



Review

Endocrine disrupters as obesogens

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ARTICLE INFO

Article history:

Received 17 January 2009

Accepted 24 February 2009

Keywords:

Endocrine disrupter

Obesogen

Obesity

Nuclear receptor

Organotin

Environmental agents

ABSTRACT

The recent dramatic rise in obesity rates is an alarming global health trend that consumes an ever increasing portion of health care budgets in Western countries. The root cause of obesity is thought to be a prolonged positive energy balance. Hence, the major focus of preventative programs for obesity has been to target overeating and inadequate physical exercise. Recent research implicates environmental risk factors, including nutrient quality, stress, fetal environment and pharmaceutical or chemical exposure as relevant contributing influences. Evidence points to endocrine disrupting chemicals that interfere with the body's adipose tissue biology, endocrine hormone systems or central hypothalamic–pituitary–adrenal axis as suspects in derailing the homeostatic mechanisms important to weight control. This review highlights recent advances in our understanding of the molecular targets and mechanisms of action for these compounds and areas of future research needed to evaluate the significance of their contribution to obesity.

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1. Introduction

Metabolite sensing and hormonal signaling balance the accumulation and mobilization of lipids from adipose tissues in response to fluctuating nutrient intake and caloric demands. However, adipose tissue is not just a passive lipid repository. Adipose depots also function as active endocrine organs that participate in the body's feedback system that fine-tunes the regulation of appetite

and the metabolic integration between organs and inflammatory responses. The etiology of obesity varies, reflecting many possible points of perturbation in the regulatory pathways that maintain fat homeostasis. A multitude of factors will influence whether an individual develops obesity. Genetic, nutritional and environmental factors are known to impact hunger and satiety (Farooqi and O'Rahilly, 2004; Martinez-Hernandez et al., 2007), basal metabolic rate (Kim, 2008; Vermorel et al., 2005), carbohydrate and lipid flux (Cota et al., 2007), and the regulation of adipocyte proliferation and differentiation and developmental programming of metabolic set points (Levin, 2006; Frontera et al., 2008). Recent evidence from many laboratories has shown that a variety of environmental endocrine disrupting chemicals can influence adipogenesis and obesity. *Obesogens* can be defined functionally as chemical agents

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Table 1
Endocrine disrupters and pharmaceutical drugs with demonstrated obesogenic properties. For each class of compound, the known or putative targets are indicated. Possible targets are indicated where some data exist to support a hypothetical mechanism of action.

Obesogen class	Target			
	Metabolic sensor	Sex steroid dysregulation	Central integration of energy balance	Metabolic set point
<i>Environmental pollutants</i>				
TBT, TPT	PPAR γ , RXRs, TR?	CYP19	PH, HPA?, EC?	GR signaling (11 β -HSD)
Phthalates	PPAR α , PPAR γ	ER	PH?	
BPA	PPAR γ ?, others?	ER? others?	PH?	
PFCs	PPAR γ ?			
PBDEs				HPT
Dithiocarbamates				GR signaling (11 β -HSD)
Alkylphenols		ERs?	NE?	
<i>Nutritional components</i>				
Phytoestrogens		ERs, AR, other?	PH?	?
Glycyrrhetic acid				GR signaling (11 β -HSD)
<i>Pharmaceuticals</i>				
DES		ER		
SSRI			NE?	?
Tricyclic antidepressants			NE?	?
Atypical antipsychotics			NE?, EC	?
TZDs	PPAR γ			HPT?

TBT, tributyltin, TPT, triphenyltin, BPA, bisphenol A, PFCs, perfluoroalkyl compounds, PBDEs, polybrominated diphenyl ethers, DES, diethylstilbestrol, SSRI, selective serotonin reuptake inhibitor, TZD, thiazolidinediones, NE, neuroendocrine effects, PH, peptidergic hormones, EC, endocannabinoid, HPT, hypothalamus–pituitary–thyroid, HPA, hypothalamus–pituitary–adrenal.

that inappropriately regulate and promote lipid accumulation and adipogenesis (Grun and Blumberg, 2007). Here we review the effects of several environmental endocrine disrupters on these pathways, discuss the data that link these “obesogens” to adipogenesis and obesity and highlight areas where future research will be helpful in ascertaining the magnitude of the risk posed by obesogen exposure (Table 1).

2. Obesogenic effects mediated by metabolic sensors

At its most basic level the progression to obesity requires both increased adipocyte number and lipid content. A number of master transcriptional regulators are critical to the regulation of gene networks controlling intracellular lipid flux, adipocyte proliferation and differentiation. Among these are nuclear hormone receptors, particularly the peroxisome proliferator activated receptors (PPAR α , δ and γ) which function as obligate heterodimers with the 9-cis retinoic acid receptor (RXR). These heterodimers play a pre-eminent role, serving as metabolic ligand sensors for a variety of lipophilic hormones, dietary fatty acids and their metabolites.

Lipid agonists of RXR–PPAR α promote peroxisome proliferation and stimulate fatty acid β -oxidation (Ferrel, 2004). Consequently, xenobiotics that target PPAR α typically act as hypolipodemic agents. In contrast, activation of RXR–PPAR γ favors lipid biosynthesis and storage, and is essential for the differentiation of resident preadipocytes and the conversion of mesenchymal progenitors to preadipocytes in adipose tissues (Rosen et al., 1999). Human allelic variants of PPAR γ produce a variety of metabolic outcomes. A hypomorphic variant of PPAR γ (Pro12Ala), is associated with lower body mass, improved insulin sensitivity and serum lipid profiles in diabetics, whereas a constitutively active allele (Pro115Gln) gives rise to obesity and insulin resistance (Ristow et al., 1998; Hara et al., 2000). Ligand modulation of PPAR γ activity causes a corresponding shift in adipogenic programs. *In vivo* treatment with PPAR γ antagonists, such as SR-202, GW9662 and JTP-426467, prevents high-fat diet induced weight gain in rodent models (Rieusset et al., 2002; Nakano et al., 2006; Nishiu et al., 2006). PPAR γ agonists, such as the thiazolidinediones (TZD) rosiglitazone and pioglitazone, are potent insulin sensitizing pharmaceuticals used to improve glycemic control and serum triglycerides in diabetics (Goldberg, 2007). Unwanted, PPAR γ -mediated side effects include periph-

eral edema followed by persistent weight gain with prolonged use (Larsen et al., 2003; Rubenstunk et al., 2007). Therefore, TZDs are pharmaceutical obesogens that exacerbate the aspects of type 2 diabetes resulting from an overabundance of adipose tissue.

