Maternal-infant nutrition and development programming of offspring appetite and obesity

Mina Desai and Michael G. Ross

In the United States and Mexico, the obesity epidemic represents a significant public health problem. Although obesity is often attributed to a Western-style, high-fat diet and decreased activity, there is now compelling evidence that this, in part, occurs because of the developmental programming effects resulting from exposure to maternal overnutrition. Human and animal studies demonstrate that maternal obesity and high-fat diet result in an increased risk for childhood and adult obesity. The potential programming effects of obesity have been partly attributed to hyperphagia, which occurs as a result of increased appetite with reduced satiety neuro-peptides or neurons. However, depending on maternal nutritional status during the nursing period, the programmed hyperphagia and obesity can be exacerbated or prevented in offspring born to obese mothers. The underlying mechanism of this phenomenon likely involves the plasticity of the appetite regulatory center and thus presents an opportunity to modulate feeding and satiety regulation and break the obesity cycle.

INTRODUCTION

The epidemic of global obesity, the resultant pathologies that develop, and their collective impact on health, well-being, and quality of life cannot be overestimated. Obesity is central to the development of metabolic syndrome, which includes a constellation of abnormalities composed of insulin resistance, elevated triglyceride levels, hypertension, and atherosclerosis.¹ Among US adults, 67% are overweight (body mass index [BMI], 25 to $<30 \text{ kg/m}^2$) and 37% are obese ($\text{BMI} \geq 30 \text{ kg/m}^2$); 17% of children are obese³ and thus at increased risk of adult obesity.⁴ The global obesity epidemic has extended to Mexico and many low- and middle-income countries where there has been a dramatic shift from maternal and child undernutrition to overnutrition.^{5,6}

As a result, obesity rates have rapidly increased in adults ($\sim 30\%$)^{7–9} and children and adolescents ($> 34\%$).^{10,11}

In parallel, chronic complications of obesity seen in pre-adolescent children and adolescents portend increased prevalence of adult metabolic syndrome.¹²

Combating obesity epidemic has been challenging. Although there is little doubt that a Western-style, high-fat diet combined with decreased activity levels is a strong determinant of obesity, the strategy of dieting combined with exercise has not always been effective. In recent years, compelling data from our laboratory and others have been reported supporting the concept that origins of obesity are in utero. Low-birth-weight newborns and infants born to mothers with maternal obesity and who consume high-fat diets or have gestational diabetes are at increased risk of obesity and

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metabolic syndrome. Importantly, interactions with the postnatal environment and neonatal growth further modulate susceptibility to obesity. In this review, we focus on the influence of maternal obesity on offspring prenatal and neonatal growth in relation to appetite regulation and risk of obesity. Strategies to combat the obesity epidemic will need to address the programming effects of early-life nutrition.

MATERNAL NUTRITION AND PROGRAMMED OFFSPRING OBESITY

Human studies

The developing fetus depends on the maternal nutritional environment and, as such, limited or excess nutrient availability influences fetal cellular and organ development, gene expression, and/or the epigenome, which may ultimately alter metabolism and function. The early studies by Barker et al^{13,14} provided evidence for the influence of maternal undernutrition on adult diseases and lead to the concept of *developmental programming*.¹⁵ Subsequent studies showed that maternal overnutrition and obesity also are associated with increased risk of offspring obesity.^{16–21} Worldwide, epidemiological studies have confirmed this association and also revealed the additive influence of postnatal infant nutrition and growth patterns on offspring risk.

Numerous studies have demonstrated the importance of the pregnancy environment wherein maternal obesity is associated with childhood obesity.^{16–21} Maternal obesity results in an increased risk of newborns being large for gestational age²²; these babies have a >2-fold risk of preschool-age obesity²³ and adult metabolic syndrome.^{24–26} The importance of the maternal environment is reinforced by the finding that obese mothers who have undergone bariatric surgery have children who are 3 times less likely to be severely obese as compared with their siblings born before their mother's surgery.²⁷ Furthermore, the critical role of the maternal environment is evidenced by the finding that paternal obesity is associated with a 4-fold increased risk of obesity in daughters at age 18 years, whereas maternal obesity results in an 8-fold increased risk.²⁸

The infancy period is also critical, because rapid newborn weight gain is associated with childhood obesity,^{29–31} and even a modest additional weight gain of 100 g/month during infancy increases the risk of childhood obesity by >25%.^{29,32–34} The highest quintile of weight gain between birth and 5 months of age doubled the odds of overweight at 4.5 years,²⁹ and rapid weight gain (>1 SD) between birth and 4 months was associated with a 5-fold risk of obesity at age 20 years in African Americans.³² Collectively, maternal obesity

during pregnancy and rapid infant-growth trajectory are critical factors contributing to the development of programmed obesity.

