Effects of Neonatal Programming on Hypothalamic Mechanisms Controlling Energy Balance

Abstract

The prevalence of overweight and obesity in most developed countries has markedly increased during the last decades. In addition to genetic, hormonal, and metabolic influences, environmental factors like fetal and neonatal nutrition play key roles in the development of obesity. Interestingly, overweight during critical developmental periods of fetal and/or neonatal life has been demonstrated to increase the risk of obesity throughout juvenile life into adulthood. In spite of this evidence, the specific mechanisms underlying this fetal/neonatal programming are not perfectly understood. However, it is clear that circulating hormones such as insulin and leptin play a critical role in the development and programming of hypothalamic circuits regulating energy balance. Here, we review what is currently known about the impact of perinatal malnutrition on the mechanisms regulating body weight homeostasis. Understanding these molecular mechanisms may provide new targets for the treatment of obesity.

The “Thrifty Phenotype Hypothesis” and Perinatal Programming

Overweight, obesity, and associated metabolic alterations are reaching epidemic levels in our society and represent a growing public health problem in both children and adults. Body weight depends on the balance between caloric intake and caloric consumption. Obesity develops when the former exceeds the latter and there is an accumulation of excess fat in peripheral tissues, such as white adipose tissue (WAT), liver, and muscle [1–6]. Malnutrition during critical developmental periods, both in utero or in the postnatal phase, is a suggested risk factor for obesity and associated metabolic disorders in later life, possibly affecting the normal development of the neuronal circuits regulating energy balance [7–15].

The ideas of Hales and Barker are directly linked to the concept of programming: a process whereby a stimulus or insult during a critical period of development has lasting or lifelong consequences [7,9]. Since this hypothesis was proposed, many studies world-wide have confirmed initial epidemiological evidence demonstrating that environmental factors like fetal and neonatal nutrition during critical perinatal periods play a key role in the development of obesity and associated metabolic pathologies, such as cardiovascular disease and type II diabetes [8,10–12,16,17]. The “Thrifty Phenotype” or “Small-Baby-Syndrome” hypotheses proposes that prenatal undernutrition leads to decreased insulin secretion and concurrent insulin resistance in the fetus which, in turn, slow down prenatal weight gain [7,9,18]. Events in early life may have long-term effects on physiology in 3 ways: 1) direct damage; 2) induction, removal, or impairment of a corporal structure; or 3) physiological setting/programming by a certain stimulus. The term programming is applicable to the last 2 processes [19].

A classical model of neonatal nutritional programming is the manipulation of rat litter size in the first days of life [8,16,17,20]. Rats growing up in small litters (SL) gain more weight than rats growing up in normal litters (NL). SL rats display hyperphagia, overweight, hyperleptinemia, hyperinsulinemia, impaired glucose tolerance, elevated triglycerides, and increased systolic blood pressure [8]. This effect could be explained in terms of increased milk intake [21]. The key aspect of the overfed model is that these rats maintain the obese phenotype and the associated metabolic disturbances throughout their

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lives [8,16,17,21]. Regarding the hyperphagic behavior, there are several discrepancies in the literature [16,17,22–24]. These data suggest that other components of body weight homeostasis, such as changes in feeding efficiency, adipogenesis, or energy expenditure might be impaired in SL adult rats. In this sense, it is interesting to note that SL rats display major alterations in hypothalamic nuclei, which are critical in the regulation of energy expenditure [25–33], as well as glucocorticoid sensitivity, which regulates fat deposition [34] and sympathetic activity [35]. Additionally, a marked reduction in the thermogenic capacity of the brown adipose tissue (BAT) further supported the increased body weight gain in SL rats. The decreased thermogenic capacity found in SL rats is not only due to reduced expression of uncoupling protein 1 (UCP1), but also problems of maintaining the supply of lipid substrates for heat generation in BAT, since both lipoprotein lipase (LPL) and hormone sensitive lipase (HSL) expression is diminished in BAT [36]. Surprisingly, before weaning, these animals have elevated levels of UCP1, suggesting increased energy expenditure similar to that experienced by animals exposed to high-fat diet (HFD). This likely reflects an adaptation in response to increased energy intake and may represent an attempt to control weight gain. However, excessive stimulation of energy expenditure in early life can lead to desensitization of thermogenesis, with consequent alterations in adulthood [36].

