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Review Article

Leptin in Early Life: A Key Factor for the Development of the Adult Metabolic Profile

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Key Words
Leptin · Metabolic programming · Hypothalamus · Adipose tissue

Abstract
Leptin levels during the perinatal period are important for the development of metabolic systems involved in energy homeostasis. In rodents, there is a postnatal leptin surge, with circulating leptin levels increasing around postnatal day (PND) 5 and peaking between PND 9 and PND 10. At this time circulating leptin acts as an important trophic factor for the development of hypothalamic circuits that control energy homeostasis and food seeking and reward behaviors. Blunting the postnatal leptin surge results in long-term leptin insensitivity and increased susceptibility to diet-induced obesity during adulthood. Pharmacologically increased leptin levels in the postnatal period also have long-term effects on metabolism. Nevertheless, this effect is controversial as postnatal hyperleptinemia is reported to both increase and decrease the predisposition to obesity in adulthood. The different effects reported in the literature could be explained by the different moments at which this hormone was administered, suggesting that modifications of the neonatal leptin surge at specific time points could selectively affect the development of central and peripheral systems that are undergoing modifications at this moment resulting in different metabolic and behavioral outcomes. In addition, maternal nutrition and the hormonal environment during pregnancy and lactation may also modulate the offspring's response to postnatal modifications in leptin levels. This review highlights the importance of leptin levels during the perinatal period in the development of metabolic systems that control energy homeostasis and how modifications of these levels may induce long-lasting and potentially irreversible effects on metabolism.

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Introduction

Leptin is a 167 amino acid peptide mainly produced by adipose tissue [1] whose main function is to maintain body weight by regulating the balance between energy intake and expenditure [2]. Leptin mRNA and protein levels in adipose tissue and plasma are positively correlated with body fat and adipocyte size [3]. Thus, obese individuals generally have higher leptin mRNA and protein levels than lean individuals [4–5].

Leptin acts on feeding centers in the hypothalamus and other brain areas, modifying the expression and release of orexigenic and anorexigenic neuropeptides, including neuropeptide Y (NPY) and pro-opiomelanocortin (POMC). In the arcuate nucleus (ARC), NPY and POMC neurons express the long form of the leptin receptor (Lep-Rb), which is functionally coupled to the Janus kinase signal transducer-signaling pathway [6]. Although there are at least six alternatively spliced isoforms of the leptin receptor (Lep-Ra, Rb, Rc, Rd, Re and Rf) in mice [7], it is activation of Lep-Rb that is reported to be most involved in metabolic control. The shorter isoforms are thought to act as leptin transporters at different sites, including plasma and the blood-brain barrier [8, 9].

Binding of leptin to Lep-Rb results in phosphorylation of Janus activated kinases 1 (JAK-1) and 2 (JAK-2) and tyrosine phosphorylation of the cytoplasmic domain of Lep-Rb and downstream transcription factors of the signal transducer and activators of transcription (STAT) family. These signaling molecules are highly expressed in the hypothalamus, brainstem, and other brain regions that control food intake and autonomic and neuroendocrine functions [10]. Reduction in the sensitivity or activation of this signaling pathway results in leptin resistance and underlies the obese phenotype of *db/db* mice and fatty rats [7, 11]. Leptin's actions are terminated by induction of silencer of cytokine signaling 3 (SOCS-3), a member of a family of proteins induced by cytokines, that blocks the JAK-STAT signaling cascade by inhibiting leptin-mediated tyrosine phosphorylation of JAK-2 [12]. SOCS-3 may also play a role in leptin resistance as SOCS-3 levels are elevated in the ARC in diet-induced obese (DIO) mice, and this is associated with reduced sensitivity to leptin's effect on food intake, body weight, and neuropeptide secretion [13]. Protein-tyrosine phosphastase 1B (PTP-1B) is also a critical downstream regulator of leptin signal transduction [14, 15]. Overexpression of PTP-1B decreases phosphorylation of JAK-2 and blocks leptin-induced transcription of SOCS-3 and c-fos [16], while deletion of the *PTP-1B* gene enhances leptin sensitivity in mice, preventing obesity [17, 18]. In addition to this cascade involving JAK-STAT, leptin also modulates other intracellular pathways including ERK, AMPK, PI3K, and cAMP [19, 20] (fig. 1).