In the United States, the age-adjusted incidence of obesity (BMI ≥ 30 kg/m²) in women was 40% in 2018,³⁵ and more than half of all pregnant women were either overweight or obese.³⁶ In Mexico, the incidence of overweight and obesity in childbearing age women in 2012 was 35% and 30%, respectively.³⁷

The ultimate offspring phenotype depends on exposures during the pregnancy and lactation periods,^{38–40} with the potential for transgenerational transmission.^{41,42} The question arises as to what mechanisms account for this generational cycle of obesity operating during the fetal and newborn periods.

Increased energy intake, not reduced energy expenditure, largely explains population weight gain in children and adults.^{43–45} Even a small mismatch (<0.5%) between intake and expenditure will lead to weight gain over time.⁴⁶ In tandem with the increased prevalence of overweight and obesity, an increase in food portion sizes and energy intake has occurred.^{47–49} By 1996, dietary surveys indicated that, per capita, adult calorie intake in the United States had increased by 200 kcal/day over the prior 20 years, primarily a result of increased portion size.⁴⁵ Similarly in Mexico, by 2000, individual adult dietary calorie intake per day had increased by 30% since 1962.⁶ Alarming, the average portions of children (aged 2–18 years) have also increased by nearly 200 kcal.^{50,51} Overeating in children is linked to low satiety responsiveness^{51–53} and is positively correlated with body weight only in children older than 4 years,⁵⁴ suggesting that the altered appetite behavior precedes body weight gain. Thus, reduced satiety in children is likely the underlying factor leading to increased food intake and obesity in both infants and adults.

Animal studies

Animal studies have replicated evidence of human programmed obesity and provide insights into potential underlying mechanisms. In rodents, offspring of maternal obesity or dams consuming a high-fat diet are predisposed to newborn overweight and, when nursed by obese dams, exhibit early onset of hyperphagia and obesity (Table 1).^{38,55,56} Studies show that *programmed hyperphagia*^{38,57–61} results from developmentally altered hypothalamic appetite regulation that produces increased appetite and reduced satiety neurons coupled with enhanced orexigenic responses.⁶² Similar to humans, the weight gain during nursing in rodents is equally important in determining the development of obesity. For instance, cross-fostering studies demonstrate that if newborns of obese dams are nursed by

Table 1 Maternal exposures and offspring phenotype

Period of exposure to maternal obesity ^a		Offspring phenotype	
Pregnancy	Lactation	Food intake	Obesity
+	+	↑↑	↑↑
+	—	↔	↔
—	+	↑	↑
—	—	↔	↔

^aSymbols: +, exposure to maternal obesity; —, no exposure to maternal obesity; ↑, increased offspring food intake and obesity; ↔, no impact on offspring food intake and obesity.

nonobese control dams, the offspring exhibit normalized neonatal weight gain and reach normal body weight and food intake as adults.^{38,63–65} Notably, nursing of control newborns by obese dams alone is sufficient to program increased food intake and offspring obesity, though to a lesser degree than those offspring exposed to maternal obesity during pregnancy and lactation (Table 1).³⁸ This suggests that the quality of milk (eg, calorie content) and/or quantity ingested by newborns is increased by maternal obesity and high-fat diet. Indeed, studies using litter-size manipulation after birth have shown that pups reared in small litters are obese as adults, due to increased milk availability and intake. Conversely, pups raised in large litters do not develop obesity—a result of reduced milk intake.^{40,66–68}

Collectively, human and animal studies suggest the effect of programmed hyperphagia may be compounded by the impact of milk caloric content and amount. Despite programmed offspring hyperphagia, prevention of excessive newborn weight gain by limiting calorie intake may prevent the obese phenotype. Thus, there is a critical period and window of opportunity to intervene to halt the cycle of obesity. Following is a review of the development and plausible plasticity of an appetite regulatory center in relation to food intake during the early postnatal period.