The existence of pharmaceutical obesogens predicts the existence of other chemicals with similar effects. Could endocrine disrupting chemicals target PPAR γ and phenocopy these same effects? Recent work identified members of the organotin class of persistent organic pollutants (POPs), specifically tributyltin (TBT) and triphenyltin (TPT), as highly selective and potent dual agonists of both the retinoid X receptors (RXR α , β , and γ) and PPAR γ (Kanayama et al., 2005; Grun et al., 2006). Organotins are used in marine anti-fouling paints, wood catalysts, plasticizers, slimicides in industrial water systems and fungicides on foods (recently reviewed in Nath, 2008). The ability to target both receptors simultaneously should be particularly effective since adipogenic signaling can be mediated through both the RXR and PPAR γ components of the heterodimer. Receptor K_ds and transcriptional activation EC₅₀ values for TBT and TPT are in the range of 5–20 nM for both RXRs and PPAR γ (Grun et al., 2006). *In vitro* and *in vivo* studies show that TBT drives the differentiation of murine 3T3-L1 adipocytes and modulates RXR–PPAR γ dependent pro-adipogenic gene networks in liver, adipose tissue and bone marrow (Kanayama et al., 2005; Grun et al., 2006; Inadera and Shimomura, 2005; Carfi et al., 2008). Developmental exposure results in precocious lipid accumulation in adipose tissues and hepatic steatosis of newborn mice (Grun et al., 2006). Long-term effects following acute fetal exposure in murine models include an increase in epididymal fat mass and a trend towards body weight gain with age (Grun et al., 2006) (and unpublished data F.G./B.B.). Chronic developmental exposure in the frog *Xenopus laevis* resulted in ectopic adipocyte formation around the gonads in both males and females (Grun et al., 2006). Similar perturbations in fatty acid homeostasis and enhanced lipid accumulation have even been observed in ramshorn snails (Janer et al., 2007). Taken together, these studies reveal both acute and long-term adipogenic effects especially if exposure occurs during fetal development or early life.

Considering its potent effects on RXR and PPAR γ , it is obviously relevant to ask whether human populations are at risk from organotin exposure. Major environmental sources of organotins include contaminated seafood, agricultural products, drinking water and

leaching from plastics (Tsuda et al., 1995; Guerin et al., 2007; Ohno et al., 2002; Sadiki and Williams, 1999; Fromme et al., 2005). Organotin levels in mammals that are dependent on marine food chains have been documented at several $\mu\text{g/g}$ (Strand and Jacobsen, 2005). Studies that have directly measured organotin compounds in human tissue and blood samples are more limited. Liver samples from the late 1990s in Europe and Asia contained on average 6 and 84 ng/g wet wt. respectively for total organotins with MBT and DBT as the most prevalent species; average TBT levels were less than 2 ng/g wet wt. (~ 6 nM) (Takahashi et al., 1999; Jones et al., 2000). However, levels of total organotins in US blood samples averaged around 21 ng/ml; TBT comprised around 8 ng/ml (~ 27 nM) (Kannan et al., 1999). More recent analyses of European blood samples found the predominant species to be TPT at 0.09 and 0.67 ng/ml (~ 0.5 – 2 nM) and only occasional trace amounts of TBT (Rantakokko et al., 2008; Lo et al., 2003). Human adipose tissue levels remain uncharacterized. These variations in geographical and historical trends primarily reflect fragmentary data. They may also result from regional differences in the types of organotin applications and a general decline in exposure as organotins are phased out in marine paints. Notwithstanding these declines, it is probable that a portion of the general population remains vulnerable to organotin exposure at levels sufficient to activate RXRs and PPAR γ given their high affinity and the ubiquity of organotins in plastics and agricultural use.

Although the mechanistic data are not as clear-cut, further threats to lipid and adipose homeostasis are posed by other common xenobiotics with PPAR activity. These include bisphenol A from polycarbonate plastics, phthalate plasticizers used to soften PVC plastics and various perfluoroalkyl compounds (PFCs) that are widely utilized surfactants and surface repellents in consumer products. Leaching of these non-bonded phthalate and PFC additives into food and water accounts for their near ubiquitous presence in humans. Transfer of primary phthalates, such as DEHP, to food during processing lies within the range of 0.01–4.4 mg/kg, resulting in an estimated average daily intake of about 160 μg (Tsumura et al., 2001, 2003). Quantitation of urinary phthalate metabolites and serum levels of major PFC species (see paper by Fenton and colleagues in this issue) are in excess of several $\mu\text{g/l}$ in more than 75% of the US population (CDCP, 2005; Apelberg et al., 2007), placing them within a range of concern for endocrine disruption. Fetal or early life exposure to phthalates has been proposed to account for perturbed male reproductive system development via decreased testicular steroidal synthesis (Parks et al., 2000; Fisher, 2004; Swan et al., 2005; Main et al., 2006).