Although fewer studies have been conducted, in other rodent models it has also been observed that perinatal overfeeding induces metabolic disorders in adulthood. Here, SL mice developed marked obesity, insulin resistance, and hepatic steatosis when given HFD after weaning. This phenotype could contribute to hypothalamic leptin resistance and decreased energy expenditure. Since postnatal overfeeding alone does not seem to affect many of the parameters analyzed, and the animals develop hyperglycemia, hyperleptinemia, and insulin resistance only after exposure to HFD, the authors proposed that the main consequence of metabolic reprogramming is sensitization to the development of obesity or type II diabetes [37]. Another study reported that mice raised in small litters eat more at each meal, have impaired satiety (as calculated by the meal size to follow inter-meal interval), and eat their first meal faster following a mild food deprivation [38]. Finally, a recent observational study in infant marmosets showed that marmosets found to be obese early in life consumed solid food sooner and craved more attention from caregivers than nonobese marmosets, indicating that the weaning process may be particularly important in the development of feeding phenotypes and the development of juvenile obesity [39].

Hypothalamic Mechanisms Regulating Energy Balance

The central nervous system (CNS) receives multiple inputs of information as diverse as the sensory experience of eating, the process of ingestion, absorption, metabolism and levels of energy storage. The hypothalamus is the brain region located below the thalamus, comprising the major portion of the ventral diencephalon. The hypothalamus is organized in anatomically defined neuronal clusters, called nuclei, forming interconnected neuronal circuits via axonal projections. The hypothalamus controls an immense number of body functions; particularly important among them is the regulation of energy balance and endocrine axes. The arcuate nucleus of the hypothalamus (ARC) is considered the “master hypothalamic center” for feeding control. Two distinct neuronal populations in the ARC integrate peripheral nutritional/feeding signals. One set of neurons expresses the orexigenic (feeding-promoting) neuropeptides agouti-related protein (AgRP) and neuropeptide Y (NPY). These neurons mostly project to “second-order” neurons located in other hypothalamic nuclei, such as the paraventricular nucleus (PVH). A second ARC population of neurons expresses the anorexigenic (feeding inhibitors) products of proopiomelanocortin (POMC), the precursor of alpha-melanocyte stimulating hormone (α-MSH) and cocaine and amphetamine regulated transcript (CART). This set of neurons projects more broadly within the CNS, to secondary hypothalamic nuclei such as the dorsomedial nucleus (DMH), the lateral hypothalamic area (LHA), and the perifornical area (PFA) as well as the PVH. Dorsal to the ARC lies the ventromedial nucleus of the hypothalamus (VMH), which mainly receives projections from AgRP/NPY and CART/POMC neurons in the ARC. Additionally, the VMH neurons project their axons to the ARC, DMH, LHA, as well as brainstem regions, such as the nucleus of the solitary tract (NTS). Hypothalamic neurons respond to peripheral nutrients, such as glucose and fatty acids, and hormones, such as leptin, ghrelin, adiponectin, resistin and insulin, by modifying the synthesis and release of neuropeptides. When energy intake exceeds expenditure, the expression of orexigenic neuropeptides, such as AgRP and NPY, decreases. On the other hand, the expression of anorexigenic neuropeptides, such as CART and POMC, increases. Opposite changes occur when energy expenditure exceeds intake [1,2,6,27–29,32,40–43].

In addition to feeding, the hypothalamus also plays a major role in the regulation of energy expenditure and in the modulation of peripheral glucose and lipid metabolism, through the autonomous nervous system (sympathetic and parasympathetic). Thus, the hypothalamus integrates peripheral and central signaling and modulates: 1) the amount of hepatic glucose production by controlling insulin action [44–51]; 2) fat depots in the WAT by controlling adipogenesis and storage or oxidation of fatty acids in adipocytes [52–60]; 3) fatty acid oxidation in skeletal muscle [61–63]; and finally 4) energy expenditure by modulating the thermogenesis program in the BAT [30,31,33,64].

