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Review

Transgenerational inheritance of prenatal obesogen exposure

Amanda S. Janesick [a], Toshihiro Shioda [b], Bruce Blumberg [a,c,*]

[a] Department of Developmental and Cell Biology, University of California, 2011 Biological Sciences 3, Irvine, CA 92697-2300, United States
[b] Center for Cancer Research, Massachusetts General Hospital, Bldg 149, 13th Street, Charlestown, MA 02129, United States
[c] Department of Pharmaceutical Sciences, University of California, Irvine, United States

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ABSTRACT

Obesity and metabolic syndrome diseases have exploded into an epidemic of global proportions. The generally accepted cause of obesity is overconsumption of calorie-dense food and diminished physical activity (the calories in–calories out model). However, emerging evidence demonstrates that environmental factors can predispose exposed individuals to gain weight, irrespective of diet and exercise. The environmental obesogen model proposes that chemical exposure during critical stages in development can influence subsequent adipogenesis, lipid balance and obesity. Obesogens are chemicals that inappropriately stimulate adipogenesis and fat storage. Numerous obesogens have been identified in recent years and some of these have been shown to act through the peroxisome proliferator activated receptor gamma, the master regulator of adipogenesis. Others act through as yet unidentified pathways. Notably, some of these obesogens elicit transgenerational effects on a variety of health endpoints, including obesity in offspring after exposure of pregnant F0 females. Thus, prenatal exposure to xenobiotic compounds can have lasting, potentially permanent effects on the offspring of exposed animals. Transgenerational effects of chemical exposure raise the stakes in the debate about whether and how endocrine disrupting chemicals should be regulated.

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1. Obesity is a growing problem

Obesity and related disorders are a public health epidemic, particularly in the U.S. Currently more than 35% of the U.S. population is clinically obese (body mass index – BMI > 30) and 68% are overweight (BMI > 25). These figures are more than double the worldwide average and 10-fold higher than the rates in Japan and South Korea (Flegal et al., 2010; Ogden et al., 2014). Obesity and obesity-related disorders impose an estimated $208 billion annual burden on the U.S. health care system (Cawley and Meyerhoefer, 2012), and childhood obesity can cost more than $30,000 over the lifetime of an obese child (Finkelstein et al., 2014). Genetics (Herbert, 2008) and behavioral factors such as smoking (Power and Jefferis, 2002), stress (Garruti et al., 2008), a sedentary lifestyle (Rippe and Hess, 1998) and excessive consumption of food (Hill and Peters, 1998) are the typically cited causes of obesity. However, environmental factors such as sleep disruption (Watenpaugh, 2009), light pollution (Fonken et al., 2013), viral infection (Mitra and Clarke, 2010;

* Corresponding author. Department of Developmental and Cell Biology, 2011 Biological Sciences 3, University of California, Irvine, CA 92697-2300, United States. Tel.: 949-824-8573; fax: 949-824-4709.
E-mail address: blumberg@uci.edu (B. Blumberg).

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van Ginneken et al., 2009), the composition of gut bacteria flora (Ley et al., 2005, 2006) and exposure to xenobiotic chemicals (Janesick and Blumberg, 2011) are emerging as significantly contributing factors to obesity. These environmental factors may interact with genetic or lifestyle factors to exacerbate the effects of diet and exercise, calling for a reassessment of the favored "calories in–calories out" model of obesity.

2. New approaches are needed

An alarming recent trend is the high rate of obesity in very young children, including infants (Koebnick et al., 2010; McCormick et al., 2010; Taveras et al., 2009). At least one study suggests that the rate of childhood obesity is reaching a plateau in some Western countries (Ogden et al., 2014), but this view is currently controversial. While one can argue that present-day children, adolescents and adults may be eating more and exercising less than in the past, this is unlikely to apply to infants. A typical infant eats until satiation and exercises very little; therefore, it is implausible that changes in caloric expenditure in infants have contributed to obesity at a young age. A more likely explanation is that the prenatal environment causes these overweight or obese infants to be born with more fat, to be predisposed to accumulate fat easily and/or that the early postnatal environment has changed significantly in recent years. In support of this hypothesis, a recent study showed that animals living in proximity to humans (pets – cats and dogs; laboratory animals – rats, mice, four species of primates; and feral rats) in industrialized societies exhibited pronounced increases in obesity over the past several decades (Klimentidis et al., 2011). While one could argue that our companion animals are pampered, overfed and under-exercised, the obese animal populations included laboratory animals living in strictly controlled environments, as well as feral animals living in cities (Klimentidis et al., 2011). The likelihood of 24 animal populations from eight different species all showing a positive trend in weight over the past few decades by chance was estimated at about 1 in 10 million (1.2×10^{-7}) – a vanishingly small possibility that this is a chance occurrence (Klimentidis et al., 2011). The most reasonable conclusion is that something has changed in the dwelling environment of these animals, making them obese in parallel with humans.

