Appetite and satiety demonstrate a remarkable heterogeneity among humans, with a spectrum contributing to both anorexia and hyperphagia.

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Developmental Programming of Appetite/Satiety by Michael G. Ross and Mina Desai

Key insights

Obesity in childhood and in later life may be the result of developmentally programmed hyperphagia. Recent data strongly suggest that maternal and/or fetal under- or overnutrition predisposes the offspring to become hyperphagic. Infants born small for gestational age and those born to obese mothers are at risk.

Current knowledge

Appetite is regulated by a complex circuit of hypothalamic nuclei involved in the generation of appetite versus satiety signals. The arcuate nucleus (ARC) is the predominant appetite regulatory site in the brain and receives signals from different areas of the brain and other tissues. The ARC contains at least two populations of neurons with opposing actions on food intake. Specific alterations in the fetal metabolic/energy environment can alter the equilibrium between orexigenic and anorexigenic neuronal systems, thus affecting appetite and satiety.

Practical implications

Imbalances in maternal nutrition (under- or overnutrition, low-protein or high-fat diets) result in a cascade of genetic, biochemical and cellular effects that can ultimately bias the appetite regulatory networks of the offspring towards hyperphagia. Specific epigenomic studies are necessary in order to pinpoint the genomic sites that act as targets for early nutritional effects.

Maternal nutrition affects appetite in the offspring. Perturbations in maternal nutrition can alter nutrient sensors, neuroendocrine levels and signaling, neurogenesis and neuropeptide levels. These pathways interact and ultimately influence appetite.

A greater understanding of the development of appetite regulatory pathways opens the door for novel interventions for the prevention and treatment of obesity.

Recommended reading

Weaver IC, Cervoni N, Champagne FA, et al: Epigenetic programming by maternal behavior. *Nat Neurosci* 2004;7:847–854.

Developmental Programming of Appetite/Satiety

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Key Messages

- The fetal and newborn nutritional environment may alter the development of appetite and satiety pathways.
- Childhood and adult obesity may be a consequence of developmentally programmed hyperphagia.
- Both maternal undernutrition and maternal obesity increase the risk of offspring hyperphagia and obesity.

Key Words

Hyperphagia · Obesity · Fetal origins

Abstract

Obesity is often attributed to a Western lifestyle, a high-fat diet and decreased activity. While these factors certainly contribute to adult obesity, compelling data from our laboratory and others indicate that this explanation is oversimplified. Recent studies strongly argue that maternal/fetal under- or overnutrition predisposes the offspring to become hyperphagic and increases the risk of later obesity. Both infants small for gestational age (SGA) or infants born to obese mothers who consume a high-fat diet are at a markedly increased risk of adult obesity. Specific alterations in the fetal metabolic/energy environment directly influence the development of appetite regulatory pathways. Specifically, SGA

infants demonstrate (1) impaired satiety and anorexigenic cell signaling, (2) enhanced cellular orexigenic responses, (3) programmed dysfunction of neuroprogenitor cell proliferation/differentiation, and (4) increased expression of appetite (NPY) versus satiety (POMC) neurons. In both hypothalamic tissue and ex vivo culture, SGA newborns exhibit increased levels of the nutrient sensor SIRT1, signifying reduced energy, whereas maternal high-fat-exposed newborns exhibit reduced levels of pAMPK, signifying energy excess. Via downstream regulation of bHLH neuroproliferation (Hes1) and neurodifferentiation factors (Mash1, Ngn3), neurogenesis is biased toward orexigenic and away from anorexigenic neurons, resulting in excess appetite, reduced satiety and development of obesity. Despite the developmental programming of appetite neurogenesis, the potential for neuronal remodeling raises the opportunity for novel interventions.

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Introduction

Currently, 66% of adults in the United States are overweight and more than one third are obese (BMI >30), representing a modern-day health crisis. Globally, it is observed in both developed and developing countries and may be a reflection of societal, economic and cultural problems. Obesity and its related diseases are the leading causes of death in Western society, with associated risks of hypertension, cardiovascular disease, stroke and diabetes. As childhood obesity is a major risk factor for adult obe-

sity [1], the increasing incidence of childhood obesity would predict a continued adult obesity epidemic. The manifestation of obesity is impacted by numerous factors including culture, genetic predisposition, economic factors and perinatal environment. The rapid increase in the prevalence of obesity has been partly attributed to environmental factors, with increasing availability of highly palatable foods and 'modern' lifestyles involving less physical work creating a more obesigenic environment. However, as obesity results from an imbalance in energy intake versus expenditure, individuals with dysfunctional appetite regulation (i.e., overeating) are at high risk of developing obesity.