Leptin's effects on metabolism are not limited to modifications in neuropeptide production or secretion, as it also induces rapid modifications in synaptic connectivity of neuronal populations involved in metabolic control [21] as well as in astrocyte morphology [22]. Leptin may also control food intake by modulating taste perception as this hormone selectively reduces the sweet taste response, most likely through direct action on the Lep-Rb expressed in sweet-sensitive receptor cells [23]. Leptin receptors are also expressed in areas involved in eating behavior [24–26], and this hormone has been shown to affect food seeking behavior, by modifying both the hedonic and motivational aspects of reward, anxiety, and food preference [27–30]. Furthermore, leptin not only regulates energy homeostasis by acting in the brain but also increases basal metabolism through stimulation of the sympathetic nervous system and thyroid hormones thus increasing energy expenditure [31].

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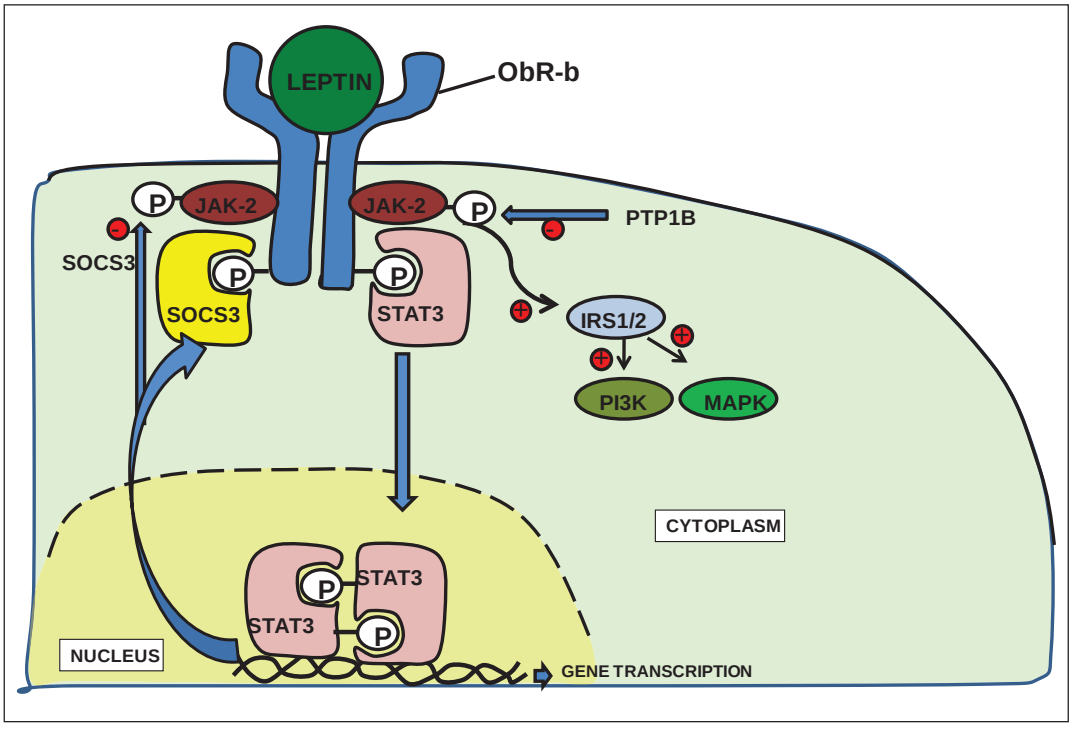

Fig. 1. Schematic representation of the intracellular signaling mechanisms of the leptin receptor 1b (Lep-b): Leptin binds to the leptin receptor, which activates JAK-2 leading to nuclear translocation of STAT3 to mediate the transcriptional regulation of neuropeptides and SOCS-3. SOCS-3 and PTP-1B inhibits leptin signaling.

