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Review

Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity☆

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ABSTRACT

The basis for the current obesity epidemic remains controversial. However, the simplistic idea that obesity can be explained by two factors: energy intake and energy expenditure, is now being challenged due to the lack of success in decreasing obesity based on a focus on only these two factors. In this article we propose an emerging hypothesis that the recent dramatic increase in obesity could be due to developmental nutrition, developmental exposure to environmental chemicals or the interaction of nutrition and environmental chemical exposures during development. Indeed, developmental exposure to environmental chemicals in animal studies has been shown to increase the susceptibility to a number of diseases including obesity. Obesity is thus one of many diseases shown to have a developmental origin. We show that factors that impact growth during fetal and neonatal life, such as placental blood flow and nutrient transport to fetuses, as well as components of the maternal and infant diets, can influence weight gain later in life. In addition, we show that developmental exposure to endocrine disrupting chemicals can create abnormalities in homeostatic control systems required to maintain a normal body weight throughout life. Eliminating exposures to these chemicals and improving nutrition during development offer the potential for reducing obesity and associated diseases.

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1. Background: factors implicated in the obesity epidemic

The prevalence of obesity has risen dramatically in the United States and in other regions of the world over the past two decades. In the United States, 30% of adults have been defined as clinically obese and 65% defined as overweight (Hedley et al., 2004). Perhaps more important is that obesity and related diseases, such as diabetes, are rising dramatically in our children. Obesity is notoriously difficult to treat; thus, a better understanding of the aetiology of obesity is critical to primary prevention. There is no doubt that nutrition and exercise are factors in obesity. However, the view that these two factors alone are the primary variables that explain the obesity epidemic is being challenged as far to simplistic, and other factors are now being considered as contributing to the obesity epidemic

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(Keith et al., 2006; Newbold et al., 2008). We propose that the recent epidemics of chronic diseases now being observed in children: such as type 2 diabetes, childhood asthma, attention deficit hyperactivity disorder (ADHD), and obesity must have an environmental, dietary and behavioral component, since classical genetic mutations cannot account for such large increases in these disease over such a short time period. Instead, it is becoming clear that all complex diseases are the result of gene–environment interactions and that epigenetic modification of gene function during critical periods in development plays a critical role in the etiology of disease. This is referred to as "the fetal basis of adult disease" hypothesis (Heindel, 2008).

With regard to the environmental component of disease, there are significant human and animal data suggesting that fetal nutrition plays an important role in susceptibility to cardiovascular diseases and type 2 diabetes later in life (Gluckman et al., 2007). This research focus has led to a new field and a new scientific society called "International Society for Developmental Origins of Health and Disease" (DOHaD). Initially, DOHaD only focused on the nutritional aspect of the environmental component of disease. However, it is apparent from animal studies that the *in utero* and neonatal developmental periods comprise "a critical window", not just for nutrition, but also for exposure to environmental chemicals. Toxicant-induced pathogenic responses are most likely the result of altered gene expression or altered protein regulation associated with altered cell proliferation and differentiation as different cell types interact and establish cell lineages. These changes may lead to abnormal morphological and/or functional characteristics of cells, tissues, organs, and systems. These alterations may be due, at least in part, to epigenetic alterations: the alteration of methylation/acetylation-related protein–DNA relationships associated with chromatin remodeling that result in altered genetic programming. Altered epigenetic programming can eventually lead to increased incidence of a variety of diseases later in life (Ho et al., 2006; Dolinoy et al., 2007). Epigenetic alterations can occur during a vulnerable window in development and in a tissue-specific manner, and usually result in non-reversible changes in tissue structure and function. The end-result is an organism that is sensitized/programmed such that it will be more susceptible to specific diseases later in life.

The results seen following developmental exposure to environmental chemicals depend, to an extent not appreciated until recently, on the dose of the environmental chemical (Welshons et al., 2003, 2006). The classical approach in toxicology was to only examine high doses of environmental chemicals, the objective being to determine the doses that resulted in death, malformations and low birth weight. In sharp contrast, the focus on effects of a class of environmental chemicals known as "endocrine disrupting chemicals" (EDCs) is on functional changes via epigenetic mechanisms due to disruption of the hormonal signals that regulate cellular differentiation, leading to increased susceptibility to diseases later in life. We discuss below that these effects are being observed at the very low levels of these chemicals to which humans are commonly exposed (based on biomonitoring studies), although these exposures were previously assumed to be "safe" because they did not cause death or gross malformations.

Several recent reviews have been published in this area (Heindel, 2007; Miller et al., 2004; Waterland and Michels, 2007), and entire issues of two journals have been devoted to the topic (Coe et al., 2008; Heindel, 2007).

With regard to obesity, we propose that developmental exposures to environmental EDCs can alter the programming responsible for control of adipose tissue development as well as the regulatory systems controlling body weight homeostasis, impacting the numbers of fat cells, food intake and metabolism, resulting in an altered "set point" for body weight (Table 1). We are not suggesting that food intake and exercise are not important, but the systems that control exercise/metabolism and food intake, and their impact on obesity, need greater attention because as discussed below, these systems can be altered by nutritional status as well as exposure to EDCs during development.