The manifestation of obesity is impacted by numerous factors including culture, genetic predisposition, economic factors and perinatal environment.

Appetite regulation develops perinatally, and hence a suboptimal environment during critical periods of development programs appetite and satiety mechanisms, thereby altering infant, childhood and adult ingestive behavior. Numerous epidemiological and animal studies have demonstrated that in utero perturbations of the nutritional, hormonal and/or metabolic environment as well as exposure to environmental toxins (e.g., endocrine disrupters) may alter the development of the appetite regulatory system, resulting in an increased risk of adult obesity.

Epidemiological Evidence for Perinatal Appetite Programming

Epidemiological studies have conclusively demonstrated associations between the early nutritional environment, patterns of postnatal growth and adult metabolic syndrome. Paradoxically, low-birth-weight infants are at increased risk of adult obesity, in part a result of programmed hyperphagia and adipogenesis. The Dutch famine in 1944/45 provided an opportunity to determine the effects of perinatal malnutrition on babies that would later be exposed to caloric surfeit. Offspring of mothers exposed to the famine during the first two trimesters of pregnancy had a higher incidence of obesity than the general population [2].

Studies indicate that 25–63% of adult diabetes, hypertension and coronary heart disease can be attributed to

the effects of low birth weight with accelerated newborn-to-adolescent weight gain [3]. Recent interest has focused on the generational effect of maternal obesity and the effect of maternal overnutrition on fetal programming. Thus, there is a U-shaped curve for the relationship between birth weight and adult metabolic disease such that those born small or large for age show an increased risk of obesity later in life [4]. Together, these processes have contributed to the population shift toward obesity. Briefly, normal-weight mothers most commonly gave birth to normal-weight infants who develop into normal-weight adults (fig. 1). The increased incidence of prematurity and intrauterine growth restriction during the last half century, combined with improved neonatal survival, overfeeding, formula feeding and exposure to a Western diet, has resulted in an increase in offspring programmed for adult hyperphagia and obesity. This process has, to a significant degree, accounted for the ongoing population shift toward an obese phenotype, with these second-generation (obese) mothers at risk of giving birth to macro-somic newborns, who themselves are at risk of adult obesity.

Recent studies have indicated that children who show a rapid weight gain may be at a higher risk of adult diseases regardless of their birth weight [5]. Formula feeding appears to predispose offspring to obesity [6] as several meta-analyses show a greater propensity to adulthood obesity amongst infants who were formula-fed versus breastfed [7]. Whether this increased weight gain is a result of formula composition or is secondary to the process of bottle- versus breastfeeding itself is controversial. The risk of disease in adulthood is already higher in individuals born thin, but this effect is compounded if they experience a rapid weight gain and early adiposity rebound in childhood [8]. Therefore, catch-up growth in the first few weeks of postnatal life appears to be particularly disadvantageous in terms of the propensity to develop hyperphagia and obesity in adulthood. In contrast to the Dutch famine, offspring of mothers exposed to the longer (28-month) Leningrad famine did not exhibit adult obesity, most likely because offspring were exposed to famine throughout pregnancy and early childhood, preventing the rapid catch-up growth [9].

Animal Models of Perinatally Programmed Hyperphagia

Manipulation of maternal and/or newborn nutrition has been done in various animal models, though the neuroendocrine regulators of appetite have been best

Fig. 1. Population shift toward obesity due to programming. IUGR = Intrauterine growth restriction.

characterized in rodents. Notably, perinatal protein restriction, undernutrition and overnutrition program offspring appetite and adiposity. Both maternal undernutrition and protein restriction during rat pregnancy result in small for gestational age (SGA) newborns. When nursed normally, SGA newborns exhibit a rapid catch-up growth with hyperphagia and adult obesity [10]. Further, SGA offspring are more susceptible to stress-induced binge eating [11] and, when weaned to a postnatal high-fat diet, show exacerbated hyperphagia and adiposity [12]. Maternal obesity resulting from a high-fat diet [13] and neonatal overnutrition (induced by nursing a smaller litter) also leads to rapid postnatal growth followed by hyperphagia and adult obesity [14]. Despite the diversity of these perinatal nutritional disturbances, the similar outcome of adult obesity suggests that the common underlying mechanism(s) may be programmed hyperphagia.

