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REVIEW ARTICLE

Obesogens, stem cells and the developmental programming of obesity

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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.

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; Muhlhausler & Smith, 2009).

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 obesity and metabolic syndrome later in life (Power & Jefferis, 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 & Dunger, 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 antipsychotic 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 twice 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 diethylstilbesterol (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 & Michels, 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; Bjorntorp, 1997; Bjorntorp & 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; Bjorntorp, 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-dehydrocorticosterone (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) (Schlumbohm *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, as 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 inhbiting 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 adipogensis 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 NIEHS/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 methylation 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.

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