Effects of Perinatal Alteration in Feeding on Hypothalamic Mechanisms Regulating Food Intake

Circulating hormones play a fundamental role during maturation and differentiation of hypothalamic neurons. Extensive work in animals, mainly in rats, has shown that malnutrition during a vulnerable period of brain development may have permanent effects on brain size, brain cell number, behavior, learning, and memory [21]. Evidence also suggests that malnutrition in neonatal periods has strong impact on the hypothalamic mechanisms and circuits regulating food intake, a key step in the development of obesity associated with malnutrition in early life [12,16,17,65,66]. The first results concerning the effect of perinatal nutrition on hypothalamic feeding circuitry were reported by Plagemann and colleagues. In a series of elegant papers, this group demonstrated that perinatal overfeeding has a powerful effect on the development of hypothalamic neurons involved in the control of food intake. Perinatally overfed SL rats showed a decreased number of cholecystokinin (CCK) neurons...
in the PVH [67] and an increase of galanin (GAL) neurons in the same nucleus and the ARC [22,68]. These data suggested that these neuropeptide changes may be responsible for the development of hyperphagia, overweight and the associated metabolic disturbances [22,67,68]. Similar results, showing hypothalamic disorganization and altered GAL function, were obtained using other models of neonatal nutrition, such as low protein malnourished mothers [66,69,70] and diabetic mothers [71] suggesting that GAL neurons play a critical function in the correct development of hypothalamic function. Further evidence has confirmed that neonatal balanced nutrition is important for the programming of almost all hypothalamic neuropeptide systems, with SL overfed rats showing changes in the sensitivity or responsiveness to orexigenic and anorexigenic neuropeptides. Altered hypothalamic action of α-MSH, AgRP, CART, corticotrophin-releasing hormone (CRH), melanin-concentrating hormone (MCH) and NPY [16,17,24,72–76], as well as neurotransmitters such as dopamine [73,77], were observed in several hypothalamic nuclei (ARC, PVH, and VMH) in SL overfed rats. In general, these changes consist of enhanced sensitivity to orexigenic signals and reduced sensitivity to anorexigenic signals, resulting in increased feeding and decreased energy expenditure [16,78]. The group of Bolaños-Jiménez has also reported that perinatal protein-restricted rats exhibited hyperphagia characterized by a delayed appearance of satiety, and also an enhanced expression of the hypothalamic orexigenic peptides AgRP and NPY, with concomitant decrease of the anorexigenic precursor POMC [79]. Other results demonstrate that postnatal obesity may be augmented by the combination of prenatal undernutrition and postnatal high-fat nutrition. This phenotype also shows significant alterations in POMC, NPY, and AgRP, and increased levels of both plasma leptin and insulin [80].

The exact mechanisms underlying impaired appetite regulation in the models described above remain unclear. One possibility could be the altered density of neuropeptide receptors in relevant hypothalamic nuclei and/or altered activity of signaling pathways. However, considering that all examined neuropeptides are affected, it is likely that these effects are mediated by alterations in a common downstream regulatory target, such as glutamate and/or GABA [81,82]. Another interesting possibility is the alteration of cellular energy sensors. Data obtained during the last decade have demonstrated that the neuropeptide systems described above are regulated by hypothalamic basic cellular metabolic pathways and energy sensors, such as AMP-activated protein kinase (AMPK), carnitine palmitoyltransferase I (CPT1), fatty acid synthase (FAS), sirtuin 1 (SIRT1), and mammalian target of rapamycin (mTOR) [30,31,46,83–103]. Further work will be necessary to elucidate whether these energy gauges are affected by programming. Regardless of the specific molecular mechanism, the impaired responses of hypothalamic neurons in overweight SL rats reflect a general mechanism of neurochemical plasticity and “altered set-up” of hypothalamic neuropeptidergic systems, which may lead to permanently altered regulatory function in adulthood.