Table 1
The developmental basis of obesity.

An emerging hypothesis is that the obesity epidemic could be due to the interaction of nutrition and chemical exposures during vulnerable windows in development
We hypothesize that environmental agents and/or nutrition act during development to: Alter the pathways responsible for control of adipose tissue development Increase the number of fat cells Alter food intake and metabolism Alter insulin sensitivity and lipid metabolism via effects on pancreas, adipose tissue, liver, GI tract, brain and muscle
The consequence is alteration of the "setpoint" or sensitivity for developing obesity later in life.
Gene–environment interaction: the focus is on development
The environment alters gene expression during vulnerable windows in development, resulting in altered epigenetic signals and increased susceptibility to obesity later in life.

2. Developmental exposure to nutrients and adult obesity

There are extensive data relating maternal pathophysiologies (for example, diabetes), excess maternal nutrients and fetal over-growth (macrosomia), as well as maternal malnutrition and intrauterine growth restriction (IUGR), to subsequent metabolic diseases in offspring. This has resulted in a focus on maternal nutrition as a primary factor in obesity and associated morbidities of offspring.

Babies with intrauterine growth restriction (IUGR) resulting in low body weight at birth that then experience rapid postnatal "catch-up" growth are at high risk for obesity and type 2 diabetes (Oken and Gillman, 2003; Yajnik, 2001). The "thrifty phenotype" hypothesis (Barker, 2004) has been proposed to explain this finding. This hypothesis proposes that a biological state adapted for subsistence conditions is created during fetal life by IUGR. IUGR is predicted to cause the fetus to respond with endocrine and metabolic adaptations via epigenetic mechanisms that put the individual at risk for excessive postnatal weight gain when exposed during postnatal life to a high calorie diet typically encountered in developed countries (Hales and Barker, 1992; Lee et al., 2005).

Since fetal over-nutrition leading to high birth weight (macrosomia, which is typical of offspring of diabetic mothers) is also associated with a higher attained adult body mass index (BMI) (Boney et al., 2005; Martorell et al., 2001), we are faced with the seeming paradox of increased adult adiposity at both ends of the birth weight spectrum. There thus appears to be a markedly different etiology of obesity in these two sub-populations relating to differences in both fetal and postnatal growth.

Changes in maternal–fetal nutrition have been shown in animal studies to result in differences in gene methylation via supplementing the diet with methyl donors such as vitamin B12, folic acid and phytoestrogens in mice. Lack of methylation of the retrotransposon with a methylation sensitive promoter was associated with subsequent obesity in offspring in mice (Cooney et al., 2002; Waterland and Jirtle, 2003). These data suggest that epigenetic alterations during development may play a role in subsequent obesity later in life.

One mechanism proposed for the effect of altered nutrition during development (either low or high birth weight) on subsequent obesity later in life is alteration of leptin. Leptin is a 16 kDa polypeptide member of the cytokine receptor call 1 family, which is synthesized by adipocytes to reduce food intake (it triggers a feeling of being "full") and increase energy utilization via binding to specific receptors in a number of peripheral and central sites, including the arcuate nucleus of the hypothalamus (Ahima, 2005). In mice, plasma leptin rises transiently at about 2 weeks of age and is involved in the formation of energy-regulation circuits in the hypothalamus (Bouret and Simerly, 2007). If a leptin surge occurs prematurely in mice via injection of leptin, or due to either fetal undernutrition or a high fat maternal diet, there is an increase in obesity and leptin resistance in adulthood (Yura et al., 2005). It appears that a premature leptin surge alters leptin programming and the developing hypothalamus, which leads to obesity in adults. It is unknown if there is a leptin surge in human infants or children, but if a surge can be shown, there is potential for translation of the animal research to human obesity. Interestingly, fetal (cord) blood levels of leptin are negatively correlated with body mass index in humans (Mantzoros et al., 2009).

3. Placental blood flow (nutrition) and fetal growth as factors in adult obesity: a new model for nutrient and nutrient-environment in chemical interactions in obesity

The methods used by scientists to study the impact of changes in fetal development on subsequent obesity and other diseases has involved a number of approaches involving manipulation of nutrients or energy expenditure (caloric restriction, protein restriction, high fat diet, and exercise), as well as manipulation of the stress–response system (dexamethasone administration, 11β-HSD knockout mice). The most common approach to studying IUGR in animal models has involved caloric restriction, which is not common in developed countries where rates of obesity have increased dramatically in recent decades. In contrast, an alternative approach has been developed that utilizes the fact that mice have two completely independent uterine horns, and removing one ovary results in a "crowded uterine horn", since the remaining ovary ovulates the entire complement of oocytes that would normally be shed by both ovaries into the associated uterine horn (Coe et al., 2008). This model thus allows a comparison of siblings showing normal fetal growth, IUGR and macrosomia within a crowded litter produced by hemi-ovariectomized CD-1 female mice, into which the one remaining ovary ovulates approximately 12 oocytes (Fig. 1). Differential fetal growth in a crowded uterine horn is due to the unique vascular anatomy of each independent uterine horns (arterial and venus blood flow is bi-directional from each end of a uterine horn). Elevated utero–placental blood flow and increased fetal growth over the mean occurs at each end of a crowded uterine horn, while fetuses in the middle are markedly growth restricted compared to other pups.