3. The obesogen hypothesis

In 2006, we proposed the existence of endocrine disrupting chemicals (EDCs) that could influence adipogenesis and cause obesity in animals and humans. This group of EDCs may be important, yet unsuspected players in the obesity epidemic. We define "obesogens" functionally as chemicals that promote obesity by increasing the number of fat cells and/or the storage of fat into existing adipocytes. Obesogens can also act indirectly to promote obesity by changing basal metabolic rate, by shifting energy balance to favor calorie storage, by promoting food storage via gut microbiota (Snedeker and Hay, 2012), and by altering hormonal control of appetite and satiety (Blumberg, 2011; Heindel, 2011; Janesick and Blumberg, 2011; La Merrill and Birnbaum, 2011; Newbold, 2011). Several obesogenic chemicals have been identified in recent years, underscoring the relevance of this new model. Estrogenic EDCs such as diethylstilbestrol (DES) (Newbold et al., 2009), bisphenol A (BPA) (Rubin, 2011; Rubin et al., 2001) and DDT (Skinner et al., 2013), organotins such as tributyltin (TBT) (Chamorro-Garcia et al., 2013; Grun et al., 2006), perfluorooctanoates (Hines et al., 2009) and phthalates (Hao et al., 2012, 2013; Manikkam et al., 2013) are obesogenic in animals. Urinary phthalate levels were correlated with increased waist diameter (Hatch et al., 2008; Stahlhut et al., 2007) and high levels of several persistent organic pollutants (e.g., DDE, HCB, polybrominated diphenylethers) were linked with obesity in humans (Tang-Peronard et al., 2011). Because this topic has been extensively reviewed in recent years, this review will focus on transgenerational effects of obesogenic chemicals and potential mechanisms through which they might act.

4. How do obesogens act?

The only obesogens with an unambiguously demonstrated pathway of action are TBT, and by implication triphenyltin (TPT). TPT is widely used in agriculture and TBT in industry. Human exposure to organotins occurs through dietary sources (seafood and shellfish), from organotin use as fungicides and miticides on food crops, in wood treatments, industrial water systems, textiles, and via leaching of organotin-stabilized PVC from water pipes, food wrap and other plastics (Golub and Doherty, 2004; Grun and Blumberg, 2006; Okoro et al., 2011). Organotins have also been found in appreciable levels in house dust, suggesting that exposure is widespread (Kannan et al., 2010). TBT and TPT are high-affinity ligands for two nuclear receptors critical for adipocyte development: the 9-cis retinoic acid receptor (RXR) and peroxisome proliferator activated receptor gamma (PPARγ), in vitro and in vivo (Grun et al., 2006; Kanayama et al., 2005). TBT promotes adipogenesis in murine 3T3-L1 pre-adipocytes (Grun et al., 2006; Kanayama et al., 2005) and in human and mouse multipotent mesenchymal stromal cells (MSCs, a.k.a. mesenchymal stem cells) via a PPARγ-dependent pathway (Kirchner et al., 2010; Li et al., 2011). In utero TBT exposure leads to strikingly elevated lipid accumulation in adipose depots, liver, and testis of neonate mice and increased adipose depot mass in adult mice (Chamorro-Garcia et al., 2013; Grun et al., 2006). Exposure of adolescent or adult mice to TBT causes increased fat depot size, accumulation of lipids in the liver and insulin resistance (Zuo et al., 2011, 2014). Placental TBT levels are positively correlated with weight gain in human male infants at 3 months of age (Rantakokko et al., 2014). Thus, although more data are needed, TBT exposure is associated with weight gain both in animals and in humans.

5. Adipogenesis in a nutshell

Adipogenesis is a differentiation event in the mesodermal lineage wherein MSCs and their more lineage-restricted derivatives give rise to adipocytes, both during development and to maintain fat cell number in adulthood (Cristancho and Lazar, 2011; Rosen and MacDougald, 2006). MSCs are thought to reside largely in the perivascular niche of most organs (Crisan et al., 2008) and some authors have suggested that they are identical to pericytes that surround most blood vessels (Crisan et al., 2008, 2009). MSC/pericytes can give rise to a variety of cell types in culture (adipose, bone, cartilage, muscle, etc.) upon stimulation with specific differentiation cocktails (Bianco, 2011). It is currently unclear whether MSC/pericytes located in different tissues normally have a restricted lineage differentiation potential in vivo, or whether they have the same broad lineage potential, in vivo, as they appear to have, in vitro (Bianco, 2011).

While many studies have demonstrated how cells already committed to the adipocyte lineage differentiate into mature adipocytes (Tontonoz and Spiegelman, 2008), we know much less about the mechanisms and intermediates through which MSCs become committed to the adipocyte lineage (Rosen and Spiegelman, 2014) and how this process might be influenced by EDCs. Bone morphogenic proteins (BMPs), Wnt, and PI3K/Akt signaling are important parts of the adipocyte commitment pathway, probably mediated by the expression of genes such as Zfp423 (Gupta et al., 2010), Zfp521 (Kang et al., 2012), TCF7-like 1 (Cristancho and Lazar, 2011), and S6K1 (Carnevalli et al., 2010). MSCs give rise to both adipocytes and osteoblasts; the commitment to one or the other lineage is mutually exclusive (Shockley et al., 2007). Expression of PPARγ commits cells to the adipogenic lineage whereas Wnt signaling inhibits PPARγ