Despite the major changes in sensitivity to almost all neuropeptides examined, their expression remains generally unaltered. Papers published by our group have demonstrated that neonatal overfed rats display alterations only in AgRP and NPY mRNA expression, in an age-dependent way, being increased in juvenile (24-day old) but unaffected in adult (60-day old) rats [17]. Additionally, the increased expression of AgRP and NPY in the ARC of SL rats is restricted to the posterior (caudal) part of the nucleus, with no change in the anterior or medial part [16,17]. These data suggest the existence of different populations of AgRP/NPY synthesizing-neurons in the ARC and, more importantly, that they play different roles. Furthermore, our data also indicate that caudal AgRP/NPY expressing neurons might be responsible, at least in part, for the obese phenotype of the SL rats. Similar evidence has shown that NPY (and then AgRP) immunopositive neurons in the ARC and NPY concentrations in the PVH are increased in SL rats [23]. We did not detect any change in the mRNA levels of other orexigenic neuropeptides, such as MCH and orexin, suggesting that these systems are not likely to be implicated in the increase in food intake observed in these animals [16,17]. Moreover, other experiments have demonstrated a decrease in the expression of CRH in the PVH of SL juvenile (21-day old) rats [104]. Overall, this evidence suggests that hypothalamic feeding mechanisms display high plasticity, showing adaptive responses to age or age-related factors. The exact mechanism underlying these age-related differences is not clear; nevertheless, recent reports suggest that leptin, and possibly ghrelin, play a neurotrophic role during the development of the hypothalamus and that this action is restricted to a crucial neonatal period that precedes leptin’s acute regulation of feeding in adults [105,106]. This result suggests that perturbations in perinatal nutrition that modify leptin levels may, consequently, have long-term consequences for the formation and function of hypothalamic circuits regulating feeding and body weight in adulthood.

**Peripheral Signals in Hypothalamic Programming**

**Insulin**

Originally, it was postulated that the alterations in hypothalamic neurons induced by neonatal overfeeding were related to the hyperinsulinemia observed in SL rats. Similar to the offspring of rats with gestational diabetes, early postnatal overfed rats display high insulin levels in both plasma and hypothalamus [8,21]. On top of its effects on glucose homeostasis and body weight control [107,108] insulin is known to be a potent modulator of neuronal differentiation and maturation [109]. During adult life, insulin is capable of crossing the blood-brain-barrier (BBB) by regulated saturable transport. However during the neonatal period this saturable mechanism is not fully developed, so that insulin crosses the BBB without regulation [110]. As a result of this, the hypothalamus is exposed to high levels of insulin in neonatal overfed animals [12]. Several papers have suggested that neuronal dysplasia and altered formation of CCK, GAL and AgRP/NPY neurons in neonatally overfed rats are primarily associated with the increased insulin during this critical hypothalamic differentiation period [67,68]. This hypothesis was further supported by central insulin treatment during early postnatal life, showing alterations of the mean area of neuronal nuclei and the mean nucleus-cytoplasm-ratio within the VMH and the DMH, as well as increased density of astrocytes in the periventricular hypothalamic area [111]. These data demonstrate that hyperinsulinism during early development leads to an unstable organization and lasting dysfunction of these hypothalamic nuclei, which might be the cause of the hyperphagia, obesity and related metabolic dysfunctions.

The relationship between hyperinsulinemia and GAL or NPY expression is intriguing. When increased within a physiological range, insulin negatively regulates GAL [112] and NPY [113]
expression (mRNA and protein levels) in the ARC. On the contrary, SL rats display an increase in GAL and NPY expression, despite increased peripheral and hypothalamic insulin levels. These results suggest that SL rats display a hypothalamic insulin resistance, acquired during the critical neonatal period of hormone-regulated development of neuroendocrine systems [114]. This conclusion is supported by the increased plasma insulin/glucose ratio [68] and the reduced insulin-sensitivity of VMH neurons of SL rats [115]. Further work will be necessary to understand the molecular mechanism underlying the “altered programming” of galanergic and other hypothalamic neurons.