In an initial experiment examining offspring that developed in crowded uterine horns, IUGR male CD-1 mice experienced very rapid "catch-up" growth during the week after weaning: males with IUGR increased body weight by 90% (similar to findings in humans with IUGR), while males with macrosomia increased body weight by only 30%, and both of these sub-populations subsequently remained heavier than males at the mean for body weight at birth. Using radiolabeled microspheres, it was determined that fetuses in the middle of the uterine horn had markedly reduced placental blood flow relative to fetuses at the ends of the uterine horn (Coe et al., 2008), similar to prior findings in rats (Even et al., 1994). This new model thus allows the study of the effects of differential fetal nutrition (due to differential placental blood flow) on obesity later in life using a model that more accurately mimics the human situation in developed countries. IUGR is not just a consequence of severe maternal caloric or protein restriction in developed countries, while manipulation of these variables are common experimental methods used to produce IUGR offspring in rodent studies.

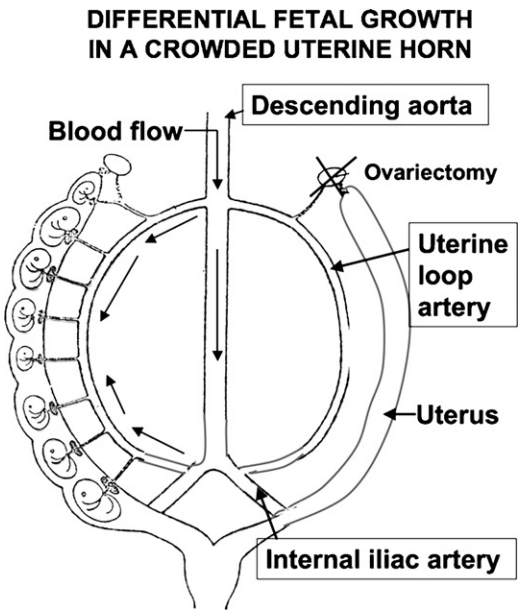

Fig. 1. The "crowded uterine horn" model is based on the fact that after hemi-ovariectomy there is a compensatory increase in ovulation from the remaining ovary, resulting in a litter of normal number in one uterine horn. There is differential growth of the pups due to a decreased blood flow to the pups in the middle of the uterine horn. This is due to bi-directional flow of blood (indicated by arrows) into the loop uterine artery from both the ovarian and cervical ends of the uterine horn (Coe et al., 2008; Even et al., 1994). The pup nearest the ovary in a crowded uterine horn may also be growth restricted if its placental artery is a branch from the smaller ovarian artery rather than the larger uterine artery.

Ongoing studies are examining the interaction between exposure to estrogenic chemicals, such as BPA, with differential fetal growth using the crowded uterine horn model. The hypothesis is that abnormal "programming" of genes involved in the control of body weight homeostasis via epigenetic mechanisms can occur as a result of exposure to endocrine disrupting chemicals (Dolinoy et al., 2007). However, it is also clear that components of the diet cannot be ignored as factors in adult obesity and other associated diseases such as type 2 diabetes (Cederroth et al., 2007; Ruhlen et al., 2008).

4. Developmental exposure to environmental chemicals and adult obesity

The EDCs that impact obesity have been referred to as "obesogens" (Grun and Blumberg, 2007). These chemicals, which are used in a wide variety of products, are categorized as EDCs because they have been found to interfere with the functioning of the endocrine system by many different mechanisms. Recent data lend support to the "obesogen" hypothesis. The obesity epidemic is recent in origin and is related to increasing exposure to "man-made" chemicals in occupational and environmental settings (Baillie-Hamilton, 2002). Although such data are only correlational, this hypothesis is supported by experimental evidence showing a role for increased exposures to environmental chemicals in the etiology of obesity.

Many substances, including anabolic steroids and the estrogenic drug diethylstilbestrol (DES), have been used for decades to promote fattening and growth of farm animals; further, other chemicals, including organophosphate pesticides, carbamates, and

antithyroid drugs, cause obesity in animals (Baillie-Hamilton, 2002). There is also increasing evidence in animal models that *in utero* exposure to environmental chemicals at environmentally relevant concentrations alters developmental programming of adipose tissue and the gastrointestinal–hypothalamic food-intake regulatory system. The subsequent obesity observed in these models has been linked to irreversible alterations in tissue-specific function as a result of altered gene expression (Godfrey et al., 2007).