Appetite Regulation

Hypothalamic Sites of Appetite Regulation

Appetite is regulated by a complex circuit of hypothalamic nuclei involved in synthesis of appetite/satiety signals, action areas where messengers act and regulatory sites. The predominant appetite regulatory site, the ar-

culate nucleus (ARC), receives input from peripheral (brain, pancreas and adipocytes) and central sources [15]. The ARC contains at least two populations of neurons with opposing actions on food intake: medial ARC orexigenic [NPY (neuropeptide Y) and AgRP (agouti-related protein)] and lateral ARC anorexigenic neurons [POMC (proopiomelanocortin) and CART (cocaine- and amphetamine-regulated transcript)]. Many of the ARC NPY/AgRP and POMC/CART neurons project to downstream neurons in the periventricular nucleus (PVN).

Hypothalamic Neuropeptides (NPY and POMC)

POMC neurons mediate anorexigenic responses by the release of alpha-melanocyte-stimulating hormone (α -MSH) which binds to PVN neurons expressing melanocortin-3 and -4 receptors (MC3/MC4-Rs). The orexigenic property of AgRP results from its competition with α -MSH at MC3/MC4-Rs. Among the five subtypes of NPY receptors, NPY-1R, which is expressed on PVN neurons, is primarily responsible for NPY-induced increases in food intake. In addition to the PVN, the ARC interacts with additional hypothalamic nuclei including the ventromedial nucleus, the lateral hypothalamus, the dorsomedial nucleus and brainstem sites (e.g., locus coeruleus, nucleus of the solitary tract) [16, 17].

Fig. 2. NPCs. **a** NPCs can self-renew or differentiate to neuronal or glial cells. **b** Hes1 promotes NPC proliferation and inhibits Mash1 and NPC differentiation. **c** Reduced Hes1 suppresses NPC proliferation and alleviates Mash1 inhibition, allowing NPC differentiation.

Peripheral Anorexigenic Hormones (Leptin and Insulin)

In addition to neural inputs, ARC neurons respond to blood-born signals (e.g., leptin, insulin and ghrelin). Leptin, which is secreted primarily by fat, is transported across the blood-brain barrier into the cerebrospinal fluid via a saturable transporter system in the choroid plexus, mediated by a short form of the leptin receptor (ObRa) [18]. Insulin, which is secreted by the pancreas, gains access to the hypothalamus by means of a saturable receptor-mediated process and diffusion from the median eminence [19]. Both are anorexigenic factors that stimulate the POMC/CART neurons and inhibit the NPY/AgRP neurons. Accordingly, ARC neurons exhibit high leptin and insulin receptor expression. Genetic mutations in the obese (ob) gene, which codes for leptin, or the diabetes (db) gene, which codes for the leptin receptor, lead to hyperphagia and obesity. Central insulin deficiency is a cause of hyperphagia. The reduction of food intake caused by central insulin is blocked by a POMC antagonist.

ARC Neurogenesis

ARC development is a relatively late process in rodents, rhesus monkeys and humans, with maturation not

achieved until later stages of postnatal development [20]. Key hypothalamic nuclei only begin to be populated during fetal life, with continued neural development during the neonatal period [21, 22]. POMC becomes detectable in rat hypothalamic neurons from gestational day E12.5, and NPY neurons first appear in the ARC at E14.5 [23], though POMC and NPY neurons do not acquire their terminal peptidergic phenotype until the postnatal period. Coinciding with ARC neuronal maturation, ARC projections in rodents are formed beginning in the second week of postnatal life [24].

The ARC neurons arise from neurogenic regions within the hypothalamus during fetal/neonatal life. During development, neuroprogenitor cells (NPCs) undergo extensive proliferation (two daughter NPCs), self-renewal (one NPC and one differentiated cell) and ultimate terminal division into cells destined for neuron, astrocyte or oligodendrocyte fate [25], which migrate and populate the hypothalamic nuclei. NPC differentiation to neurons, and ultimately to appetite or satiety neurons, is regulated by a complex spatial/temporal interplay of pathways, including cell communication factors (Notch/Hes1), energy/nutrient sensors (SIRT1, AMPK) and a series of neuroregulatory basic helix-loop-helix (bHLH) transcription

factors, such as Mash1 and Neurogenin-3 (Ngn3) [26], among others.