Leptin

The exact role of leptin in the development of hypothalamic circuitry is not fully understood, but evidence suggests that leptin plays a neurotrophic role during the development of the hypothalamus, and that this action is restricted to a crucial neonatal period that precedes leptin’s acute regulation of feeding in adults [105, 106]. Leptin-deficient (ob/ob) mice differ from wild-type mice in the numbers of excitatory and inhibitory synapses and postsynaptic currents on NPY and POMC neurons. Leptin treatment of ob/ob mice rapidly normalizes synaptic density. Remarkably, this effect has been detected within 6h, preceding leptin’s effect on food intake with several hours, indicating that leptin-mediated hypothalamic plasticity may trigger some of the hormone’s behavioral effects [105]. Consistent with the developmental role of leptin, neural projections from the ARC are permanently disrupted in ob/ob mice. Leptin treatment in adult ob/ob mice does not reverse these defects. However, leptin administration to ob/ob neonates recovers the outgrowth of projections from the ARC, and leptin promotes neurite development from ARC neurons in vitro [106]. These results suggest that leptin plays a neurotrophic role during the development of the hypothalamus, but that this activity is limited to a crucial neonatal period before leptin’s acute regulation of food intake in adulthood [105, 106].

Circulating leptin levels are tightly correlated with adipose tissue mass. Overfeeding during the neonatal stage results in higher adiposity [16, 116]. In agreement with this, overfed SL rats are hyperleptinemic in both the neonatal and adult stage [16, 17, 117]. Interestingly, despite high leptin levels, SL rats are hyperphagic (at least during the juvenile state), which contributes to persistent increased body weight [16, 17, 116–118]. The molecular mechanisms responsible for leptin resistance in the neonatal overfed rats have been extensively investigated. It has been demonstrated that hyperleptinemia per se is not enough to explain the leptin resistance observed in these animals, suggesting the involvement of other factors besides leptin, probably hyperinsulinemia [116].

Leptin resistance in neonatal overfed rats results in impaired sensitivity of hypothalamic neurons. It has been demonstrated that SL rats display different responsiveness to leptin in both VMH and ARC neurons. VMH neurons of normal rats are mainly activated by leptin, whereas VMH neurons of SL rats are inhibited [119]. On the other hand, leptin inhibits ARC neurons from normal rats, but it does not have any effect on ARC neurons from SL rats [118]. Other studies have also demonstrated that this programmed leptin resistant state of neonatal overfed rats shows an age-dependent molecular basis. In juvenile SL rats (24-day old), similarly to gestation [120, 121], there is a specific decrease of the mRNA levels encoding OB-Rb in the hypothalamus [16]. These data fully agree with the increase in NPY and AgRP expression in the ARC of SL rats, in spite of their marked hyperleptinemia [16, 17]. On the other hand, adult (60-day old) neonatal overfed rats do not show any change in the expression of OB-Rb or any other leptin receptor isoforms [17]. Interestingly, adult SL rats show abnormally low cerebrospinal fluid (CSF) leptin levels, despite increased plasma leptin levels, suggesting that the rate of leptin influx into the CNS is not enhanced [17]. This evidence suggests, as in other obese models, that resistance to peripheral leptin in the SL adult rats [17, 117, 118] may be related, at least partially, to saturation of the transport of leptin into the hypothalamus through the BBB [17, 122–125]. It cannot be excluded that SL adult animals have defects in the intracellular transduction mechanism of the JAK/STAT or SOCS-3 pathways [2]. However, these rats display a robust response to central administration of leptin [17] suggesting that hypothalamic leptin-signaling mechanisms are not altered.