4.1. Nicotine

Smoking during pregnancy is an environmental factor that provides "proof-of-principle" for the role of developmental exposure to environmental insults in the etiology of obesity later in life. Maternal smoking during pregnancy is associated not only with low birth weight and intrauterine fetal growth retardation, but also causes complications in postnatal growth and development including a propensity to weight gain later in life (Toschke et al., 2002; Wideroe et al., 2003). Chronic administration to rats during gestation of low doses of nicotine (at doses that are relevant to human exposures due to smoking) or during gestation and neonatally, resulted in normal weight at birth but a significant increase in weight gain after birth (Holloway et al., 2005; Levin, 2005), as well as a significant increase in body fat (Williams and Kanagasabai, 1984); there is also altered glucose metabolism and metabolic changes associated with type 2 diabetes, characterized by beta cell apoptosis and loss of beta cell mass. Since hypothalamic control of appetite is likely influenced during the fetal and neonatal period, exposure to environmental agents like nicotine that affect hypothalamic development may alter appetite set-points and contribute to programming of adult obesity. Approximately 20% of pregnant women smoke, so this remains a major public health problem, and one that is modifiable to reduce the risk of developing obesity.

4.2. Estrogenic chemicals

Our focus has been primarily on the enigmatic role of environmental estrogens as obesogens, since in adulthood, exposure to endogenous estrogen or manmade estrogens such as BPA is associated with reduced body weight (Cooke and Naaz, 2004; Nunez et al., 2001), while after menopause and the marked decrease in ovarian estrogen, body weight typically increases. In contrast to its effects in adulthood prior to old age, exposure to estrogenic chemicals, such as BPA and the estrogenic drug DES, during fetal/neonatal life in mice (equivalent to fetal life in humans) results in a subsequent increase in body weight (Howdeshell et al., 1999; Newbold et al., 2007). It should be noted that in epidemiological studies, levels of BPA are positively related to body weight in people, although this may reflect the increased depot of BPA, which is a lipophilic compound, in fat in obese people (Takeuchi et al., 2004; Lang et al., 2008; Stahlhut et al., 2009).

Mouse preadipocytes are located in blood vessels (Tang et al., 2008), and both human and mouse preadipocytes and adipocytes express nuclear estrogen receptors (ERα and ERβ). During development, estrogen is implicated in an increase in adipocyte number as well as subsequent effects on adipocyte function (Cooke and Naaz, 2004). In addition to endogenous estrogen, exposure (at human exposure levels) of rats and mice to estrogenic chemicals used in household products during fetal/neonatal organogenesis can alter differentiation of adipocytes and create functional changes in body weight homeostasis that only become apparent after birth. For example, exposure during fetal or neonatal development to low doses of BPA, which is used to make polycarbonate plastic and the lining of cans as well as in many other products, increases the rate of postnatal growth and obesity in mice and rats (Akingbemi et al., 2004; Howdeshell et al., 1999; Markey et al., 2003, 2001; Miyawaki et al., 2007; Nikaido et al., 2004; Rubin et al., 2001; Takai et al., 2000). Furthermore, BPA has been shown *in vitro* to increase glucose transport in preadipocytes (Sakurai et al., 2004), and in combination with insulin, to increase conversion of mouse 3T3-L1 fibroblasts into adipocytes while also increasing lipoprotein lipase activity and triacylglycerol accumulation (Masuno et al., 2002), although these *in vitro* effects in a mouse fibroblast cell line required concentrations higher than those found in human serum, possibly due to the relatively low sensitivity of this cell line to any estrogen.

Exposure to BPA during fetal/neonatal life thus has a similar effect on adult body weight as does exposure during development to low doses of DES. Low doses of DES (1 μg/(kg day)), either prenatal or neonatal, caused an increase in body weight of CD-1 mice that was not evident at birth but reached significance by 6 weeks of age. At 16 weeks of age, DES exposed animals had 27.6% body fat compared to controls with 20.9% body fat (Newbold et al., 2005). The DES-treated mice thus had excessive abdominal fat, which is associated with cardiovascular disease and diabetes in humans (Newbold et al., 2007). These mice also had elevated levels of leptin, adiponectin, IL-6 and triglycerides that actually developed before the obesity was apparent. Increased leptin levels may be due to altered leptin programming due to chemical exposure.

Other chemicals that mimic estrogens in that they bind to and activate nuclear estrogen receptors and also result in obesity when exposure occurs during development, include the heavy metal cadmium, used as a stabilizer in PVC plastic (Batzer, 1983). Cadmium exposure is associated with both obesity and type 2 diabetes (Haswell-Elkins et al., 2008). It has been surprising to learn that cadmium mimics the action of estradiol via binding to estrogen receptors, and the effects can be inhibited by co-administration of the estrogen-receptor blocker ICI-182,780 (Johnson et al., 2003). Neonatal exposure to other estrogens, such as 2OH-estradiol, 4OH-estradiol, and the naturally occurring phytoestrogen genistein (an estrogenic component of soy that acts primarily via ERβ in adipocytes) also caused a significantly increased body weight at 4 months of age in mice (Newbold et al., 2007).

The effects of soy phytoestrogens such as genistein are complex and depend on the dose and timing of the exposure. For example, the complete absence of phytoestrogens from the diet of rats and mice results in adult obesity and other aspects of metabolic syndrome (Atanassova et al., 2000; Cederroth et al., 2007; Ruhlen et al., 2008), indicating an important role for phytoestrogens in preventing obesity, at least in some rodent models. Since the amount of phytoestrogens in soy-based feed can vary dramatically while the amount of protein is held constant, controlling the amount of phytoestrogens in soy-based feed is required for consistency of results in rodent studies, while completely eliminating phytoestrogens from the feed, which might seem to be a reasonable solution, actually dramatically interferes with the ability to study the factors involved in obesity in rodents (Heindel and vom Saal, 2008).