Receptor binding, transactivation and toxicogenomic studies confirm that phthalates and PFCs can function as agonists for one or more of the PPARs, providing a mechanistic link to disturbed lipid and steroid metabolism (Bell, 1982; Lapinskas et al., 2005; Maloney and Waxman, 1999; Rosen et al., 2008; Vanden Heuvel et al., 2006). Typical responses in rodents include a strong induction of hepatic peroxisome proliferation and tumorigenesis (Rusyn et al., 2006; Warren et al., 1982; Abdellatif et al., 1991; Ikeda et al., 1985). Di(2-ethylhexyl)phthalate (DEHP) or perfluorooctanoic acid (PFOA) increase PPAR α dependent lipid mobilization, fatty acid oxidation and adipose tissue atrophy during periods of experimental exposure (Itsuki-Yoneda et al., 2007; Xie et al., 2002, 2003). Consequently, these hypolipidemic and anti-adipogenic effects might be expected to result in an overall reduction in adipose mass and body weight. Depressed birth weight can be induced by low to moderate prenatal exposure (>5 mg/kg bw) of PFOA in rodents (Abbott et al., 2007; Wolf et al., 2007) and an association between depressed birth weight and levels of PFOA in human umbilical cord blood has been documented (Apelberg et al., 2007). PFOA probably exerts anorexigenic effects through a central hypothalamic mechanism that triggers a decrease in food intake in adult rodents (Asakawa

et al., 2007). This phenotype is not observed in PPAR α knockout animals (Asakawa et al., 2008).

If activating PPAR α reduces adipose mass and body weight, how might EDCs targeting PPAR α promote obesity? Several experimental observations provide insights into possible mechanisms. First, PPARs contain some of the largest and most promiscuous ligand and binding pockets within the nuclear hormone receptor family, allowing PPAR agonists or their metabolites to activate multiple isoforms. Metabolites of the potent PPAR α agonist DEHP, such as mono(2-ethylhexyl)phthalate (MEHP), also activate PPAR γ thereby providing a possible route for a pro-adipogenic response. MEHP promotes 3T3-L1 adipocyte differentiation and lipid accumulation (Hurst and Waxman, 2003; Feige et al., 2007). PPAR α -dependent stimulation of fatty acid oxidation and peroxisomal proliferation requires continuous exposure; however, PPAR γ activators may require only single or perhaps episodic exposure to effectively drive permanent changes in adipocyte differentiation and increased cell number. Second, fetal or perinatal exposure to phthalates and PFCs disturbs transcriptional regulation of testicular steroidogenesis, decreasing androgen biosynthesis (Parks et al., 2000; Gray et al., 2000; Jarfelt et al., 2005; Jensen and Leffers, 2008) and decreased androgen activity is itself obesogenic (Braga-Basaria et al., 2006). Third, low birth weight as a consequence of a poor nutritional uterine environment is an established risk factor for obesity. Hypolipidemia mediated through increased fatty acid metabolism in the developing fetus may mimic an undernourished environment that is sensed and acted upon to program long-term metabolic changes. Human epidemiological data and numerous animal studies support the generalization that nutritional restriction, exposure to disparate developmental toxicants or intrauterine stress frequently results in a biphasic growth response: depressed birth weight, followed by a period of catch-up growth and an elevated risk for body weight gain and obesity in the long term (Levin, 2006).

Two recent studies support these contentions. Mice prenatally exposed to low levels of PFOA exhibited reduced birth weight followed by increased adipose mass and body weight after puberty (Betts, 2007) (see article by Fenton and colleagues in this issue). Epidemiological studies documented a positive correlation between the presence of the specific urinary phthalate metabolites, mono-benzyl phthalate (MBzP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), with increased waist circumference in men. The metabolites mono-butyl phthalate (MBP), mono-ethyl phthalate (MEP) and mono-benzyl phthalate (MBzP) were also associated with measures of insulin resistance, a marker of metabolic syndrome (Stahlhut et al., 2007).

Overall, it appears quite plausible that xenobiotic mimics of endogenous ligands for nutrient sensing nuclear receptors, such as the PPARs, are sufficiently potent and prevalent to inappropriately regulate transcriptional programs controlling adipogenesis. The relative contributions of developmental versus adult exposures to obesity remain to be determined; however, it is reasonable to suppose that developmental exposures would have larger and more pervasive effects.

3. Obesogenic effects mediated by sex steroid dysregulation

Nutrient sensing nuclear receptors are just one aspect of adipocyte regulation. Nuclear receptors for sex steroid hormones also influence adipose tissue development. Knockout models of sex steroid pathway components, e.g., FSH receptor (FORKO), aromatase (ArKO), estrogen receptor (α ERKO) and androgen receptor (ARKO), confirm a role for sex steroids in regulating adipocyte hypertrophy and hyperplasia, as well as influencing the sexually dimorphic deposition and remodeling of specific adipose sites

(Danilovich et al., 2000; Murata et al., 2002; Heine et al., 2000; Matsumoto et al., 2003). Typically, sex steroids, in conjunction with peptide hormones such as growth hormone (GH), mobilize lipid stores and help to counteract the actions of insulin and cortisol on lipid accumulation. Imbalances in these hormones, therefore, are commonly observed in genetic, clinical and physiological conditions, (i.e., Cushing's syndrome, polycystic ovary syndrome (PCO), GH-deficiency, menopause, aging, alcoholism and depression), that produce dyslipidemias and obesity. The hormonal defects frequently include a relative deficiency or altered ratios in androgen/estrogen levels, lowered growth hormone secretion, hypercortisolemia and increased insulin resistance (Bjorntorp, 1997). Consistent with this overall picture, anti-androgenic therapies for prostate cancer and PCO syndrome produce weight gain, whereas estrogenic hormone replacement therapy is generally protective against the changes in body fat remodeling seen with age and menopause in women (Jones et al., 2000). Notably, dietary factors such as isoflavone phytoestrogens modulate estrogen receptor signaling and effect similar positive changes on adipose tissues. Hence, nutritional levels of genistein and daidzein reverse fat accumulation in the trunks of post-menopausal women and ovariectomized rodent models (Naaz et al., 2003; Kim et al., 2006; Goodman-Gruen and Kritz-Silverstein, 2003; Wu et al., 2006). These effects by phytoestrogens are not seen in α ERKO animals indicating the importance of estrogen receptor alpha (ER α) (Cooke and Naaz, 2005). Since phytoestrogens are more potent activators of ER β than of ER α , and ER β regulates the expression of ER α (Henley and Korach, 2006), more work remains to be done before the relative contributions of the two ERs to phytoestrogen effects on obesity can be determined.