Metabolic Programming: A General Overview

In the last decades, the prevalence of obesity during childhood has dramatically increased worldwide [32–34]. This phenomenon is of great concern since infant and juvenile obesity are significantly correlated with an increased risk of suffering health problems in adulthood, including cardiovascular diseases, hypertension, and obesity [35, 36]. Based on multiple epidemiological studies, it is now clear that environmental factors acting early in life, including nutrition, play an important role in the pathogenesis of diseases in adulthood, particularly in obesity development [37–39]. Interestingly, both overnutrition and undernutrition during pregnancy and lactation are reported to induce long-lasting effects on energy balance and predispose the offspring to incurring metabolic diseases in adulthood [40–42].

Barker and colleagues in their hypothesis ''developmental origins of health and disease'' proposed that an adverse environment in early life can cause disruptions in normal growth and development, increasing the propensity to obesity and other related diseases in adulthood [43]. There is considerable evidence supporting this proposal, such as the representative example of the Dutch famine during the last 6 months of World War II where males born to women exposed to poor nutrition in the first and second terms of pregnancy were more likely to become obese than those whose mothers did not experience poor nutrition during gestation [44, 45]. In support of the Barker hypothesis, it is well established that abnormal fetal growth affects long-term metabolic health [46]. Indeed, high maternal body mass index (BMI) is a risk factor for large-for-gestational-age (LGA) infants, with these children having increased susceptibility to disease throughout life [47]. Maternal obesity

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increases the risk of metabolic complications in children approximately twofold [46, 48] and doubles the risk of stillbirth and neonatal death [49]. Likewise, women with poor glycemic control and/or gestational diabetes have a high risk of giving birth to a macrosomic baby that is more likely to develop obesity and insulin resistance later in life [50, 51].

Not only is the prenatal environment important but also the immediate postnatal period since critical windows of organ development extend into early postnatal life. For example, in rodents, pancreatic islets and brain circuits continue their development after birth [52–54]. In humans, the postnatal feeding regime affects infant growth trajectories since weight gain during the first weeks of life is positively associated with later obesity [55]. In addition, an earlier age of adiposity rebound is also associated with a higher risk of obesity later on [56].

Thus, both gestational and early postnatal cues are critical for the development of central and peripheral systems involved in metabolic control, including the hypothalamus and adipose tissue, modulating their responses to metabolic signals and increasing the probability of excess weight gain in adulthood. Moreover, recent evidence suggests that behaviors associated with feeding can also be affected by early nutritional influences.

The Hypothalamus in the Control of Energy Homeostasis

The hypothalamus plays a key role in the control of energy homeostasis, with special attention being paid to neurons in the ARC as these neurons express receptors for circulating hormones involved in appetite regulation and energy expenditure such as leptin, insulin, or ghrelin [57]. In the ARC, orexigenic neurons expressing NPY and AgRP are activated by appetite-stimulating signals such as ghrelin to promote food intake [58]. Another population of neurons express POMC and CART and are activated by anorexigenic signals such as leptin or insulin to promote appetite inhibition and weight loss [59]. Both NPY/AgRP and POMC/CART neurons extend projections to other key parts of the hypothalamus including the paraventricular (PVN), ventromedial (VMH) and dorsomedial (DMH) nuclei and the lateral hypothalamus (LHA), with these regions also participating in food intake regulation [57, 59]. Extrahypothalamic brain areas involved in the regulation of feeding and energy balance include the ventral tegmental area (VTA) and the nucleus of tractus solitarius (NTS) which receive signals from the gastrointestinal system through the dorsal vagal complex.

There are also behavioral aspects of feeding that must be taken into consideration, as some inputs are based on the palatability and reward of food that can override the satiety signals. These hedonic neurocircuits include the nucleus accumbens (NAc), the ventral pallidus (VP), the VTA, and higher cortical areas such as the prefrontal cortex, all of which converge on the LHA. These pathways use biological substrates such as glutamate, opioids, endocannabinoids, and dopamine and are responsive to peripheral metabolic signals like leptin [60, 61] and ghrelin [62, 63]. The effects of these compounds on mood highly contribute to the impact of the hedonic pathways in food intake.