APPETITE REGULATION

Hypothalamic sites of appetite regulation

Appetite is primarily controlled by a complex circuit of hypothalamic nuclei involved in synthesis of appetite and satiety signals, action areas where messengers act, and regulatory sites. The predominant appetite regulatory site, the arcuate nucleus (ARC) receives input from peripheral (eg, pancreas, adipocytes) and central sources.⁶⁹ The ARC contains at least 2 populations of neurons with opposing actions on food intake: primarily medial ARC orexigenic (neuropeptide Y [NPY] and agouti-related peptide [AgRP]) and lateral ARC anorexigenic (pro-opiomelanocortin [POMC] and cocaine- and amphetamine-regulated transcript) neurons.

Development of hypothalamic ARC

The development of ARC can be broadly categorized in 2 phases: (1) neurogenesis, which determines cell number, neuronal migration, and cell death; and (2) the formation of functional circuits, which includes axon growth and synaptogenesis.^{70,71} These critical processes, which are under control of tightly regulated spatiotemporal extrinsic and intrinsic cell factors, are vulnerable to programming effects. The timing of ARC development differs significantly among species.⁷² In rodents, nonhuman primates, and humans, neurogenesis primarily occurs during early to mid gestation. The postnatal hypothalamic axon growth in rodents, however, differs from that in nonhuman primates and humans, in which hypothalamic neural projections develop almost entirely during fetal life.^{70,71,73–76} Thus, hypothalamus development in rodents occurs during intrauterine and early postnatal life, whereas in humans and nonhuman primates, it primarily develops during intrauterine life (Figure 1).

Prenatal neurogenesis and nutrient effects

The hypothalamic ventricular region is a neurogenic region in fetal and neonatal life,⁷⁷ during which hypothalamic neural progenitor cells in the peri-third ventricular zone undergo extensive proliferation, self-renewal, and ultimate terminal division into cells destined for neuronal or glial fate.^{72,78,79} The vast majority of neurons in the mouse ARC terminally divide between e10.5 and e18, with the peak occurring between e10.5 and e12.5.^{77,80}

As stated, fetal ARC development in the environment of maternal obesity results in programmed hyperphagia at birth.^{38,55} Studies consistently show that maternal obesity increases offspring orexigenic drive; that is, increased offspring food intake and weight gain, increased ratio of orexigenic to anorexigenic neuronal number, and increased orexigenic to anorexigenic peptide expression and signaling. In newborns of obese dams, hypothalamic expression (mRNA and protein) of NPY and AgRP is increased,^{57,81} whereas that of POMC is reduced (Figure 2).⁸² Consistent with increased NPY and reduced POMC expression,^{80,83–85} numbers of neurogenic regulators that promote POMC expression (Ngn3 and Mash1) are decreased.^{57,86} Importantly, maternal obesity also affects offspring neurogenesis, with stimulation of neuroprogenitor cell proliferation in the embryonic hypothalamus and an increase in orexigenic neurons.⁸⁷

Figure 1 Hypothalamic arcuate nucleus. (A) Development of functional hypothalamic arcuate nucleus (ARC) comprises neurogenesis, which occurs during the prenatal period, and neuronal circuitry formation, which occurs during the early postnatal period. Whereas neurogenesis occurs from early to mid gestation in humans and rodents, the neuronal circuitry formation in rodents occurs during the postnatal period; in humans, it occurs during the prenatal period. (B) Appetite neurons (neuropeptide Y [NPY]; agouti-related peptide [AgRP]) and satiety neurons are located in the hypothalamic ARC with projections to the paraventricular nucleus (PVN). *Abbreviation:* POMC, pro-opiomelanocortin.

Figure 2 Effect of maternal obesity on offspring neuropeptide. Exposure to maternal obesity results in increased hypothalamic neuropeptide Y (NPY) and decreased pro-opiomelanocortin (POMC) expression in the newborns. Continued exposure to maternal obesity during the nursing period favors arcuate nucleus remodeling towards additional NPY formation.