Ghrelin

Ghrelin is a protein-acylated hormone mainly synthesized and secreted by the stomach [126]. Ghrelin acts on growth hormone secretagogue receptor (GHSR) in AgRP/NPY ARC neurons to potentely increase food intake [58, 95–97, 127–131]. Furthermore, it has been demonstrated that ghrelin affects synaptic organization of POMC neurons in the ARC. This effect is contrary to leptin’s action on synaptic plasticity and results in a global inhibition of POMC tone, associated with increased feeding [65, 105]. Increasing evidence suggests that the biological actions of ghrelin differ between adults and neonates. For example, in sharp contrast to the potent orexigenic effects of ghrelin on adults, ghrelin treatment does not induce intake nor body weight during the first 2–3 postnatal weeks in rats and mice [132–134]. The reasons of this divergence are unclear, but they appear not to be related either to impaired GHSR expression or lack of response in the ARC, at least in terms of c-Fos, POMC and NPY expression [133, 134]. Whatever the case, and considering ghrelin’s effects on synaptic organization [65, 105], as well as its promoting effects on cell proliferation and neurogenesis [133, 134], it is tempting to postulate a role for this hormone in hypothalamic programming. In this sense, alterations in perinatal ghrelin levels result in structural differences in various peripheral organs, such as the pancreas and gastrointestinal tract, where ghrelin reduces growth and alters DNA synthesis and content [133–136]. Thus, exposure to factors that alter ghrelin’s impact on development may induce lasting effects on physiological regulation.

Glucocorticoids

Glucocorticoids (GCs) are steroid hormones, which are secreted from the adrenal gland into the circulation under the control of the hypothalamic-pituitary-adrenal (HPA) axis [137]. Glucocorticoids play a major role in body weight homeostasis, metabolism, and food intake [138–140]. Glucocorticoids are also fundamental organizers of neuroendocrine systems. Hypercortisolism in early life may predispose individuals to the same condition in adulthood [141, 142]. Other groups showed that overfed SL rats display accelerated maturation of the HPA axis, a permanent upregulation of the HPA axis and increased adipose tissue glucocorticoid sensitivity in adulthood [104, 143]. The HPA upregulation is associated with altered CRH expression in the PVH specifically with a faster maturation to adult levels [104]. Moreover, prenatal glucocorticoid overexposure in rats is
associated with the development of fatty liver when animals are maintained on a HFD following weaning, in association with altered expression of genes that are important in lipid metabolism [144], suggesting that fatty liver may be a common consequence of prenatal exposure to an “adverse environment”, particularly when combined with postnatal obesity. These alterations probably play a role in the development of the obese phenotype of SL rats.

Environmental Influence on Genes: Epigenetic Factors

Epigenetic studies concern the inheritance of information beyond the DNA sequence, for example, through biochemical changes such as DNA methylation and histone modifications controlling spatial, temporal and parent-specific, highly coordinated gene expression patterns. A number of elegant animal studies have shown that nutritional factors can modify the epigenome of the developing offspring, thus affecting fetal programming. For example, Park et al. showed that epigenetic silencing of the transcription factor pancreatic and duodenal homeobox 1 (PDX1), which regulates pancreas development and β-cell differentiation, contributes to the development of type II diabetes in rats with intrauterine growth retardation [145]. In the same animals it was shown that histone code modifications underlie repression of the Slc2a4 gene, which encodes the glucose transporter 4 (GLUT4) in muscle [146].

Regarding epigenetic regulation of expression during the postnatal stage, a low number of studies have been published so far; however, it has been reported that the promoter region of POMC in hypothalami from rats overfed during lactation undergoes hypermethylation in 2 related binding sequences in the specificity protein (Sp1) [147], a major POMC transcriptional activator. Hypermethylation may therefore affect the expression POMC in SL rats through a mechanism of “silencing”. In addition, the same group has shown that excessive nutrition during lactation produces hypermethylation of the promoter region of the insulin receptor in the hypothalamus of overfed rats [148]. Finally, recent evidence in sheep has demonstrated that twinning and periconceptional undernutrition are associated with methylation changes in fetal hypothalamic POMC and glucocorticoid receptor genes, leading to altered energy balance regulation in the offspring [149].