Neuronal Differentiation to POMC or NPY

Once NPCs differentiate to neurons, those cells destined for the ARC further differentiate to express orexi-genic (NPY, AgRP) or anorexigenic (POMC, CART) pep-tides. The bHLH factor Mash1 is required for the normal development of POMC neurons [27]. Downstream from Mash1, Ngn3 also promotes the development of POMC neurons, while inhibiting NPY expression (fig. 2). Ac-cordingly, Mash1(-/-) mice demonstrate ARC hypoplasia with minimal expression of POMC neurons, Mash1(+/-) mice actually overexpress NPY neurons and Ngn3(-/-) mice express markedly re-duced POMC but increased NPY ARC neurons [28]. Thus, perturbations in Mash1 and Ngn3 expression may markedly alter the development of appetite regulatory neurons [28]. Hes1, an upstream reg-ulator which promotes NPC proliferation while inhibit-ing differentiation, also acts as a transcriptional regulator (together with corepressors) of both Mash1 and Ngn3.

Neuronal Growth Factors (Insulin and Leptin)

Although insulin and leptin regulate adult ingestive behavior, these factors have important roles in appetite neurogenesis. Exogenous insulin promotes cell growth and serves as a trophic factor in fetal neuron cell culture [29]. In rat fetal brain cell culture, axonal growth is stim-ulated in insulin medium. Leptin also has been recog-nized as a major neurotrophic factor during the devel-opment of the rodent brain, partly because of the initial observation that animals that are either leptin-deficient or -insensitive have decreased brain size and develop-ment [30].

Neurogenesis and Energy Sensors (AMPK and SIRT1)

Emerging evidence indicates that energy metabolism during development is a critical regulator of NPC prolif-eration/differentiation [31], providing insight into a pu-tative mechanism for nutrient programming of offspring hyperphagia. Two key proteins which serve as central en-ergy/nutrient sensors are AMP-activated protein kinase (AMPK) and SIRT1, an NAD⁺-dependent histone de-acetylase, both of which have the potential to influence

ARC neuronal differentiation and expression of POMC and NPY neurons.

AMPK is a heterotrimer complex which is activated by phosphorylation (pAMPK) in response to reduced ener-gy levels. In adult life, hypothalamic AMPK plays a key role in the control of whole-body energy homeostasis [32], as pAMPK increases the expression of NPY and re-duces the expression of POMC. During development, AMPK levels modulate neurogenesis, as the AMPK acti-vator AICAR inhibits NPC proliferation, which is res-cued, in part, by AMPK inhi-bition (compound C). Con-versely, a complete absence of AMPK (AMPK β 1-/- mice) reduces NPC proliferation.

Sirtuins are NAD⁺-de-pendent (class III) histone deacetylases which express greater activity under low-energy (high NAD⁺) con-ditions. Among the mammali-an sirtuins, only SIRT1 is

directly implicated in NPC biology. SIRT1 is highly expressed in metabolically active sites (e.g., in the ARC) and orchestrates key metabolic responses to nutrient al-terations [33]. During development, SIRT1 and Hes1 form a complex that binds to and deacetylates histones at the Mash1 promoter [34], decreasing Mash1 expression. Similarly, SIRT1 and Hes1 may inhibit Ngn3 expression, and SIRT1 may inhibit Hes1. Consistent with this mech-anism, NPCs prematurely differentiate [35] in Hes1-de-ficient brains, reducing the NPC pool.

Mechanisms of Perinatal Appetite Programming

Mechanisms of perinatally programmed appetite re-sulting from altered maternal nutrition (undernutrition, low-protein diet, overnutrition, high-fat diet) may in-volve multiple interacting factors/pathways that influ-ence offspring hyperphagia. These include altered hypo-thalamic ARC neuropeptides, neuroendocrine signaling, neurogenesis, neurotrophic factors, energy sensors and/ or epigenetics as discussed below (fig. 3).