Postnatal ARC remodeling and nutrient effects

Whereas ARC anatomy and structure are developed by birth, there is a remarkable postnatal ARC remodeling through early adult life in rodents (ie, 12 weeks of age). In mice at 4 weeks of age, embryonic cells (from e10.5) represented <10% and 5% of total POMC and NPY cells, respectively, indicating a greater remodeling of NPY as compared with POMC cells (Figure 2).⁸⁸ Mature neurons do not divide; thus, significant, if not dramatic, ARC apoptosis^{89–91} and remodeling must occur during the postnatal life. Cell-lineage experiments further revealed that subpopulations of embryonic POMC-expressing precursors subsequently adopt a mature NPY phenotype.⁹²

Similar to the prenatal nutritional impact on fetal ARC development, there is compelling evidence that ARC remodeling can be altered by postnatal overnutrition.^{81,88,93} Human studies have demonstrated a marked influence of postnatal nutrition and early growth rates on adult obesity,^{94,95} consistent with an effect on postnatal ARC development and/or regulation. Similarly, animal studies show that newborns of obese mothers who continue to be exposed to maternal obesity during nursing period show persistent change in the expression levels and ARC neuronal phenotype as adults. Notably, these offspring have significantly increased food intake with greater adiposity as compared with offspring exposed only during pregnancy or lactation periods.^{57,86,87,96} Furthermore, neonatal overnutrition induced by rearing in small litters results in hyperphagia.⁹⁷ Specific functional studies on appetite neuropeptides demonstrate that offspring born to and nursed by dams fed a high-carbohydrate diet exhibited increased NPY release in the paraventricular nucleus (PVN).⁹⁸ In addition, maternal obesity combined with postweaning high-fat diet increased ARC NPY signaling (PVN NPY1R) and reduces POMC expression, suggesting an additive influence of postnatal nutrition.⁶² Although the findings of these studies suggest the influence of postnatal nutrition on ARC remodeling, direct evidence of postnatal ARC remodeling is demonstrated in both diet-induced obese offspring (eg, leptin-resistant) and leptin-deficient mice wherein it is markedly reduced.⁸⁸ Notably in high-fat-fed animals, introduction of resveratrol in the diet or calorie restriction led to generation of more POMC than NPY neurons.⁹⁹ In addition, remodeling of the orexigenic projections from the ARC to the hypothalamic PVN can be induced

by fasting.¹⁰⁰ These findings suggest implications for the effects of both pre- and postnatal nutrition on ARC development and remodeling.

Postnatal growth modulation to prevent programmed obesity

Whereas overnutrition during fetal life or the newborn period may alter ARC development and remodeling, respectively, with either or both resulting in programmed hyperphagia, neonatal ARC remodeling provides a unique early-life opportunity to normalize ARC anatomy and appetite and satiety balance and prevent offspring obesity. Studies in humans show that the milk fat content correlates with both maternal BMI and dietary intake,^{101–103} and that milk composition is altered by maternal glucose tolerance¹⁰¹ and insulin and leptin levels.^{104,105} In rodents, a maternal high-fat diet results in higher milk total caloric content with significantly higher lipid, protein, and lactose concentrations.^{61,106–109} Although human ARC remodeling has not been demonstrated, the evidence that postnatal nutrition influences early growth rates and obesity suggests ARC remodeling likely also occurs. The potential plasticity of ARC remodeling during the postnatal period presents an opportunity to modulate feeding and satiety regulation and break the obesity cycle.

CONCLUSION

Combating the childhood obesity epidemic remains an important public health priority because it is a major predictor of adult obesity. In tandem with the increased prevalence of overweight and obesity, an increase in food portion sizes and energy intake has occurred in children. This may be partly a result of developmental programming effects. The importance of both the pregnancy and nursing periods is emphasized by studies showing an association of maternal obesity with childhood and adult obesity, and a marked influence of postnatal nutrition. Mechanistically, the exposure period-dependent effects may be explained by the development of hypothalamic ARC. In rodents, ARC anatomy and structure are developed by birth and ARC remodeling occurs postnatally through early adult life. Although both these periods are susceptible to influence by maternal obesity, they also provide a unique opportunity to intervene in the health of newborns of obese mothers to prevent adult hyperphagia and obesity. Although ARC remodeling in humans has not been demonstrated, the evidence that postnatal nutrition influences early growth rates and obesity suggests that ARC remodeling likely also occurs. Targeting the infancy period for overweight and obesity prevention presents an

opportunity to modulate feeding and satiety regulation and break the obesity cycle.

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