In contrast to its effects in adults, exposure to estrogens at critical periods of development produces obesogenic effects. For example, mice derived from dams maintained on diets with low phytoestrogen levels during pregnancy and lactation experience elevated serum estradiol levels and undergo fetal estrogenization syndrome (FES). These mice have a lower birth weight, but develop obesity, high leptin levels, and impaired glucose responses (in males), at puberty when maintained on soy supplemented chow (Ruhlen et al., 2008). Exposure of adult male mice to low dietary phytoestrogen levels led to decreased adipose mass, in agreement with previous animal and human studies (Penza et al., 2006).

New data on diethylstilbestrol (DES) have uncovered broadly similar obesogenic responses in rodents (see article by Newbold and colleagues in this issue). DES is a potent synthetic estrogen that was widely prescribed to women until 1971, primarily for the management of miscarriage risk. Exposure also resulted in a higher incidence of breast cancer in DES exposed mothers, and reproductive tract abnormalities and neoplasias, infertility and autoimmune disorders in daughters of DES treated mothers; sons also show abnormalities (Rubin, 2007). Recent studies in rodents identified weight gain as another significant change following neonatal DES exposure. Weight gain was preceded by elevated levels of leptin, adiponectin, IL-6, triglycerides and glucose, and altered insulin signaling. High doses of DES (1 mg/kg) given to neonatal female mice during the period of adipocyte differentiation initially depressed body weight, but a period of catch-up growth followed until 2 months of age and a persistent enlargement of abdominal fat pads continued thereafter. Low doses of DES (10 μ g/kg) did not depress weight initially, but also led to later weight gain (Newbold et al., 2007a, 2007b). DES exposed male mice did not become obese but rather showed a dose-dependent decrease in overall body weight, underscoring the important and often contrasting role gender may play in the overall response.

Obesogenic effects have also been observed with other xenoestrogenic compounds. Bisphenol A (BPA) is widely found in human populations (0.3–4.4 ng/ml in human serum (Inoue et al., 2000;

vom Saal et al., 2007)) as a consequence of leaching from polycarbonate plastics and products coated with epoxy resins (see article by Rubin and colleagues in this issue). In conjunction with insulin, BPA accelerates murine preadipocyte cell line differentiation by up-regulating adipogenic genes (Masuno et al., 2002; Phrakonkham et al., 2008). In addition to its action on the nuclear estrogen receptors, BPA can also act at low doses in a non-genomic manner via cell membrane associated estrogen receptors (Thomas and Dong, 2006; Watson et al., 2007), directly modulate the insulin dependent P1 3-kinase/Akt kinase pathway and enhance glucose uptake (Masuno et al., 2005; Sakurai et al., 2004). Gestational and perinatal exposure of rodents to 0.1–1.2 mg/kg bw/day BPA in drinking water, predicted to give equivalent serum exposure levels, resulted in long-term increased body weight and hyperlipidemia (Rubin et al., 2001; Miyawaki et al., 2007). A positive correlation for human serum BPA levels with obese and PCO syndrome females has also been clinically observed (Takeuchi et al., 2004).

Together, these data suggest that dysregulated signaling through sex steroid receptors can produce pro-adipogenic effects; although, the nature of the effects may depend critically on the timing of exposure and the sex of the exposed individual.

4. Obesogens and central integration of energy balance

Environmental pollutants targeting nuclear hormone receptors directly relevant to adipocyte biology are relatively obvious obesogen candidates. Another important class of obesogens will be those that interact with central mechanisms that coordinate the whole body response to daily nutritional fluctuations. The control over appetite exerted by the hypothalamic–pituitary–adrenal (H–P–A) axis plays a critical role to prevent hyperphagia and regulate energy homeostasis. Could some of the numerous monoaminergic, peptidergic and endocannabinoid signals generated by the digestive tract, adipose tissue and within the brain that are critical mediators of these circuits be potential targets for environmental obesogens? The prevalence of body weight disruption observed in various neurological disorders and their pharmaceutical treatments are suggestive of this possibility.

4.1. Neuroendocrine effects

Individuals with schizophrenia, bipolar disorder or major depression already display elevated co-morbidity for cardiovascular disease and significant clustering for metabolic syndrome risk factors, including diabetes, hypertension, dyslipidemias and obesity (Casey, 2005; Ruetsch et al., 2005). Annual prevalence rates in the US for schizophrenia (1.1%, 2.4 million), bipolar disorder (2.6%, 5.7 million) and major depression (6.7%, 14.8 million) reveal a sizable and growing population undergoing prescription drug treatment (Kessler et al., 2003, 2005). Unfortunately, a wide range of neuroactive drug regimens to treat these disorders, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), atypical antipsychotics or mood stabilizers promote weight gain to the point where non-compliance with therapy is a serious concern (Ruetsch et al., 2005; Baptista et al., 2004). The atypical antipsychotic olanzapine is a useful example to detail the magnitude of the problem. Olanzapine therapy induces weight gain of around 5 kg/year at 10 mg/day that rises in a dose-dependent manner to more than 10 kg/year at 15 mg/day (Nemeroff, 1997). Prolonged use elevates serum glucose levels, promoting glucose intolerance and increases the risk of diabetes more than 4-fold compared to patients on typical antipsychotics (Wirshing et al., 2002; Koro et al., 2002). Olanzapine impairs the actions of insulin, decreases glucose uptake and promotes SREBP-1 mediated adipogenesis in 3T3-L1 cells (Yang et al., 2007; Vestri et al., 2007). The diversity in chemical class and modes of action for these neu-

ropharmaceuticals effectively illustrates the point that targeting neurotransmitter receptors, particularly subtypes that overlap with behavioral and metabolic regulatory circuits such as 5-HT(2C) and H1 receptors, is effective at eliciting obesogenic phenotypes.