Hypothalamic Appetite-Regulating Network

Altered maternal nutrition biases the offspring regu-latory network toward hyperphagia by increasing the production of and the sensitivity to the appetite peptide NPY and/or decreasing those of the satiety peptide

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POMC. Specific studies on rats demonstrate increased levels of hypothalamic NPY mRNA in fetuses [36] and adult offspring as well as in other regions (PVN and lateral hypothalamic area) [37]. Other studies demonstrate decreased mRNA of ARC POMC [38]. In addition, exposure to gestational and lactational maternal diabetes also increases offspring NPY and AgRP as well as decreases POMC and α -MSH [39]. Overall, in response to maternal malnutrition, offspring exhibit an increased ratio of appetite/satiety gene expression. Nonetheless, there are subtle differences dependent upon maternal and post-weaning diets. For example, maternal obesity combined with a post-weaning high-fat diet increases ARC NPY signaling (PVN NPY1R), reduces POMC expression [40] and decreases sensitivity to leptin [41], whereas offspring born to dams fed a high-carbohydrate diet demonstrate increased NPY release in the PVN [42]. In maternally undernourished offspring, brain slice electrophysiology techniques demonstrate enhancement of NPY inhibition of hypothalamic ARC anorexigenic neurons [43].

ARC Neuronal Development

Newborns born SGA due to maternal undernutrition have NPCs that exhibit impaired migration *in vivo* as well as reduced proliferation and neuronal differentiation *in vitro* [44, 45]. Consistent with this finding, 1-day-old SGA newborns express decreased Hes1 and Ngn3 both in the hypothalamic tissue and NPCs cultures. Importantly, even in culture media outside the fetal environment, NPCs of SGA offspring are programmed to preferentially differentiate to appetite (NPY/AgRP) as compared to satiety neurons.

Hypothalamic Nutrient Sensors

Consistent with their energy-deprived status, SGA newborns express increased hypothalamic and NPC SIRT1 expression which persists to adulthood. Notably, SIRT1 silencing via transfection with SIRT1-specific siRNA promotes NPC proliferation with increased Hes1 protein expression in control NPCs, suggesting a SIRT1 regulation of Hes1-mediated NPC proliferation.

Similar to SIRT1 changes, SGA adults allowed *ad libitum* access to food exhibit upregulated ARC AMPK activity with reduced Akt activity [46]. As these changes correspond to fasting conditions, SGA offspring have an enhanced appetite drive that contributes to hyperphagia and obesity.

Fig. 3. Perinatally programmed appetite. Perturbations in maternal nutrition (undernutrition, low-protein diet, overnutrition, high-fat diet) can alter nutrient sensors, neuroendocrine levels and signaling, neurogenesis and/or neuropeptide levels. These pathways can interact and ultimately impact appetite.

Leptin and Insulin Neuroendocrinology

Both high-fat feeding during gestation and lactation as well as a maternal food restriction-induced SGA condition result in offspring with impaired leptin sensitivity [41]. In growth-restricted fetuses and SGA newborns, plasma leptin and insulin levels are decreased [10, 47]. Moreover, SGA newborns show dysregulated hypothalamic leptin and reduced insulin signaling. When nursed normally, obese SGA adults show increased plasma leptin and insulin levels [10]. An examination of the anorexic effects of sibutramine revealed a significantly lower reduction in body weight in SGA offspring. Nonetheless, SGA offspring were leptin- and insulin-resistant as evidenced by a lack of response to peripheral leptin and oral glucose treatment [48]. Maternal high-fat diets during gestation cause offspring to have an impaired hypophagic response to insulin as adults [49]. Additionally, adult rats that are obese due to neonatal overfeeding demonstrate a reduced ARC neuronal response to leptin and insulin [50, 51]. Interestingly, rats that have a genetic predisposition to develop diet-induced obesity also have a preexisting reduction in central insulin sensitivity, and high-fat diets further reduce the sensitivity to insulin [52].

Treatment of *ob/ob* leptin-deficient mice with leptin does not restore ARC projections to the PVN unless it occurs during postnatal days 4–12 [53]. Recent evidence also indicates that, in offspring of rat dams 70% nutrient-deprived throughout gestation, leptin supplementation from postnatal day 3 to postnatal day 13 prevents programming of high susceptibility to diet-induced obesity

[54]. However, in control pups, leptin given between postnatal days 1 and 10 causes adult hyperleptinemia, leptin resistance, increased food intake and excess body weight [55]. Furthermore, studies have demonstrated that maternal food restriction during both pregnancy and lactation, which results in further newborn growth restriction, prevents offspring hyperphagia and obesity [10]. Thus, neonatal leptin excess can induce obesity, while fetal/newborn leptin deficiency can prevent obesity. Therefore, further research is needed in this area to determine just how leptin levels during the early postnatal period can affect long-term appetite regulation.