An interesting recent finding is that BPA and genistein have opposite effects on gene methylation during fetal life in mice. Specifically, BPA resulted in hypomethylation at a specific locus in the viable yellow agouti mouse, while concurrent treatment with genistein negated this effect. Furthermore, mice prenatally exposed to BPA became obese while genistein exposure countered development of an obese phenotype (Dolinoy et al., 2007). Similar to the findings with genestein and BPA, genistein blocked the effects of cadmium in some tissues (Paik et al., 2003). While the significance of these findings for the aetiology of human obesity is not clear, what is important is that these agents that can cause obesity can also alter epigenetic marks at specific loci. While there are few data at this time, our hypothesis concerning the etiology of obesity proposes that an important mechanism by which environmental chemicals impact obesity is via alterations in gene

expression resulting from epigenetic programming of gene activity during development.

4.3. Other obesogens

Developmental exposures to other environmental chemicals have also been linked with obesity. Lead, in addition to causing brain damage as a result of exposure during development, also results in late-onset obesity in male mice (Leasure et al., 2008).

Organotins are persistent and ubiquitous chemicals found as contaminants in fish and shellfish, food crops, and wood (due to antifungal treatment). Organotin compounds are also stabilizers of polyolefin plastics. All of these uses can lead to significant human exposures. Organotins are a potentially new class of EDCs that impact adipogenesis via targeting key transcription factors in the adipogenic pathway. Specifically, *in utero* exposure to tributyltin leads to strikingly elevated lipid accumulation in adipose tissue, liver and testis of neonate mice, and results in increased gonadal (abdominal) adipose mass in adults (Grun et al., 2006). Organotins also stimulate an increase in the differentiation of adipocytes *in vitro*. The mechanism by which organotins impact adipocytes is by acting as a potent dual affinity ligand for the retinoid (RXR) receptor and peroxisome proliferation activated receptor gamma (PPARγ), which play important roles in adipocyte differentiation and energy balance. Subsequent to adipocyte differentiation, these transcription factors increase the expression of genes that promote fatty acid storage and decrease expression of genes that induce lipolysis; as a result, they promote insulin sensitivity and increase fat cell mass via increased triglyceride storage. The effects of tribuyltin on adipogenesis are observed in mice at dose levels within the range of human exposures (Grun et al., 2006).

In summary, there are a growing number of environmental chemicals that when administered during development have been shown in animal models to result in obesity later in life. It is therefore likely that obesity can occur due to altered nutrition as well as exposure to environmental chemicals during development via programming of the activity of specific genes. If further research shows this to be true, then the focus on obesity should be changed to prevention by reducing environmental stressors (chemical exposures and nutrition) during development, rather than intervention only after obesity has occurred.

Since we know that there are several environmental chemicals that can cause obesity in offspring when exposure occurs during gestation, and that all of these chemicals are found in humans from biomonitoring studies, it seems logical that a prudent approach to understanding the role of environmental chemicals in obesity would be to study the effects of the mixtures of naturally occurring and manmade chemicals that are found in the majority of people, rather than taking the traditional toxicological/regulatory approach of examining the effects of each chemical one at a time. Studies of effects of mixtures have the potential to yield unexpected outcomes (Kortenkamp, 2008). Also, the components of the diets used in laboratory animal research (and the type of nutrients human infants and children are fed) are clearly also a major factor that many researchers have not taken into account in terms of the interaction of components of food with environmental chemicals. Furthermore, it is not only the chemicals directly added to food but chemicals that are "indirect food additives",which get into food by leaching out of products that food and beverages are stored in, that are a concern. A prime example is BPA, which is used in polycarbonate reusable food and beverage storage containers and the resin lining of cans, which can lead to substantial levels of human exposure (Vandenberg et al., 2007; vom Saal and Hughes, 2005). Finally, we consider it likely that as more chemicals are examined for effects of exposure during development on subsequent obesity, the list of "obesogens" will continue to grow (Fig. 2).

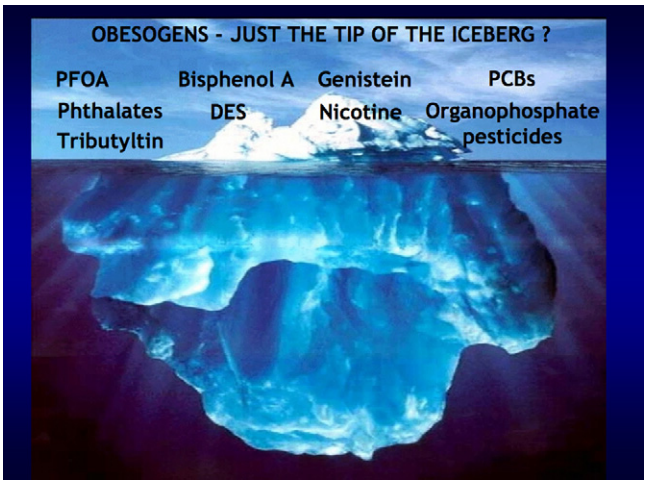

Fig. 2. The "tip of the iceberg" indicates that while there is evidence that exposure during development to a few endocrine disrupting chemicals results in obesity in laboratory animals studies, only a few chemicals have been studied. It is thus possible that many more chemicals will be found to impact obesity.