4.2. Peptidergic hormones

Genetic mutation or misregulation of peptidergic hormones is also known to interfere with effective hypothalamic neuronal integration and when unbalanced leads to obesity (Farooqi and O'Rahilly, 2004). Brain derived neuropeptide Y (NPY), orexins, agouti-related peptide (AgRP), melanin-concentrating hormone and peripheral hormones such as ghrelin are major stimulators of appetite. Intracerebroventricular injection induces feeding behavior whereas long-term infusion promotes hyperphagia and obesity (Raposinho et al., 2001; Sakurai et al., 1998; Klebig et al., 1995; Tschop et al., 2000). In contrast, the postprandial release of neuroendocrine, pancreatic, gastrointestinal and adipocyte hormones, as well as nutrient metabolites, balances these signals and counteracts excessive food intake. Cholecystokinin (CCK), glucagon-like peptide 1, peptide YY, insulin, leptin, and pro-opiomelanocortin (POMC)-derived peptides are effective satiety signals when administered centrally or promote obesity when absent (Farooqi and O'Rahilly, 2004; Corp et al., 1997; Turton et al., 1996; Batterham et al., 2003; Sipols et al., 2002; Campfield et al., 1995; Montague et al., 1997; Krude et al., 2003).

Several of these peptidergic hormone factors are sensitive to modulation by nuclear receptor signaling pathways, which makes them potential transcriptional targets for endocrine disrupting chemicals. For example, estrogenic signaling intersects at several levels with hypothalamic appetite control. In clonal hypothalamic neuronal cell lines for instance, NPY and AgRP expression exhibits a complex biphasic response to estradiol, with repression or activation dependent on cellular ER α / β status (Titolo et al., 2006). Hence, direct injection of estrogen into the ventromedial hypothalamus, an area where localized estrogen synthesis overlaps with leptin receptor positive neurons, can substantially mimic the actions of leptin on orexigenic NPY and anorexigenic POMC neurons. This results in decreased food intake and general anti-obesity properties (Gao and Horvath, 2008). Some evidence also points to xenoestrogens as modulating peptidergic hormone expression. BPA, nonylphenol and DEHP have been reported to affect NPY expression in the midbrain (Masuo et al., 2004a, 2004b) and manipulation of phytoestrogen content in rodent chow diets significantly shifted feeding behavior (see article by Nef and colleagues in this issue).

Paradoxically, food and water intake were significantly enhanced in an adult feeding study despite an overall decrease in total body weight and adipose mass with higher phytoestrogen content (Lephart et al., 2004). An important message from this study is that weight gain does not automatically follow from increased caloric intake. Rather, it also depends on the body's adaptive responses in setting the overall metabolic rate. The associated dose-dependent reduction in leptin levels may help to explain this effect. An alternative is that other hormonal regulators, such as the gastric meal initiator hormone ghrelin, are responsible for this behavioral and metabolic sensitivity to phytoestrogens. Recent work found that ghrelin expression is positively regulated by localized estrogen synthesis and signaling in the stomach (Sakata et al., 2006), although others have ascribed the primary stimulant for this changing expression to low leptin levels (Zhao et al., 2008). Experiments with 3T3-L1 cells also indicate that ghrelin may have an important role in the regulation of adipocyte cell number through its mitogenic and adipocyte differentiation properties (Kim et al., 2004).

In this context, it is interesting to ask whether endocrine disrupting organotins (such as TBT) can exert some of their obesogenic

effects through disturbed estrogen receptor signaling acting on the central H–P–A axis. TBT has been extensively studied for its ability to cause imposex in marine invertebrates and some fish species (Boyer, 1989; Shimasaki et al., 2003; McAllister and Kime, 2003). One mechanism proposed to explain the imposex phenotype is the inhibition of aromatase, which leads to increased testosterone levels. Indeed both direct enzyme inhibition and transcriptional down regulation of aromatase by organotins are well documented in invertebrates and mammals (Heidrich et al., 2001; Cooke, 2002; Horiguchi, 2006). Local control over estrogen production results from differential use of aromatase tissue specific promoters. While the effects of organotins on the brain specific aromatase promoter in mammals are currently unknown, aromatase in some tissues (e.g., ovarian granulosa cells), is sensitive to regulation by TBT and other RXR and PPAR γ specific ligands (Mu et al., 2000; Saitoh et al., 2001). Brain isoforms and aromatase activity in fish can be either up-regulated or down-regulated following exposure to different levels of TBT (Lyssimachou et al., 2006; Cheshenko et al., 2008). Therefore, it is plausible that TBT exposure may produce a localized disruption of hypothalamic aromatase regulation leading to inappropriate peptidergic H–P–A responses. Other organotin species, such as trimethyltin (TMT) and triethyltin (TET), are well-described neurotoxins that preferentially target a subset of hippocampal neurons. TMT has been shown to induce hippocampal NPY and NPY Y2 receptor expression in the short term but this response later falls below controls due to neuronal degeneration in the lesions (Ishikura et al., 2002; Sadamatsu et al., 1998). The consequences of such signaling deficits or of site-specific neuronal lesions would be particularly pronounced if exposure occurs during fetal development or in the perinatal period when hypothalamic nuclei involved in appetite regulation mature and programming of adaptive nutritional responses become entrained.