Hypothalamic Development

Hypothalamic development differs between species. Whereas in nonhuman primates this process is thought to occur entirely during the third trimester of pregnancy [64, 65], in rodents it begins prenatally but does not finalize until the second week of postnatal life [66]. In rodents, development of hypothalamic nuclei begins around embryonic day (E) 12

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with neurogenesis in the neuroepithelium of the third ventricle. Once generated, the postmitotic neurons migrate from the proliferative zone of the third ventricle to form the various nuclei and areas that constitute the hypothalamus [52, 67, 68]. The neurons from the different hypothalamic areas are created at different time points, with neurons of the PVN appearing around E 12 and those of other nuclei such as the ARC being born between E 12 and E 16. Neurons in the ARC express POMC around E 12 [69] and NPY around E 14 [70]. The expression of both orexigenic and anorexigenic neuropeptides continues to increase during the postnatal period, reaching their maximum values around postnatal day (PND) 15 [71]. Although neurogenesis occurs prenatally, the establishment of connections between neurons in the different nuclei takes place postnatally, with innervation between neurons of the ARC and DMH being established at PND 6 and between neurons of the ARC and PVN and LH occurring at PND 10 and PND 12, respectively [72]. Since projections from the DMH and VMH develop prior to those from the ARC [72], it is suggested that these neural pathways could be the primary regulators of feeding and metabolism during early postnatal life [67].

Leptin's Impact on Hypothalamic Development

Apart from its actions in the control of energy homeostasis in adult life, leptin plays an important role in brain development and specifically in the establishment of hypothalamic circuitry [73]. Indeed, leptin-deficient *ob/ob* mice show several brain disruptions such as reduced brain weight, structural abnormalities, and impaired myelination [74, 75] as well as a reduction in cell density and synaptic and glial proteins in various brain regions, including the hypothalamus [76]. These mice also have modifications in the number of projections and synaptic inputs to hypothalamic areas and neuronal populations that control metabolism [21, 77].

Leptin can restore normal brain weight in *ob/ob* mice only when this hormone is injected during early life [78], suggesting that specific critical periods exist for its developmental actions. Indeed, Bouret et al. [77] demonstrated that leptin has a powerful trophic action in the brain, increasing the density and length of axons from ARC neurons in vitro, and that leptin treatment to *ob/ob* animals only restored the abnormalities in ARC projections when it was administered during the first days of postnatal life, and not in adulthood.

In 1998 Ahima et al. [79] reported that there is a postnatal leptin surge in rodents, with leptin levels increasing around PND5 and peaking between PND 9 and PND 10. However, these increased leptin levels were not related to increased fat mass although a transient upregulation of leptin mRNA was found in adipose tissue during this period [79]. In sheep this peak occurs between PND 6 and PND 9 [80], and in humans leptin levels decrease after birth [81].

The characteristics of the leptin peak can be modified by both the prenatal and postnatal nutritional environment. Both maternal under- and overnutrition are reported to increase the leptin surge in the offspring [82, 83] while the postnatal rise in leptin does not occur in lambs born to obese mothers [80]. However, all of these scenarios result in increased weight in the offspring during later stages of life.

Although the leptin receptor is expressed and functional during neonatal life [84, 85], leptin is unable to modulate feeding or energy expenditure until the second postnatal week [86]. Thus, during this period leptin seems to be more involved in hypothalamic development than in the regulation of body weight and food intake.

The fact that leptin levels are elevated during embryonic development in humans [87], particularly during the third trimester of pregnancy [65, 88], and the observation that leptin

