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Review

Maternal nutrition and risk of obesity in offspring: The Trojan horse of developmental plasticity☆,☆☆,★

Sebastian D. Parlee, Ormond A. MacDougald *

Department of Molecular & Integrative Physiology, School of Medicine, University of Michigan, Ann Arbor, MI, USA

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ABSTRACT

Mammalian embryos have evolved to adjust their organ and tissue development in response to an atypical environment. This adaptation, called phenotypic plasticity, allows the organism to thrive in the anticipated environment in which the fetus will emerge. Barker and colleagues proposed that if the environment in which the fetus emerges differs from that in which it develops, phenotypic plasticity may provide an underlying mechanism for disease. Epidemiological studies have shown that humans born small- or large-for-gestational-age, have a higher likelihood of developing obesity as adults. The amount and quality of food that the mother consumes during gestation influences birth weight, and therefore susceptibility of progeny to disease in later life. Studies in experimental animals support these observations, and find that obesity occurs as a result of maternal nutrient-restriction during gestation, followed by rapid compensatory growth associated with ad libitum food consumption. Therefore, obesity associated with maternal nutritional restriction has a developmental origin. Based on this phenomenon, one might predict that gestational exposure to a westernized diet would protect against future obesity in offspring. However, evidence from experimental models indicates that, like maternal dietary restriction, maternal consumption of a westernized diet during gestation and lactation interacts with an adult obesogenic diet to induce further obesity. Mechanistically, restriction of nutrients or consumption of a high fat diet during gestation may promote obesity in progeny by altering hypothalamic neuropeptide production and thereby increasing hyperphagia in offspring. In addition to changes in food intake these animals may also direct energy from muscle toward storage in adipose tissue. Surprisingly, generational inheritance studies in rodents have further indicated that effects on body length, body weight, and glucose tolerance appear to be propagated to subsequent generations. Together, the findings discussed herein highlight the concept that maternal nutrition contributes to a legacy of obesity. Thus, ensuring adequate supplies of a complete and balanced diet during and after pregnancy should be a priority for public health worldwide. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

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1. Introduction

1.1. Plasticity during mammalian development helps optimize phenotype to environment

In mammals, the complex process of fetal development occurs through sequential events including morulation, gastrulation and organogenesis. Each step is dependent upon meticulous orchestration of cell differentiation, migration, proliferation and apoptosis, which are regulated by signaling pathways including Notch, TGFβ and Wnt [1,2]. Interactions between intrinsic fetal factors (e.g. genetics) and extrinsic environmental factors (e.g. maternal pre-pregnancy weight and nutrition, placental insufficiency) influence these developmental signaling pathways and may culminate in abnormal organ development [3,4]. However, aberrant fetal environments do not necessarily cause a deleterious developmental program. Specifically, mammalian embryos have evolved with the capacity to adjust their pattern of development in response to atypical fetal environments, in a process called developmental (or phenotypic) plasticity. As an example, neonatal rats exposed to a low (10%), medium (18%) or high (36%) protein diet during gestation and lactation have a greater survival rate when their post-weaning diet matches the diet consumed by their respective dam during gestation and lactation [5]. Thus, developmental plasticity allows the organism to thrive in the anticipated environment in which the fetus will emerge [6–8].

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* Corresponding author at: John A Faulkner Collegiate Professor of Physiology, Department of Molecular & Integrative Physiology, University of Michigan Medical School, Brehm Center, 1000 Wall Street, Rm 6313, Ann Arbor, MI 48105, USA. Tel.: +1 734 647 4880; fax: +1 734 232 8175.

E-mail address: macdouga@umich.edu (O.A. MacDougald).

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1.2. Disease occurs when there is a mismatch between pre- and post-natal environments

Barker and colleagues proposed that phenotypic plasticity may become maladaptive and cause disease in the long term if there is a mismatch between the environment in which the organism develops and that in which it emerges [9–12]. Accordingly, mice exposed to a low (10%), medium (18%) or high (36%) protein diet in utero and through lactation have lower survival rates at two years if weaned onto a diet that differed from that of their mother [5]. Barker termed this concept the "developmental origins of health and disease" [9–12].

1.3. Phenotypic plasticity and the development of obesity

Although not currently a pervasive problem in industrialized nations, food shortages have been very common for the larger part of human history. Consequently, nutritional restriction is believed to have been a powerful force on human evolution, favoring individuals who effectively stored calories in times of surplus. The plasticity of developing organs, especially in times of nutritional restriction, is therefore thought to have favored a thrifty metabolic phenotype [13,14]. The developmental origin of disease predicts that a fetal environment promoting metabolic thriftiness, coupled to an adult environment of nutrient surplus, causes dysfunction in the metabolic systems controlling food intake and storage, and results in obesity. In recent years, epidemiological, clinical and basic research has established the interrelationships between fetal nutrition, adipose tissue development, central control of energy balance and the propensity for obesity in adult life.