Neurotrophic Effects of Leptin and Insulin

Studies have shown that both leptin and insulin induce NPC proliferation and differentiation. Insulin potentiates greater proliferation and astrocyte lineage than leptin. In contrast, leptin promotes neuronal lineage. NPCs of SGA newborns have reduced responses to leptin and insulin [45]. There is also evidence that leptin specifically promotes the development of ARC neuronal projections, consistent with a role in brain development. *ob/ob* mice have been shown to have significantly higher levels of oligodendrocyte precursor cells than wild-type mice [56], confirming the role of leptin as a regulator of neural progenitor fate. Gestational diabetes that interferes with the ability of insulin to act as a neurotrophic factor causes offspring to have impaired neuronal development specifically in the hypothalamic nuclei responsible for the regulation of appetite. These animals exhibit decreased neuronal cytoplasm in the ARC, the ventromedial nucleus and the parvocellular division of the PVN, as well as an increase in the glia-to-neuron ratio in the periventricular region of the hypothalamus [57].

Epigenetics

The demographic shift of populations toward a more obese phenotype in a relatively short period of one or two generations argues against a major genetic contribution and instead in favor of environmental or epigenetic mechanisms underlying this phenomenon. Genome-wide epigenetic modification occupies a critical role in regulating gene expression at critical stages of embryonic development. Epigenetics more specifically refers to an

environmental factor that leads to the chemical modification of DNA or chromatin such that it is fixed in the 'on' or 'off' position. Major mechanisms associated with epigenetic changes are post-translational modifications (acetylation, methylation or phosphorylation) of core histones and DNA methylation. For example, methylation of CpG-rich clusters (called CpG islands) – which often span the promoter regions of genes – is associated with transcriptional repression, whereas hypomethylation of CpG islands is associated with transcriptional activity. Epigenetic modifications such as these are hypothesized to be the primary basis for the programming phenomenon, and the structural and regulatory effects on many organ systems are likely to be secondary to these environmentally induced changes in gene expression.

Data are now emerging to suggest that alterations in DNA methylation and other epigenetic processes are central to developmental programming in multiple physiological systems. Maternal food restriction that causes offspring to have hyperphagia that is exacerbated by exposure to a high-fat diet also causes increased promoter methylation of energy balance-related receptors, namely the glucocorticoid receptor and the peroxisome proliferator-activated receptor in the liver [12, 58]. In addition, enhanced maternal care early in the postnatal period decreases

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CpG island methylation of the glucocorticoid receptor, increasing its expression in the brain [59]. It is possible that perinatal environmental perturbations could cause similar DNA modifications in the promoters of genes related specifically to appetite in hypothalamic neurons, although this has not been studied to date. However, one study has investigated a potential epigenetic mechanism for alterations in leptin sensitivity in a cell culture model. Hypermethylation of CpG islands of the functional SOCS3 promoter correlates with transcriptional silencing, and this leads to the constitutive activation of the JAK/STAT pathway in cell culture [60]. Should the perinatal environment also influence the SOCS3 methylation status, then this could be a mechanism for programmed obesity. Only by applying such epigenomic approaches will we eventually be able to determine, in animal models, the specificity and breadth of genomic sites that act as targets for early nutritional effects.

Conclusion

Although food intake is a critical survival function, appetite and satiety demonstrate a remarkable heterogeneity among humans, with a spectrum contributing to both anorexia and hyperphagia. Whereas obesity was often viewed as dietary indiscretion combined with reduced energy expenditure, it is now recognized that enhanced appetite may predispose to obesity, and obesity itself may impair satiety. The maternal and thus fetal nutritional environment may respond to altered energy/nutrient levels during critical embryological and developmental periods so as to alter neurogenesis. Through the interplay of ex-

tracellular signaling factors, intracellular transcription responses and nutrient-induced epigenetic alterations, the maternal environment can program fetal/newborn appetite/satiety pathways resulting in newborn and adult hyperphagia. An understanding of the timing, mechanism and potential plasticity of appetite pathway development offers the opportunity for novel interventions for the prevention or treatment of obesity.

Disclosure Statement

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