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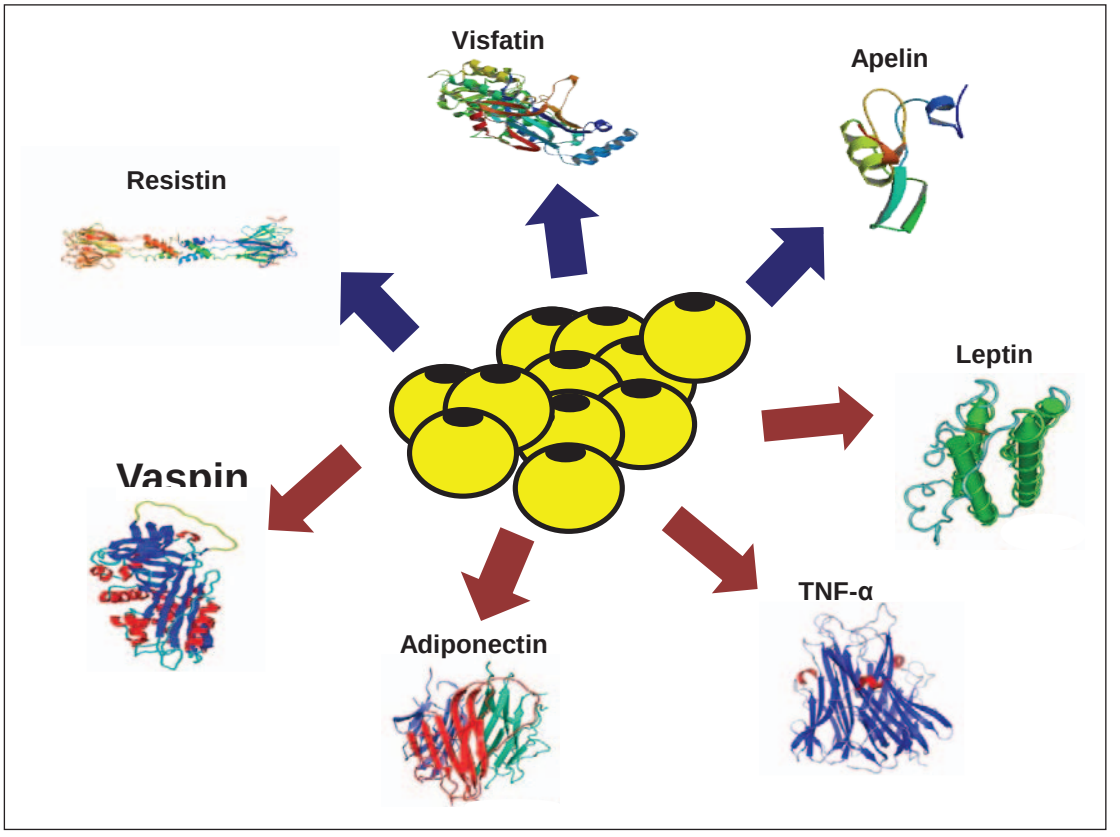

Fig. 2. Adipocytes secrete different adipokines such as leptin, visfatin, resistin, apelin, TNF-α and adiponectin among others.

levels at birth are correlated with head circumference [89] supports the hypothesis that leptin also influences brain development in humans. In addition, leptin-deficient patients show modifications in different brain structures [90–92]. These changes are anatomically specific, with leptin administration exerting sustained effects on neural tissue composition.

Moreover, modifications in leptin levels during development also induce long-term effects in some leptin-modulated behaviors. Fraga-Marques et al. [93] reported that increased neonatal leptin levels program anxiety-like behaviors, but not memory in rats. In humans with congenital leptin deficiency, leptin replacement modifies brain activity in areas associated with emotions, including hunger and reward in response to food-related stimuli [90, 94, 95]. Likewise, in mice neonatal leptin treatment has been recently shown to have long-term effects on behavior and brain anatomy [96].

Adipose Tissue Development

Adipose tissue has been historically considered as an inert organ with little influence on physiology apart from its role as a storage depot for excess energy. However, in recent years much evidence has highlighted it as a dynamic participant in regulating whole-body metabolism. In fact, changes in the distribution, structure, and function of adipose tissue dramatically influence the ability of an individual to maintain energy balance and resist weight gain [97, 98] (fig. 2).

