Hormones and Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Our stolen figures: The interface of sexual differentiation, endocrine disruptors, maternal programming, and energy balance

Jill E. Schneider [a,*], Jeremy M. Brozek [a], Erin Keen-Rhinehart [b]

[a] Lehigh University, Department of Biological Sciences, Bethlehem, PA 18015, USA
[b] Susquehanna University, Department of Biological Sciences, Selinsgrove, PA 17870, USA

ARTICLE INFO

Available online xxxx

Keywords:
Adiposity
Ingestive behavior
Obesity
Food intake
Bisphenol A
Diethylstilbestrol

ABSTRACT

This article is part of a Special Issue "Energy Balance".

The prevalence of adult obesity has risen markedly in the last quarter of the 20th century and has not been reversed in this century. Less well known is the fact that obesity prevalence has risen in domestic, laboratory, and feral animals, suggesting that all of these species have been exposed to obesogenic factors present in the environment. This review emphasizes interactions among three biological processes known to influence energy balance: Sexual differentiation, endocrine disruption, and maternal programming. Sexual dimorphisms include differences between males and females in body weight, adiposity, adipose tissue distribution, ingestive behavior, and the underlying neural circuits. These sexual dimorphisms are controlled by sex chromosomes, hormones that masculinize or feminize adult body weight during perinatal development, and hormones that act during later periods of development, such as puberty. Endocrine disruptors are natural and synthetic molecules that attenuate or block normal hormonal action during these same developmental periods. A growing body of research documents effects of endocrine disruptors on the differentiation of adipocytes and the central nervous system circuits that control food intake, energy expenditure, and adipose tissue storage. In parallel, interest has grown in epigenetic influences, including maternal programming, the process by which the mother's experience has permanent effects on energy-balancing traits in the offspring. This review highlights the points at which maternal programming, sexual differentiation, and endocrine disruption might dovetail to influence global changes in energy balancing traits.

Contents

* Corresponding author at: Department of Biological Sciences, 111 Research Drive, Bethlehem, PA 18015, USA. Fax: +1 610 758 4004.
E-mail address: js0v@lehigh.edu (J.E. Schneider).

http://dx.doi.org/10.1016/j.yhbeh.2014.03.011

Introduction

A global rise in the incidence of adult obesity has occurred over the past 150 years, with a slow and steady increase prior to 1970 and a sharp rise between the years 1970 and 2000 (Bundred et al., 2001; Flegal et al., 1998, 2002, 2010; Ogden et al., 1997, 2006, 2007). In spite of well publicized government guidelines, medical advice, and a proliferation of diet books, weight-watcher's programs, prescription diet pills, "fat-burning" herbs, and "appetite suppressing" supplements (Taubes, 2007), the prevalence of obesity remains high. Despite recent reports by the news media that childhood obesity has decreased significantly in the last decade (e.g., Tavernise, 2014), the Centers for Disease Control and Prevention (CDC) concludes that "Overall, there have been no significant changes in obesity prevalence in youth or adults between 2003–2004 and 2011–2012. Obesity prevalence remains high and thus it is important to continue surveillance." This quote is from the same CDC report that provoked the optimistic news media headlines about the putative decrease in childhood obesity (Ogden et al., 2014). Thus, more than a decade into the 21st century, the high incidence of obesity has not reversed (Ogden et al., 2013, 2014).

The relatively rapid rate of increase in body weight and the failure to reverse the high incidence of obesity present a challenging puzzle with many missing pieces. Some of the important pieces of this puzzle are in place, whereas others have yet to be fully appreciated and integrated with the other pieces.

For many years, the focus has been on three factors: Genetic influences, diet, and sedentary behavior. This review will emphasize three overlapping biological processes that interact with these factors: Sexual differentiation, maternal programming, and endocrine disruption. We begin with a very brief review of the role of genes, diet, and exercise, noting that global obesity patterns are not explained by these factors alone. Other evidence suggests the existence of widespread environmental obesogen acting on humans, laboratory rodents and nonhuman primates, domestic animals, and even feral animals. We therefore discuss endocrine disrupting compounds, natural and synthetic molecules from the environment that interfere with endocrine processes, including energy balance and ingestive behavior (Auwerx, 1999). A clear understanding of their mechanism of action, however, requires that we understand sex differences in energy-balancing systems. In most species including our own, males differ from females in many energy-balancing characteristics. Some of these sexual dimorphisms are behavioral in that they involve caloric intake, diet preferences, the rewarding aspects of food, and central nervous system circuits that control these behaviors. Other sexual dimorphisms are morphological and physiological; they involve the distribution of adipose tissue, adipocyte differentiation, glucose homeostasis, and other peripheral systems. We discuss the significance of these sex differences and the importance of understanding how these differences come about. This brings us to the process of sexual differentiation, the process whereby physiological traits are either masculinized or feminized by sex chromosomes, hormones secreted perinatally, hormones secreted during other critical periods of development (e.g., puberty), and interactions among these factors. Reproductive biologists have defined multiple mechanisms involved in sexual differentiation and experimental designs that discriminate among them, but few have been employed in obesity research. Some of these mechanisms involve fetal steroid receptor action, and endocrine disruptors act on these same receptors. Thus, experimental approaches used in sexual differentiation research will be critical in understanding the effects of endocrine disruptors on obesity.