Effects of Perinatal Overfeeding in Humans

Considering the evidence for molecular mechanisms triggered by perinatal overfeeding in animals, it is tempting to extrapolate these findings to humans. Programming in people is not easy to investigate, given that most conclusions are necessarily based on epidemiological retrospective associations. Additionally, there are many more studies concerning the long-term consequences of neonatal undernutrition than overnutrition. In humans, perinatal overnutrition predisposes to metabolic alterations such as diabetes and obesity [7, 150, 151]. Low birth weight is associated with cardiovascular disease in adulthood and poor maternal nutrition during gestation contributes to low birth weight [11]. One of the most remarkable examples of this is based on data from the Dutch 1944–1945 winter famine, the outcomes of which have yielded substantial information on the importance of early life nutrition [152–154]. In this cohort, the prevalence of coronary heart disease, raised serum lipids, obesity, and glucose intolerance was higher in people exposed to famine during gestation than people not exposed to famine. Interestingly, the timing (early, mid-, or late gestation) was crucial to determine which organ(s) were affected. In keeping with this, data from 7874 adults born between 1954 and 1964 from the 2002 China National Nutrition and Health Survey show that exposure to the Chinese famine during fetal life or infancy was associated with an increased risk of metabolic syndrome in adulthood [155, 156]. Interestingly, exposure to famine in early gestation may affect dietary preferences in humans, and thus eating habits, for the entire lifespan. A study including 1797 participants from the Helsinki Birth Cohort Study, aged 56–70, whose birth weight and length were recorded, concluded that prenatal growth may modify food and macronutrient intake later in life, and altered dietary habits could potentially explain the increased risk of chronic disease in individuals born with small body size [157]. These findings demonstrate that maternal undernutrition during gestation has important effects on health in adulthood [152, 153]. Other retrospective and epidemiological studies have confirmed this evidence [11, 21]. On the other hand, evidence has also demonstrated that higher birth weight correlates with increased risk of overweight in adolescence. In a cohort study of over 14000 adolescents, a 1 kg increment in birth weight in full-term infants was associated with an approximately 30% increase in the risk of overweight at ages 9–14 [158]. In this sense, another cohort study of 300 African Americans born at full term was followed from birth to 20 years of age, providing evidence that a pattern of rapid weight gain during early infancy is associated with obesity not only in childhood but also in young adulthood, proposing that infancy constitutes a critical period for the development of obesity [159].

Examining the growth of rural Croatian infants, a preventive influence of breastfeeding on the development of obesity in infancy was observed [160]. Data concerning the effect of early nutrition on mechanisms controlling feeding in humans are scarce. Plasma leptin concentrations are low in growth-restricted newborns at birth, but by 1 year of age these children have higher leptin levels than age-matched infants with normal birth weight. On the other hand, newborns with low birth weight also have higher leptin concentrations in adulthood than people of normal birth weight with matched BMI [161]. Thus, programming of relative leptin concentrations by early diet may be one mechanism linking early nutrition with later obesity. In this sense, the existence of programmed leptin responsiveness in humans has recently been demonstrated. High leptin concentrations during early postnatal life (associated with greater body adiposity) decrease the response to circulating leptin in later life [162]. Although there are no data concerning the mechanism of this reduced leptin sensitivity, it is tempting to speculate that it may be due to acquired leptin resistance [2], as described in adult SL rats [17]. Further work will be necessary to clarify this issue.

Concluding Remarks

Early postnatal overfeeding leads to obesity and associated metabolic syndrome in adult life. Although the precise mechanisms of neonatal programming are not fully elucidated, it is clear that the programming of hypothalamic neuroendocrine systems is highly complex, originating in the homeostatic loop regulating
feeding and body weight (Fig. 1). The relationship between the impairment of hypothalamic circuitry and peripheral signals is increasingly understood. Several hormones involved in body weight regulation, such as insulin, leptin, and ghrelin [105,106, 133,134,163–169], exert neurotrophic roles in the hypothalamus, modulating neuronal plasticity. The individual contribution of these signals remains to be established, but it seems that they act in a very precise and orchestrated way. Current and future investigations will penetrate the underlying molecular mechanisms of obesity and the metabolic syndrome, aiding the identification of new pharmacological targets for treatment strategies to manage the consequences of human malnutrition. In this sense, it has been reported that long-term dietary intervention postweaning can override the effects of litter size-induced obesity in rats [143]. Further work will be necessary to address these issues in the treatment of human obesity.

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Conflict of Interest ▼

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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