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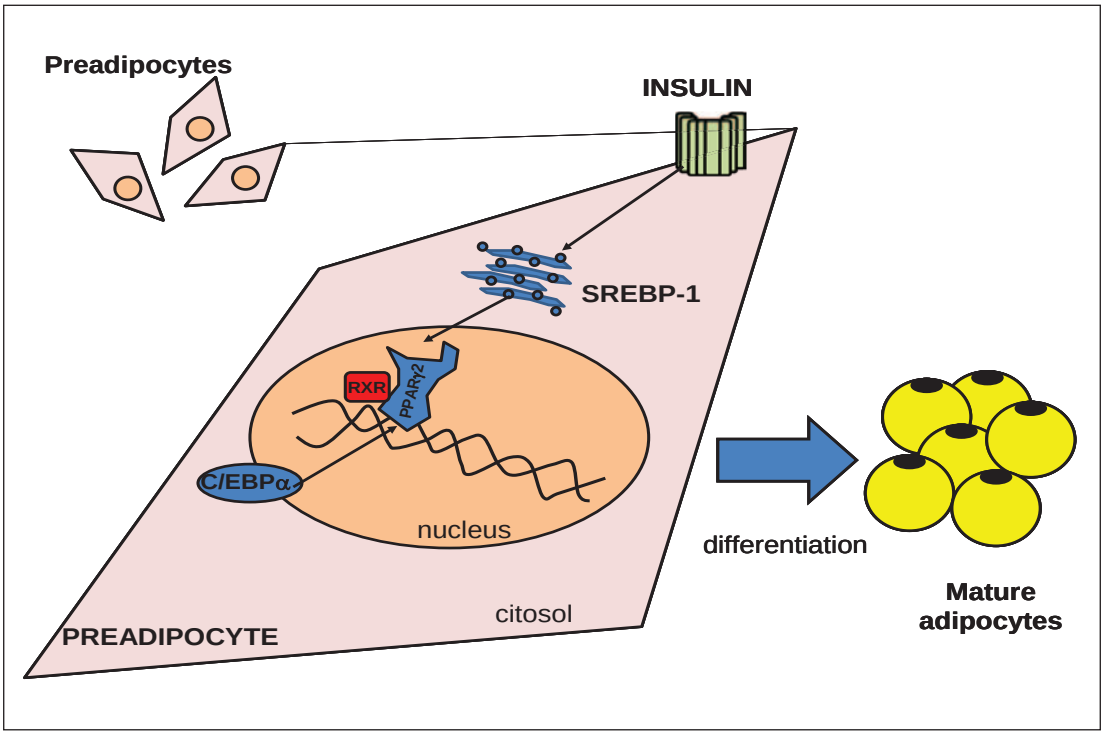

Fig. 3. Adipogenesis is regulated by peroxisome proliferator-activated receptor γ (PPARγ) that is activated by CAAT enhancer binding proteins (C/EBPs) and regulatory element-binding protein 1 (SREBP-1). Different factors can initiate the differentiation process, with insulin being and indispensable factor for the formation of mature adipocytes.

In humans adipogenesis occurs primarily during late fetal and early postnatal life although it can also be stimulated in adulthood under certain conditions like obesity [99, 100]. The first traces of adipose tissue are detectable between the 14th and 16th week of human gestation [101]. Some of the key regulators identified in the adipogenic process include peroxisome proliferator-activated receptors (PPARs), CAAT enhancer binding proteins (C/EBPs) and sterol regulatory element-binding protein (SREBP-1) [102], which are expressed early in immature adipocytes. These transcription factors operate synergistically, regulating the expression of other adipocyte-specific genes and resulting in the formation of mature adipocytes with capacity for lipid storage, lipid degradation, and adipokine secretion [103] (fig. 3).

From the beginning of adipogenesis until the 23rd week of prenatal life, the number of fat lobules remains constant, with the size of the lobules growing in subsequent weeks and acquiring the typical multilocular morphology of adipocytes [101, 104, 105]. Around the third trimester, small adipocytes can be found in the main sites of fat deposition, with body fat accounting for approximately 16% of body weight at birth. During the first 12 months of postnatal life the increase in body fat is due to an increase in fat cell size, while adipocyte numbers remain unchanged [105, 106]. However, it has been reported that both changes in adipocyte volume and number can also occur at later stages of life under certain conditions like obesity [100].

