persist in future generations.

Conclusions and future prospects

Unhealthy food consumed in excessive amounts and insufficient physical activity are undoubtedly associated with obesity. Whether these are the major and proximate causes of obesity, as is commonly believed, or whether there are other significant causes for obesity remain to be demonstrated. Moreover, it currently remains unknown to what extent obesogen exposure interacts with dietary excesses and lifestyle factors to affect obesity. It is indisputable that following commonly espoused nutritional guidelines (decreased fat consumption, increased carbohydrate consumption) has not resulted in a leaner population. Rather, the opposite is true; we now have an epidemic of obesity in infants (Kim et al., 2006), as well as in children and adults. This suggests that obesity is being programmed prenatally or in early childhood. There is increasing evidence that supports the proposal that environmental endocrine disrupting chemicals (Janesick & Blumberg, 2011a), together with calorie-dense modern diets (Lustig, 2006) may contribute to the early life programming of obesity. Prenatal exposure to obesogens is likely to be an underestimated contributor to the obesity epidemic; moreover, a variety of persistent organic pollutants have been linked with obesity in human studies (Carwile & Michels, 2011; Lee et al., 2011a,b, 2012; Mendez et al., 2011; Tang-Peronard et al., 2011). It will be important in the future to determine which of these chemicals are causally linked with adipogenesis and obesity using studies in appropriate animal models. Prenatal exposure to TBT, a chemical for which the mechanism of action is known, predisposed exposed individuals to produce more fat cells (Kirchner et al., 2010) and accrue increased adipose depot mass (Grun et al., 2006). This suggests that the DOHaD model is applicable to the effects of chemical exposure.

There are numerous EDCs (e.g., BPA, brominated flame retardants and phthalates), more prevalent in the environment than TBT that have been linked to metabolic disease (Casals-Casas et al., 2008; Desvergne et al., 2009; Rubin & Soto, 2009; Vandenberg et al., 2009; Eskenazi et al., 2011; Harley et al., 2011; Rubin, 2011). The metabolic pathways targeted by most of these chemicals remain to be determined; although, some likely pathways are currently under study. The establishment of firm links between EDC exposure and obesity will require elucidation of the underlying mechanisms. Understanding how chemicals enter the body and are transferred to the developing foetus is still not well understood and requires further study. Determining the epigenetic basis of how early life exposure to EDCs modulates the developmental programming of future health and disease will provide answers to the mechanistic questions regarding how obesogens disrupt the endocrine system. There is much yet to learn about how EDC exposures reprogram stem cell fate to favour obesity and diabetes and to what extent these effects can be reduced or eliminated by dietary, behavioural or pharmaceutical interventions.

Acknowledgements

Work in the authors’ laboratory was supported by a grant from the NIH R01 ES015849. A.J. is a pre-doctoral trainee of NSF IGERT DGE 0549479.

References


Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C et al. (2011) Epigenetic gene promoter methylation at...
Obesogens reprogram stem cell fate

A. Janesick and B. Blumberg

birth is associated with child’s later adiposity. Diabetes 60, 1528–1534.