4.3. Endocannabinoid signaling

A third major circuit for appetite and body weight regulation that is a candidate for obesogenic disruption involves the endocannabinoid system (ECS) pathway (reviewed in Arias Horcajadas, 2007). Endogenous or dietary agonists of the cannabinoid receptor type 1 (CB1), including the lipid derivatives anandamide (AEA) and 2-arachidonyl glycerol (2-AG), have central orexigenic effects in the hypothalamus, even in satiated animals (Williams and Kirkham, 2002), and impact metabolic functions in peripheral tissues including adipose. CB1 receptors are also the target for the active component of cannabis, Δ^9 -tetrahydrocannabinol (THC). The carbohydrate cravings induced by THC from smoking marijuana are a well-established behavioral response and can produce modest weight gain albeit only in the short term (Greenberg et al., 1976). Smoking tobacco is also obesogenic under the appropriate conditions. Epidemiological studies of maternal smoking show that the adjusted odds ratio for obesity is between 1.5- and 2.0-fold greater if children were exposed during, but not prior or after, the pregnancy (Al Mamun et al., 2006; Oken et al., 2005; Power and Jefferis, 2002). In adults, weight gain is associated instead with cessation and nicotine withdrawal symptoms (Yun et al., 2005).

A prominent role for CB1 receptor signaling in obesity is further confirmed by knockout animals, which are leaner and resistant to diet induced obesity (Ravinet Trillou et al., 2004). Polymorphisms in human CB1 and the cannabinoid metabolic enzyme FAAH tell a similar story (Gazzerro et al., 2007; Sipe et al., 2005). Elevated endocannabinoid levels are found in obese subjects and correlate with increased visceral fat mass, suggesting that hyperactivity in cannabinoid signaling drives the obesogenic response (Engeli et al., 2005; Blucher et al., 2006). Hence, pharmacological CB1 receptor antagonists, like rimonabant, are effective at reducing food intake, weight loss and eliciting favorable metabolic parameters, including

reduced leptin, insulin, free fatty acids and cholesterol levels, and improving insulin resistance (Colombo et al., 1998; Hildebrandt et al., 2003).

Aside from mimics of endocannabinoid lipids like THC that target CB1 receptors, could environmental factors disturb the general endocannabinoid signaling cascade? A common point of downstream convergence between the ECS and peptidergic pathways involves activation by protein phosphorylation of the master intracellular energy charge sensor, 5'-AMP-activated protein kinase (AMPK) that responds to regulate both cellular and whole body energy levels. AMPK activity modulates metabolic enzymes and transcription factors, including the PPARs, involved in balancing intracellular carbohydrate and lipid utilization. The phosphorylation status of AMPK is dependent on a wide range of metabolic and hormonal signals and exhibits reciprocal peptidergic activation in central versus peripheral tissues. In the hypothalamus, leptin and insulin are inhibitory, whereas AgRP, ghrelin and endocannabinoids activate AMPK to provoke an orexigenic response and increased sympathetic activity (Andersson et al., 2004). In contrast, leptin and adiponectin are activating in liver or adipose and antagonized by ghrelin and endocannabinoids. Hence, peripheral tissues increase lipogenic capabilities, and decrease fatty acid oxidation and expression of thermogenesis-related uncoupling proteins by both peripheral inhibition of AMPK and central sympathetic adrenergic stimulatory effects when ghrelin or endocannabinoids levels rise (Kola et al., 2005; Theander-Carrillo et al., 2006). Studies with CB1 antagonists in wild type and knockout animals show that the orexigenic effects of ghrelin in the hypothalamus are dependent on a functional ECS pathway and mediated through AMPK activation (Kola et al., 2008). Obesogenic atypical antipsychotic pharmaceuticals acting through histamine H1 receptors can also activate hypothalamic AMPK (Kim et al., 2007). These results suggest that a broad range of environmental pollutants that perturb levels of hypothalamic peptidergic hormones, mimic endogenous lipid activators of the cannabinoid system or directly target the activity of AMPK would have the ability to drive obesogenic responses.

Two examples serve to illustrate this possibility. TBT was recently shown to activate AMPK in neuronal cell cultures (Nakatsu et al., 2008). Another study noted that the dioxins, 2-, 3-, 7-, 8-tetrachlorodibenzo-p-dioxin (TCDD) and 1-, 2-, 3-, 4-, 7-, 8-hexachlorodibenzo-p-dioxin (HxCDD), which typically induce a profound wasting syndrome at high doses (3.2 and 80 µg/kg, respectively), could instead stimulate significant body weight gain in rats at low exposure levels (0.05 and 1.25 µg/kg). Peripheral AMPK activation, inhibition of phosphoenolcarboxykinase (PEPCK) activity and decreased serum levels of insulin like growth factor (IGF-1) were associated with increasing dioxin exposure dose (Crouch et al., 2005). Furthermore, dynamic expression changes in orexigenic and anorexigenic hypothalamic neuropeptides, including NPY, POMC, CART and MCH, are observed in the dioxin wasting syndrome. This effect is believed to be a consequence of aryl hydrocarbon receptor (AhR) activity on xenobiotic response elements in the promoters of these genes (Fetissov et al., 2004; Linden et al., 2005). TCDD also appears to disrupt the proper processing of CCK peptide in intestinal cells (Lee et al., 2000). Loss of tissue specific regulation for key molecular targets, such as AMPK, and activation of competing hormonal signals at different doses may explain why increasing doses of dioxin (and perhaps other potential obesogens highlighted above) lead to a switch from weight gain to loss.

5. Obesogens and programming of metabolic set points

Hyperphagia resulting from disruption of hypothalamic appetite centers is one way that obesogens could unbalance the energy

equation, but may not be sufficient to produce obesity. Outputs from the hypothalamus regulate adaptive responses that alter metabolic efficiency and establish metabolic set points. Unless this adaptive component to the basal metabolic rate is chronically exceeded or disturbed, diet induced thermogenesis and futile metabolic cycles will work to defend energy and body weight equilibrium.