Using a few well-designed studies as examples, we connect four new pieces of the obesity puzzle. First, endocrine disruptors are ubiquitous in the environment (Baillie-Hamilton, 2002; Colborn et al., 1993; Simonich and Hites, 1995). Second, they affect energy balancing systems (Heindel, 2003; Mackay et al., 2013; Manikkam et al., 2013; Newbold et al., 2005; Oken and Gillman, 2003; Ruhlen et al., 2008; Skinner et al., 2013; Tracey et al., 2013; Vom Saal et al., 2012). Third, energy balancing phenotypes are sexually dimorphic in humans, with the masculine phenotype most closely linked to metabolic diseases such as type II diabetes and heart disease (Bonora, 2000; Kotani et al., 1994; Lemieux, 2001; Macotela et al., 2009; Wajchenberg, 2000). Fourth, endocrine disruptors have masculinizing effects on sexually dimorphic phenotypes, and might also act through other defined mechanisms of sexual differentiation (e.g., Mackay et al., 2013). We also explain how peripheral changes in lipogenesis, lipolysis, and fuel oxidation bring about changes in ingestive behavior. The remainder of the review examines the consequences for future generations. New information on the epigenetic effects of endocrine disruptors, their overlap with fetal programming (Manikkam et al., 2013; Skinner et al., 2013; Tracey et al., 2013), and their potential for unmasking cryptic genetic variation (Ledon-Rettig et al., 2008, 2009, 2010) provides plausible basis for hypothesizing that endocrine disruptors are responsible for the rapid increase in obesity at the end of the last millennium. Finally, we summarize and propose new research frontiers.

Genes, poor diet, and sedentary behavior cannot explain obesity

There is no doubt that genetic influences determine many aspects of energy balance, but does this mean that the rapid, sharp rise in human obesity can be explained by natural selection for obese phenotypes? We know of many single gene mutations that can influence various aspects of metabolism and ingestive behavior (Campfield et al., 1995; Farooqi et al., 1998; Geary et al., 2001; Halaas et al., 1995; Heine et al., 2000; Pelleymounter et al., 1995; Vaisse et al., 2000). Yet, point mutations or major genes cannot account for a large proportion of the variance in body weight (Garver et al., 2013; Hinney and Hebebrand, 2008; Rankinen et al., 2006). Human body weight is controlled by many genes that influence various aspects of body composition, eating behavior, and energy expenditure (Chaput et al., 2014). The sharpest rise in human obesity spans only a few decades. Given the large population size, long generation time, and a lack of a strong selective advantage for obesity in humans (Speakman, 2006), it seems unlikely that changes in gene frequencies alone can explain the recent sharp rise in global obesity.

Even studies aimed at documenting genetic influences on human obesity find strong evidence for the effects of diet and energy expenditure on body weight. The Quebec Family Study (QFS) was designed to estimate the extent of familial and genetic effects on energy balance using data from more than 700 families assessed between 1979 and 2002. The authors conclude that, "Unhealthy diet and physical inactivity are thus the two major factors … for obesity …. The influence of these "traditional" risk factors for obesity has been largely documented, including in the QFS." (Chaput et al., 2014).

Diet alone is not a good explanation for the recent global rise in obesity because many individuals fail to gain weight on putative obesogenic diets. In human or nonhuman animal populations, some individuals are predisposed toward body fat accumulation when exposed to obesogenic diets or after they end a period of calorie restriction, whereas other individuals are resistant to body weight gain under the same conditions (e.g., Akieda-Asai et al., 2013; Blundell and Cooling, 2000; Jackman et al., 2006; Ji and Friedman, 2007; Ji et al., 2005; Levin et al., 1987; Mutch et al., 2011; Pierce et al., 2010; Schemmel et al., 1970; Schmidt et al., 2013; and reviewed by Astrup, 2011; Blundell and Cooling, 1999; Levin, 2009). One explanation is genotype × environment interaction (e.g., Bouchard and Tremblay, 1990; Garver et al., 2013; Levin, 2009; Madsen et al., 2010; Martinez et al., 2003; Novak et al., 2006). Yet, in many populations, even those individuals on the lower end of the body weight spectrum are beginning to gain weight (Lustig, 2006). Thus, if there is a susceptible phenotype, we must ask, "Is the incidence of this susceptible phenotype on the rise, and if so, why?"

In this regard, it is important to note that rises in the rates of obesity are not restricted to human populations, but also include domestic cats, dogs, horses, and laboratory rodents and nonhuman primates (German, 2006; Klimentidis et al., 2011; Raffan, 2013; Thatcher et al., 2009). It is

Please cite this article as: Schneider, J.E., et al., Our stolen figures: The interface of sexual differentiation, endocrine disruptors, maternal programming, and energy balance, Horm. Behav. (2014), http://dx.doi.org/10.1016/j.yhbeh.2014.03.011