obesity in the elderly: the prospective investigation of the vascular- 
Lehmann JM, Moore LB, Smith-Oliver TA, Wilkinson WO, Willson TM  
& Kliewer SA. (1995) An anti diabetic thiazolidinedione is a high  
affinity ligand for peroxisome proliferator-activated receptor gamma  
Li S, Washburn KA, Moore R, Uno T, Teng C, Newbold RR, McLach- 
lan JA & Negishi M. (1997) Developmental exposure to diethylstil- 
bestrol elicits demethylation of estrogen-responsive lactoferrin gene  
Li X, Ycaza J & Blumberg B. (2011) The environmental obesogen trib-
utiltychloride acts via peroxisome proliferator activated receptor  
gamma to induce adipogenesis in murine 3T3-L1 preadipocytes.  
Lillycrop KA. (2011) Effect of maternal diet on the epigenome; implica-
Lillycrop KA & Burdge GC. (2011) Epigenetic changes in early life and  
Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA & Bur-
dge GC. (2008) Feeding pregnant rats a protein-restricted diet per-
sistently alters the methylation of specific cytosines in the hepatic  
Livingstone DE, Jones GC, Smith K, Jamieson PM, Andrew R, Kenyon  
CJ & Walker BR. (2000) Understanding the role of gluco corticoids  
in obesity: tissue-specific alterations of corticosterone metabolism in  
(2011) Brain ppar-gamma promotes obesity and is required for the  
insulin-sensitizing effect of thiazolidinediones. Nat Med 17, 618– 
622.  
Lustig RH. (2006) Childhood obesity: behavioral aberration or bio-
chemical drive? Reinterpreting the first law of thermodynamics. Nat  
Lustig RH. (2010) Fructose: metabolic, hedonic, and societal parallels  
genome in an adult man: reinforced evidence on the relationship  
between congenital oestrogen deficiency, adiposity and the metabolic  
le Maire A, Grimaldi M, Roecklin D, Dagnino S, Vivat-Hannah V,  
het erotidimers by organotin environmental endocrine disruptors.  
EMBO Rep 10, 367–373.  
Maloney EK & Waxman DJ. (1999) Trans-activation of pparalpha and  
ppargamma by structurally diverse environmental chemicals. Toxicol  
Marin P, Darin N, Amemiya T, Andersson B, Jern S & Björntorp P.  
(1992) Cortisol secretion in relation to body fat distribution in  
Mendez MA, Garcia-Esteban R, Guxens M, Vrijheid M, Kogevinas M,  
Goni F, Fochs S & Sunyer J. (2011) Prenatal endocrine disruptor com-
 pound exposure, rapid weight gain, and overweight in infancy. Envi-
 ron Health Perspect 119, 272–278.  
Muhlhauser B & Smith SR. (2009) Early-life origins of metabolic  
Myers MG Jr & Burant CF. (2011) Ppar-gamma action: it’s all in your  
J Clin Psychiatry 58(Suppl. 10), 45–49.  
Newbold RR. (2010) Impact of environmental endocrine disrupting  
chemicals on the development of obesity. Hormones (Athens) 9,  
206–217.  
Newbold RR. (2011) Perinatal exposure to endocrine disrupting chem-
ica ls with estrogenic activity and the development of obesity. In:  
Springer, US.  
Developmental exposure to estrogenic compounds and obesity. Birth  
Recall 57, 4356–4359.  
estrogens and obesity. Mol Cell Endocrinol 304, 84–89.  
Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R,  
Rosenfeld MG, Willson TM, Glass CK & Milburn MV. (1998)  
Ligand binding and co-activator assembly of the peroxisome prolifer-
action: why should we consider influences by environmental chemi-
(2005) Associations of maternal prenatal smoking with child adiposi-
Ong KK & Dunger DB. (2002) Perinatal growth failure: the road to  
obesity, insulin resistance and cardiovascular disease in adults. Best  
Ong KK, Ahmed ML, Emmett PM, Preece MA & Dunger DB. (2000)  
Association between postnatal catch-up growth and obesity in child-
Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca  
JD, Moorman MA, Simonetti DW, Craig S & Marshall DR. (1999)  
Multilineage potential of adult human mesenchymal stem cells.  
Science 284, 143–147.  
Piver WT. (1973) Organotin compounds: industrial applications and  
biological investigation. Environ Health Perspect 4, 61–79.  
Power C & Jefferis BJ. (2002) Fetal environment and subsequent obes-
Rask E, Olsson T, Soderberg S, Andrew R, Livingstone DE, Johnson O  
& Walker BR. (2001) Tissue-specific dysregulation of cortisol metabol-
Safety issues and prospects for future generations of ppar modula-
Rubin BS. (2011) Bisphenol a: an endocrine disruptor with widespread  
Rubin BS & Soto AM. (2009) Bisphenol a: perinatal exposure and  
Rubin BS, Murray MK, Damassa DA, King JC & Soto AM. (2001)  
Perinatal exposure to low doses of bisphenol a affects body weight,  
patterns of estrous cyclicity, and plasma lh levels. Environ Health  
Perspect 109, 675–680.  
Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ & Seeley RJ.  
(2010) Perinatal exposure to bisphenol-a and the development of  
Ryan KK, Li B, Grayson BE, Matter EK, Woods SC & Seeley RJ.  
(2011) A role for central nervous system ppar-gamma in the regula-