5. Conclusions

The issues facing biomedical researchers investigating the causes of obesity are obviously multi-faceted and complex. However, new findings are beginning to shift the focus from the simplistic notion that adult obesity can be understood and controlled by focusing only on energy intake and expenditure. There is now compelling evidence that factors that impact fetal growth are related to postnatal growth rate and adult body weight in humans (Barker, 2004) and laboratory animals (Coe et al., 2008). While the realization that obesity is related to factors in early development is a step in the right direction, the biomedical community has yet to embrace the hypothesis that in addition to nutritional impacts on fetal growth, environmental endocrine disrupting chemicals can act as "obesogens" that can permanently derange developing regulatory systems required for body weight homeostasis.

If this hypothesis concerning the developmental origins and the role of environmental chemicals in the aetiology of obesity is supported by additional research, as we expect it will be, then there would be significant public health implications. This hypothesis changes the focus from treatment of children and adults to prevention during early development. It also changes the focus from classical genetics to epigenetics and to nutrition and environmental chemical exposures during development; most importantly, it changes the focus from intervention to prevention. Our prediction is that the focus should be on pregnancy and infancy, and possibly also early childhood through puberty, as sensitive periods for the development of obesity. Thus, the focus should be on improving nutrition and prevention of exposure to environmental chemicals during vulnerable windows in development.

The optimistic view is that if the chemicals that are related to the obesity epidemic are able to be removed from products that are the primary contributors to human exposures, there would be reason to hope that the current trend of increasing obesity can be reversed.

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References

Ahima, R.S., 2005. Central actions of adipocyte hormones. Trends Endocrinol. Metab. 16 (7), 307–313.

Akingbemi, B.T., Sottas, C.M., Koulova, A.I., Klinefelter, G.R., Hardy, M.P., 2004. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. Endocrinology 145 (2), 592–603.

Atanassova, N., McKinnell, C., Turner, K.J., Walker, M., Fisher, J.S., Morley, M., et al., 2000. Comparative effects of neonatal exposure of male rats to potent and weak (environmental) estrogens on spermatogenesis at puberty and the relationship to adult testis size and fertility: evidence for stimulatory effects of low estrogen levels. Endocrinology 141, 3898–3907.

Baillie-Hamilton, P.F., 2002. Chemical toxins: a hypothesis to explain the global obesity epidemic. J. Altern. Complem. Med. 8, 185–192.

Barker, D.J., 2004. The developmental origins of adult disease. J. Am. Coll. Nutr. 23 (Suppl 6), 588S–595S.

Batzer, H., 1983. Use and possibilities for substitution of cadmium stabilizers. Ecotoxicol. Environ. Safe. 7 (1), 117–121.

Boney, C.M., Verma, A., Tucker, R., Vohr, B.R., 2005. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 115 (3), e290–e296.

Bouret, S.G., Simerly, R.B., 2007. Development of leptin-sensitive circuits. J. Neuroendocrinol. 70, 295–301.

Cederroth, C.R., Vinciguerra, M., Kuhne, F., Madani, R., Doerge, D.R., Visser, T.J., et al., 2007. A phytoestrogen-rich diet increases energy expenditure and decreases adiposity in mice. Environ. Health Perspect. 115 (10), 1467–1473.

Coe, B.L., Kirkpatrick, J.R., Taylor, J.A., vom Saal, F.S., 2008. A new 'crowded uterine horn' mouse model for examining the relationship between foetal growth and adult obesity. Basic Clin. Pharmacol. Toxicol. 102 (2), 162–167.

Cooke, P.S., Naaz, A., 2004. Role of estrogens in adipocyte development and function. Exp. Biol. Med. 229 (11), 1127–1135.

Cooney, C.A., Dave, A.A., Wolff, G.L., 2002. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. J. Nutr. 132 (8 (Suppl)), 2393S–2400S.

Dolinoy, D.C., Huang, D., Jirtle, R.L., 2007. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc. Natl. Acad. Sci. 104 (32), 13056–13061.

Even, M.D., Laughlin, M.H., Krause, G.F., vom Saal, F.S., 1994. Differences in blood flow to uterine segments and placentae in relation to sex, intrauterine location and side in pregnant rats. J. Reprod. Fertil. 102, 245–252.

Gluckman, P.D., Hanson, M.A., Beedle, A.S., 2007. Early life events and their consequences for later disease: a life history and evolutionary perspective. Am. J. Hum. Biol. 19 (1), 1–19.

Godfrey, K.M., Lillycrop, K.A., Burdge, G.C., Gluckman, P.D., Hanson, M.A., 2007. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. Pediatr. Res. 61 (5 Pt 2), 5R–10R.

Grun, F., Blumberg, B., 2007. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev. Endocr. Metab. Disord. 8 (2), 161–171.