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Leptin's Impact on Adipose Tissue Development

During early life, adipocyte proliferation and differentiation are highly sensitive to the nutritional environment, in particular to the concentrations of circulating hormones and nutrients such as insulin-like growth factors, glucose, insulin, and glucocorticoids [107, 108]. Nutrient availability during this period is reported to determine fat mass in adulthood since overfeeding during the first weeks of life induces an overexpansion of adipose tissue in rats which is associated with an increase in the number of fat cells [109–111], whereas undernutrition permanently reduces adipose cell number [112]. Studies in sheep and pigs also show that exposure to excess nutrients during late gestation significantly increases fat mass, adipocyte size, and the capacity of fat cells for storing lipids in postnatal life [113]. Some of these nutrition-induced changes may be mediated through modifications in leptin levels.

In the fetus, leptin levels follow the evolution of adipose tissue development, with low levels being found during the first half of gestation and dramatically increasing during the last part of the third trimester [87, 114]. Shortly after birth, circulating leptin levels decline [81]. The conversion of preadipocytes into mature adipocytes is accompanied by an increase in leptin gene expression [115], and abundance of leptin in fetal adipose tissue is related to fetal body weight [116]. Indeed, children born small for gestational age have lower cord blood leptin levels than those born normal for gestational age [117]. Leptin levels in cord blood have been suggested to predict adiposity in later years [118], suggesting that in utero leptin levels also have long-term influences on metabolism in humans.

Since leptin is produced by the placenta and is also found in breast milk [119], maternal leptin levels during pregnancy and lactation may have an impact on adipose tissue development in the offspring. Studies show that diet-induced hyperleptinemia in the mother results in increased body weight and adiposity in the offspring [53, 120]. However, in addition to hyperleptinemia, obesity is associated with many other alterations; so it is difficult to determine the exact influence of leptin from overweight mothers on the increased adiposity of their offspring.

Controversial results have been obtained regarding maternal leptin administration during pregnancy. In lean rats, maternal leptin treatment during the first 10 days of lactation results in increased food intake and body weight gain as well as in increased visceral fat, leptin resistance, hyperglycemia, and hyperleptinemia in the offspring, with these alterations becoming evident after puberty and aggravating with age [121]. In contrast, leptin treatment of pregnant rats during the last week of gestation prevents the diet-induced increase in body and fat pad weights when the offspring are later exposed to a high-fat diet [122]. In sheep, maternal leptin infusion until the end of gestation altered adipose tissue morphology, increasing the number of multilocular adipocytes and the expression of UCP-1 [123].

The effect of leptin administration during the postnatal period is far from being clear since it has been reported to both protect [124] and predispose [125] to obesity later in life. The nutritional status of the mother seems to play a key role in the offspring's response to postnatal leptin administration [126]. The controversial effects could also be explained by differences in the dosages used, the routes of administration, the treatment duration, or the different time points of leptin administration. Indeed, recent data from our laboratory indicate that not only are leptin levels important in the suckling period for the development of metabolic systems but also the exact moment in which they are modified. We found that acute hyperleptinemia on PND 2 reduces food intake in the adult offspring without affecting body weight gain, whereas blunting leptin levels on PND 9 decreases adiposity at adulthood without affecting food intake [127].

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Prolonged neonatal hypoleptinemia also has delayed effects on metabolism. Blunting the postnatal leptin surge from PND 2 to PND 13 results in long-term leptin insensitivity and increased susceptibility to diet-induced obesity [128]. In addition, maternal deprivation-induced hypoleptinemia decreases body weight and leptin levels in adult rats [129–130].

In conclusion, leptin levels during early life are important for the development of the adult metabolic profile as they affect the development of central and peripheral systems involved in energy homeostasis. Moreover, it is clear that modulation of the levels of this important hormone during development, whether increased or decreased, acutely or chronically, can have diverse effects on these systems. Further elucidation of this phenomenon and the mechanisms involved may help us to understand the recent and dramatic rise in obesity in many countries and to develop a strategy for its prevention.

Disclosure Statement

The authors declared no conflict of interest.

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