A significant portion of the control over these adaptive responses is dependent on activity in the hypothalamus–pituitary–thyroid (HPT) axis that determines systemic thyroid hormone output, which exerts widespread effects on carbohydrate, lipid and protein metabolism. Local conversion of thyroxin (T4) to the thyroid hormone receptor (TR) agonist, triiodothyronine (T3), by type 2 deiodinase (DIO2) increases TR signaling in a tissue specific manner. Combined with sympathetic adrenergic activity, elevated TR signaling regulates expression of a number of respiratory components, including uncoupling protein-1 (UCP-1) in BAT and muscle, which reduces metabolic efficiency and increases energy expenditure (de Jesus et al., 2001). Polymorphisms in UCPs are linked to specific obesity phenotypes (Alonso et al., 2005; Cha et al., 2006; Herrmann et al., 2003; van Abeelen et al., 2008). An association between a combination of polymorphisms in DIO2 and PPARγ and insulin resistance and metabolic syndrome has also been described (Fiorito et al., 2007). Interestingly, a recent report ascribes the net positive energy balance elicited by the PPARγ agonist rosiglitazone to its ability to reduce sympathetic activity to BAT and WAT, down-regulate thyroid axis signaling by reducing expression of type 2 and type 1 deiodinases, and also decrease pro-energy expenditure peptides CRH and CART in the hypothalamus (Festuccia et al., 2008). Hence, depression of circulating T4 levels, decreased localized peripheral T3 synthesis or reduced sympathetic activity are likely to blunt adaptive responses and promote a propensity for obesity and metabolic syndrome.

In this regard, endocrine disruption by polybrominated diphenyl ethers (PBDEs) exposure is a potential concern. PBDEs are extensively used in manufactured goods as flame retardants and are frequently present in human populations. Human adipose and liver tissue samples contain respectively on average 5.3 ± 3.0 and 3.6 ± 2.1 ng/g lipid weight of PBDE congeners (Covaci et al., 2008). The adjusted odds ratio for diabetes and metabolic syndrome are respectively 1.9- and 3.1-fold in groups with the highest quartile serum levels for prevalent PBDE congeners (Lim et al., 2008). Animal studies showed that PBDEs disturb the thyroid hormone axis, among their other effects. For instance, a 2–4 weeks exposure of adult rats to PBDEs was found to lower plasma thyroxin levels to 30% and affect lipolysis and insulin stimulated glucose oxidation in isolated adipocytes (Hoppe and Carey, 2007). Low dose PBDE exposure during gestation and lactation also decreased serum thyroxin levels and caused long-term changes in thyroid gland morphology (Ellis-Hutchings et al., 2006; Kuriyama et al., 2007; Talsness et al., 2008). A developmental toxic insult may be particularly relevant given the contributing role neonatal thyroid status has in integration of maternal environmental signals for long-term metabolic and body weight programming. For example, dietary intrauterine growth restriction, quantified as low birth weight, is a strong prognostic indicator for metabolic syndrome in humans (Yajnik, 2000; Hales and Barker, 2001; Cottrell and Ozanne, 2007). Neonatal hyperthyroidism is one response evoked in rats by maternal protein restriction during gestation and lactation. Subsequently, adult offspring exhibit decreased thyroid stimulating hormone (TSH) secretion, together with altered pituitary and muscle DIO2 and DIO1 expression (Lisboa et al., 2008). Furthermore, neonatal hyperthyroidism mediated by direct thyroxine administration in rodents was shown to evoke secondary hypothyroidism resulting in increased adipose mass accompanied by hyperleptinemia in the long term (Moura et al., 2008). Thus, targeting of the thyroid axis

by endocrine disrupting obesogens is a plausible contributing factor for obesity.

Appropriate regulation over glucocorticoid hormone signaling is a critical component of HPA output that mediates stress responses and metabolic functions in peripheral tissues. Glucocorticoids also play an important role in promoting adipocyte differentiation. A stressful perinatal environment, whether from unbalanced nutrition or psychosocial influences, can disrupt glucocorticoid signaling to the point that it affects long-term programming or sensitivity of central and peripheral tissues to physiological challenges (Acharid et al., 2006; Nyirenda et al., 1998). Over-stimulation of glucocorticoid production, or perturbed local metabolism of cortisol by modulating 11 β -steroid dehydrogenase type 1 (reactivating) and type 2 (inactivating) activities, and glucocorticoid receptor (GR) signaling are implicated as contributing factors in the development of obesity (Bjorntorp and Rosmond, 2000; Pasquali et al., 2006). Postnatal overfeeding of rats resulted in moderately overweight adults and was associated with increased basal and stress-induced corticosterone secretion and enhanced GR and 11 β -steroid dehydrogenase type 1 expression in visceral adipose tissue (Boullu-Ciocca et al., 2005). Transgenic overexpression of 11 β -HSD1 targeted to adipose tissue is sufficient to increase corticosterone levels, resulting in visceral obesity, glucose intolerance and insulin resistance. In contrast, targeted overexpression of 11 β -HSD2 protected against diet-induced obesity (Kershaw et al., 2005). Intrauterine protein restriction also elevates maternal glucocorticoids, which can affect fetal development and HPA axis maturation if not adequately protected against by inactivation via placental 11 β -HSD2 (Stocker et al., 2005; Dy et al., 2008).