Grun, F., Watanabe, H., Zamanian, Z., Maeda, L., Arima, K., Cubacha, R., et al., 2006. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. Mol. Endocrinol. 20 (9), 2141–2155.

Hales, C.N., Barker, D.J.P., 1992. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35, 595–601.

Haswell-Elkins, M., Satarug, S., O'Rourke, P., Moore, M., Ng, J., McGrath, V., et al., 2008. Striking association between urinary cadmium level and albuminuria among Torres Strait Islander people with diabetes. Environ. Res. 106 (3), 379–383.

Hedley, A.A., Ogden, C.L., Johnson, C.L., Carroll, M.D., Curtin, L.R., Flegal, K.M., 2004. Prevalence of overweight and obesity among US children, adolescents, and adults 1999–2002. J. Am. Med. Assoc. 291 (23), 2847–2850.

Heindel, J.J., 2007. Role of exposure to environmental chemicals in the developmental basis of disease and dysfunction. Reprod. Toxicol. 23 (3), 257–259.

Heindel, J.J., 2008. Animal models for probing the developmental basis of disease and dysfunction paradigm. Basic Clin. Pharmacol. Toxicol. 102 (2), 76–81.

Heindel, J.J., vom Saal, F.S., 2008. Meeting report: batch-to-batch variability in estrogenic activity in commercial animal diets—importance and approaches for laboratory animal research. Environ. Health Perspect. 116 (3), 389–393.

Ho, S.M., Tang, W.Y., Belmonte de Frausto, J., Prins, G.S., 2006. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res. 66 (11), 5624–5632.

Holloway, A.C., Lim, G.E., Petrik, J.J., Foster, W.G., Morrison, K.M., Gerstein, H.C., 2005. Fetal and neonatal exposure to nicotine in Wistar rats results in increased beta cell apoptosis at birth and postnatal endocrine and metabolic changes associated with type 2 diabetes. Diabetologia 48 (12), 2661–2666.

Howdeshell, K.L., Hotchkiss, A.K., Thayer, K.A., Landenberg, J.G., vom Saal, F.S., 1999. Exposure to bisphenol A advances puberty. Nature 401, 763–764.

Johnson, M.D., Kenney, N., Stoica, A., Hilakivi-Clarke, L., Singh, B., Chepko, G., et al., 2003. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nat. Med. 9 (8), 1081–1084.

Keith, S.W., Redden, D.T., Katzmarzyk, P.T., Boggiano, M.M., Hanlon, E.C., Benca, R.M., et al., 2006. Putative contributors to the secular increase in obesity: exploring the roads less traveled. Int. J. Obes. 30 (11), 1585–15894.

Kortenkamp, A., 2008. Low dose mixture effects of endocrine disrupters: implications for risk assessment and epidemiology. Int. J. Androl. 31 (2), 233–240.

Lang, I.A., Galloway, T.S., Scarlett, A., Henley, W.E., Depledge, M., Wallace, R.B., et al., 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults: evidence from NHANES 2003/4. J. Am. Med. Assoc. 300 (11), 1303–1310.

Leasure, J.L., Giddabasappa, A., Chaney, S., Johnson Jr., J.E., Pothakos, K., Lau, Y.S., et al., 2008. Low-level human equivalent gestational lead exposure produces sex-specific motor and coordination abnormalities and late-onset obesity in year-old mice. Environ. Health Perspect. 116 (3), 355–361.

Lee, H.K., Park, K.S., Cho, Y.M., Lee, Y.Y., Pak, Y.K., 2005. Mitochondria-based model for fetal origin of adult disease and insulin resistance. Ann. N.Y. Acad. Sci. 1042, 1–18.

Levin, E.D., 2005. Fetal nicotinic overload, blunted sympathetic responsivity, and obesity. Birth Defects Res. A: Clin. Mol. Teratol. 73 (7), 481–484.

Mantzoros, C.S., Rifas-Shiman, S.L., Williams, C.J., Fargnoli, J.L., Kelesidis, T., Gillman, M.W., 2009. Cord blood leptin and adiponectin as predictors of adiposity in children at 3 years of age: a prospective cohort study. Pediatrics 123, 682–689.

Markey, C.M., Coombs, M.A., Sonnenschein, C., Soto, A.M., 2003. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs. Evol. Dev. 5 (1), 67–75.

Markey, C.M., Michaelson, C.L., Veson, E.C., Sonnenschein, C., Soto, A.M., 2001. The mouse uterotrophic assay: a reevaluation of its validity in assessing the estrogenicity of bisphenol A. Environ. Health Perspect. 109 (1), 55–60.

Martorell, R., Stein, A.D., Schroeder, D.G., 2001. Early nutrition and later adiposity. J. Nutr. 131 (3), 874S–880S.

Masuno, H., Kidani, T., Sekiya, K., Sakayama, K., Shiosaka, T., Yamamoto, H., et al., 2002. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. J. Lipid Res. 43, 676–684.

Miller, K.P., Borgeest, C., Greenfeld, C., Tomic, D., Flaws, J.A., 2004. In utero effects of chemicals on reproductive tissues in females. Toxicol. Appl. Pharmacol. 198 (2), 111–131.