Obesity is a disorder characterized by excess white adipose tissue and is the result of chronic positive energy imbalance [15]. As obesity develops, excess energy is stored in adipocytes as triacylglycerol, resulting in increased adipocyte size (hypertrophy) [16]. When demand for lipid storage exceeds the capacity of existing adipocytes, the pool of adipocytes increases through hyperplasia, with new adipocytes arising from differentiation of preadipocytes [16]. Impaired adipogenesis is hypothesized to contribute to the development of type 2 diabetes, because engorgement of adipocytes with excess lipids triggers pathological changes to adipose tissue. These include adipose tissue inflammation, which is characterized by increased macrophage infiltration into the adipose tissue and altered adipokine (e.g. TNFα) secretion [17]. Surplus lipids that cannot be stored in adipocytes are ectopically deposited in the liver, muscle and pancreas, and also circulate at higher levels [18–20]. Together these metabolic abnormalities trigger systemic insulin resistance, which along with insufficient insulin production, results in type 2 diabetes. It is important to note that while an increase in total body weight often occurs in parallel with an increase in fat mass and associated metabolic derangements, it is not a necessary precondition. Metabolic derangements can occur as a result of a shift in body composition without a change in body weight. In humans, studies have indicated that individuals with similar body mass index but with increased visceral adipose tissue (e.g. TOFI patients: thin outside, fat inside) have increased prevalence of metabolic comorbidities [21]. Accordingly within this review, the term obesity will be used to indicate both an increase in body weight and fat mass, or a shift toward elevated fat mass alone.

Using developmental plasticity and the developmental origin of disease as a conceptual framework, we explore in this review how exposing progeny to nutrient-restriction or excess in utero and/or through lactation influences development of obesity in later life. Obesity due to developmental plasticity appears to be propagated to subsequent generations, which is worrisome given the rising rates of obesity worldwide [22,23]. While the current review will discuss the effects of maternal nutrition in terms of white adipose tissue and metabolic derangements exclusively, Symonds et al. [24] provide an elegant review of fetal programming of brown adipose tissue.

2. Epidemiological evidence for the developmental origin of human obesity

2.1. The Dutch famine: maternal malnutrition during gestation influences likelihood of developing obesity in adulthood

From October 1944 until May 1945 cities in the western Netherlands, including Amsterdam, suffered extreme famine resulting from an embargo of food supplies imposed by the Nazi régime and an inability to transport food through the frozen waterways. Rations were reduced from 1800 calories per capita per day in December 1943 to below 800 calories at the height of the famine from December 1944 to April 1945 [25]. While initially pregnant and lactating women were given supplemental food, at the heart of the famine this could not be provided. Thus at 800 calories, women were receiving approximately ~40% of the recommended calories during pregnancy [26]. The homogenous and sharply defined famine, in addition to the traceability of those afflicted, provided a unique circumstance for studying the long-term effects of extreme nutritional deprivation [27]. Based on relative conception and birth dates, analysis of the Dutch cohort identified two groups of males whose obesity rates at 19 years of age were significant deviations from the norm. Males exclusively exposed to famine prenatally during the first two trimesters of gestation had about 2-fold higher prevalence of obesity (2.77%) than control counterparts (1.45%). Of note, the likelihood of developing obesity in either group is far below the national average for overweight and obese individuals in westernized countries today [28]. In contrast, males exposed to famine prenatally during the third trimester, and post-natally during the first three to five months of life, were found to be approximately half as likely to develop obesity (0.82%) than the controls (1.32%) at age 19 [29], although these thin men were more likely to be glucose intolerant at 50 years of age [30]. Following adjustment for known obesogenic conditions e.g. socioeconomic status at birth, present level of education, and smoking, women at age 50 who were similarly exposed to prenatal famine in early gestation had elevated body weight, body mass index (BMI) and waist circumference [31]. Men at 50 years of age did not show this trend even though their reported weight was elevated at 20 years of age. These results suggest that developmental plasticity resulting from neonatal exposure to global maternal nutrient-restriction has a time dependent, profound and opposing effect on the propensity to develop obesity. Furthermore, the absence of sustained elevated body weight from age 19–20 to age 50 in men, but not women, suggests a distinct sexual dimorphic effect of maternal nutrition on obesity. Finally, the development of glucose intolerance but not obesity in males exposed to famine during the third trimester suggests differential mechanisms for these pathologies.

2.2. Fetal birth weight and adult obesity follow a J- or U-shaped relationship

Using birth weights relative to parental size as an indicator of fetal restricted or excess nutrition, Parsons et al. [32] identified a linear relationship between birth weight and BMI at age seven, eleven, sixteen and twenty-three years of age. By age thirty-three, however, the relationship shifts toward a J-shape curve in which both low and high birth weights are weakly correlated with subsequent obesity [32]. A J- or U-shaped relationship between birth weight and later BMI, waist-to-hip ratio and percent body fat was also identified in numerous independent studies (Fig. 1) [33–40]. Nevertheless, this connection is not without controversy: a meta-analysis of fifteen epidemiological and clinical studies involving a total of ~22,000 individuals found that higher, but not lower, birth weight is associated with an increased risk of being overweight or obese [41]. Considering that nutritional deficiency has opposing effects on adult obesity, depending on its timing within gestation [29], discrepancies in the epidemiological literature may be