A number of dietary and environmental agents with the ability to elevate or depress glucocorticoid signaling have now been described (Odermatt et al., 2006; Odermatt and Gummy, 2008). Glycyrrhetic acid, commonly used as a sweetening agent, or a synthetic derivative carbenoxolone, acts as an inhibitor of 11 β -HSD activities. Hypertension resulting from activation of mineralocorticoid receptors after inhibition of renal 11 β -HSD2 is observed above 2 mg/day glycyrrhetic acid in humans, equivalent to about 6 g licorice daily (van Gelderen et al., 2000). Furthermore, maternal gestational exposure to carbenoxolone in rats reduces birth weight, raises basal corticosterone, alters hypothalamic expression of GR and induces hyperglycemia (Welberg et al., 2000; Lindsay et al., 1996). Likewise, dithiocarbamates present in cosmetics and agricultural products inhibit 11 β -HSD2 (Atanasov et al., 2003). The dithiocarbamate pesticide thiram is also suspected to interfere with GR ligand binding (Garbrecht et al., 2006). In addition, other studies report inhibition of 11 β -HSD2 by the organotins DBT (Gummy et al., 2008) or TBT (Atanasov et al., 2005) by targeting critical cysteine residues necessary for enzymatic activity. Significant transfer and accumulation of organotins to fetal placenta, liver and brain occur with maternal dosing (Cooke et al., 2008), suggesting a mechanism for localized hypercortisolism whereby the protective actions of 11 β -HSD2 in fetal tissues become compromised.

The important role that the fetal nutritional environment and stress responses exert on long-term regulation of metabolic functions is becoming more evident (Bjorntorp, 1997). Epigenetic programming is one established route whereby early life experiences, including exposure to sub-optimal nutrients, behavioral stress or toxicants, can persist and lead to maladapted physiological responses later in life (the fetal basis of adult disease paradigm). For example, in the agouti mouse hypomethylation of a regulatory region in the agouti locus drives constitutive overexpression leading to obesity, hyperinsulinemia, diabetes and increased somatic growth (Miltenberger et al., 1997). Optimal maternal dietary supplementation with methionine, folic acid and choline increases methylation, reduced ectopic expression and improves outcome in offspring (Cooney et al., 2002). Imprinting is therefore sensitive to

nutritional influences, but can also be affected by maternal behavior. Stress-induced behaviors in rat dams during lactation alter DNA methylation patterns in their offspring, including a region of the hippocampal promoter for GR (Weaver et al., 2004). Indeed, epigenetic imprinting of the glucocorticoid receptor and its targets are observed following perinatal nutrient restriction, exposure to a variety of hormones, including the synthetic glucocorticoid dexamethasone, or toxicant hormone mimics like benzpyrene (Nyirenda et al., 1998; Drake et al., 2005; Lillycrop et al., 2005; Csaba and Inczeff-Gonda, 1998). Depression in human mothers is also associated with an increased methylation of a GR promoter site and altered stress responses in newborns (Oberlander et al., 2008). Furthermore, stress by social deprivation appears to enhance visceral fat deposition and increases the incidence of metabolic syndrome phenotypes in macaque and mouse models (Kaufman et al., 2007; Nonogaki et al., 2007). Imprinting in some cases persists across multiple subsequent generations (Drake et al., 2005; Csaba and Inczeff-Gonda, 1998). This suggests that such an epigenetic process could provide a plausible mechanism for amplifying acquired environmental effects to evoke sudden and dramatic changes in population health trends like the current obesity epidemic.

6. Conclusions and future directions

The progressive increase in obesity rates worldwide (Mokdad et al., 2003; SUS, 2006) suggests that a fundamental shift is occurring in how the human body integrates changing nutritional and environmental variables to maintain metabolic balance and body weight. The modern lifestyle, with its increased intake of energy-dense foods and decreased physical activity, may have pushed populations closer to the edge of a critical biological tipping point that is exposing vulnerabilities in our ability to adapt to plentiful, palatable food supplies. The obesogen hypothesis proposes that perturbations in metabolic signaling that result from exposure to novel environmental influences are superimposed on these trends of energy intake and expenditure. These obesogens include, but are not limited to endocrine disrupting compounds that alter fat cell differentiation or function and that initiate or exacerbate misregulation of homeostatic controls.

A few recurring themes are illustrated by the obesogenic examples listed above. To date most candidate environmental obesogens identified represent either chemical mimics of lipophilic hormones (e.g., bisphenol A, TBT) or inhibitors of endogenous hormone metabolism (e.g., TBT action on aromatase activity). Consequently, the sites of action are varied and the interactions complex, especially when compounds like organotins have multiple molecular targets. In many cases, dose response curves are not monotonic but exhibit changing phenotypes across dose ranges (as seen with phytoestrogens and DES). Typically high dose exposures are metabolic toxicants often leading to weight loss or growth restriction. At lower levels more similar to environmental exposures, these effects may be reversed (e.g., dioxins). Additional complexity is also introduced by timing of exposure, gender and genetic predisposition. Developmental exposure represents a limited window of heightened sensitivity wherein long-term effects distant from the initial insult can be established, and then perhaps only in a limited subset of the population. This delay in response and the experimental difficulty in establishing cause and effect for environmental factors may provide a partial answer to the underappreciated role chemical obesogens might play. The increased obesity risk due to prenatal maternal smoking certainly provides a proof-of-concept that long-term dysregulation of metabolic homeostasis is relevant at a population level. Epigenetic changes from obesogenic exposures are currently poorly understood. This will become an area for future intensive research efforts given their potential for long lasting, trans-generational effects.

Much remains undiscovered about the possible molecular mechanisms for environmental obesogens and their overall significance to the obesity epidemic. However, given the data already available on numerous obesogen candidates, the myriad chemical influences we experience daily, and the multiple targets with which they might intersect, it seems quite likely that obesogen exposure will play an important role in the current obesity epidemic. Research directed at fully understanding their mechanisms of action will be needed to fully appreciate the risks involved and possible strategies for remediation and prevention.

Acknowledgements

Work in the authors' laboratory was supported by grants from the University of California, Toxic Substances Research and Training Program (F.G.), the US Environmental Protection Agency (B.B.) and the National Institute of Environmental Health Sciences (B.B.).

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