Miyawaki, J., Sakayama, K., Kato, H., Yamamoto, H., Masuno, H., 2007. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. J. Atheroscler. Thromb. 14 (5), 245–252.

Newbold, R., Padilla-Banks, E., Snyder, R., Jefferson, W.N., 2005. Developmental exposure to estrogenic compounds and obesity. Birth Defects Res. 73, 478–480.

Newbold, R.R., Padilla-Banks, E., Jefferson, W.N., Heindel, J.J., 2008. Effects of endocrine disruptors on obesity. Int. J. Androl. 31 (2), 201–208.

Newbold, R.R., Padilla-Banks, E., Snyder, R.J., Jefferson, W.N., 2007. Perinatal exposure to environmental estrogens and the development of obesity. Mol. Nutr. Food Res. 51 (7), 912–917.

Nikaido, Y., Yoshizawa, K., Danbara, N., Tsujita-Kyutoku, M., Yuri, T., Uehara, N., et al., 2004. Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. Reprod. Toxicol. 18 (6), 803–811.

Nunez, A.A., Kannan, K., Giesy, J.P., Fang, J., Clemens, L.G., 2001. Effects of bisphenol A on energy balance and accumulation in brown adipose tissue in rats. Chemosphere 42, 917–922.

Oken, E., Gillman, M.W., 2003. Fetal origins of obesity. Obes. Res. 11, 496–506.

Paik, M.K., Lee, H.O., Chung, H.S., Yang, S.O., Kim, J.H., Om, A.S., 2003. Genistein may prevent cadmium-induced bone loss in ovariectomized rats. J. Med. Food 6 (4), 337–343.

Rubin, B.S., Murray, M.K., Bamassa, D.A., King, J.C., Soto, A.M., 2001. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environ. Health Perspect. 109, 657–680.

Ruhlen, R.L., Howdeshell, K.L., Mao, J., Taylor, J.A., Bronson, F.H., Newbold, R.R., et al., 2008. Low phytoestrogen levels in feed increase fetal serum estradiol resulting in the "fetal estrogenization syndrome" and obesity in CD-1 mice. Environ. Health Perspect. 116 (3), 322–328.

Sakurai, K., Kawazuma, M., Adachi, T., Harigaya, T., Saito, Y., Hashimoto, N., et al., 2004. Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. Br. J. Pharmacol. 141 (2), 209–214.

Stahlhut, R.W., Welshons, W.V., Swan, S.H., 2009. Bisphenol A data in NHANES suggest longer than expected half-life, substantial non-food exposure, or both. Environ. Health Perspect., doi:10.1289/ehp.0800376 (available at http://dx.doi.org/) Online 28 January 2009.

Takeuchi, T., Tsutsumi, O., Ikezuki, Y., Takai, Y., Taketani, Y., 2004. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocr. J. 51 (2), 165–169.

Takai, Y., Tsutsumi, O., Ikezuki, Y., Kamei, Y., Osuga, Y., Yano, T., et al., 2000. Preimplantation exposure to bisphenol A advances postnatal development. Reprod. Toxicol. 15, 71–74.

Tang, W., Daniel Zeve, D., Suh, J.M., Bosnakovski, D., Kyba, M., Hammer, R.E., et al., 2008. White fat progenitor cells reside in the adipose vasculature. Science 322, 573–586.

Toschke, A.M., Koletzko, B., Slikker Jr., W., Hermann, M., von Kries, R., 2002. Childhood obesity is associated with maternal smoking in pregnancy. Eur. J. Pediatr. 161 (8), 445–448.

Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol A (BPA). Reprod. Toxicol. 24 (2), 139–177.

vom Saal, F.S., Hughes, C., 2005. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environ. Health Perspect. 113, 926–933.

Waterland, R.A., Jirtle, R.L., 2003. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol. Cell Biol. 23, 5293–5300.
Waterland, R.A., Michels, K.B., 2007. Epigenetic epidemiology of the developmental origins hypothesis. Annu. Rev. Nutr. 27, 363–388.
Welshons, W.V., Nagel, S.C., vom Saal, F.S., 2006. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at human exposure levels. Endocrinology 147 (6 (Suppl)), S56–S69.
Welshons, W.V., Thayer, K.S., Taylor, J., Judy, B., vom Saal, F.S., 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ. Health Perspect. 111, 106–904.
Wideroe, M., Vik, T., Jacobsen, G., Bakketeig, L.S., 2003. Does maternal smoking during pregnancy cause childhood overweight? Paediatr. Perinat. Epidemiol. 17 (2), 171–179.
Williams, C.M., Kanagasabai, T., 1984. Maternal adipose tissue response to nicotine administration in the pregnant rat: effects on fetal body fat and cellularity. Br. J. Nutr. 51 (1), 7–13.
Yajnik, C.S., 2001. Fetal origins of adult disease: where do we stand? Int. J. Diab. Dev. Countries 21, 42–50.
Yura, S., Itoh, H., Sagawa, N., Yamamoto, H., Masuzaki, H., Nakao, K., et al., 2005. Role of premature leptin surge in obesity resulting from intrauterine undernutrition. Cell Metab. 1 (6), 371–378.