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Neurodevelopmental Actions of Leptin

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Abstract

Leptin is well known as an important hormone in the central control of feeding behavior. During development, fetuses and newborns are exposed to leptin and recent evidence has shown that leptin receptors are widespread throughout the developing brain. Accordingly, leptin affects brain development during both pre- and post-natal life. The actions of leptin in the developing brain are generally permanent and range from the establishment of hypothalamic circuits to plasticity in cortical pathways. The cellular events mediated by leptin include the following: neurogenesis, axon growth, and synaptogenesis. Nutritional manipulation of leptin secretion during perinatal life has generated considerable concern, and the developing brain appears to be a particularly sensitive target for these environmental changes.

Keywords

hormones; nutrition; hypothalamus; programming; obesity; axon growth

Introduction

Leptin is a 16-kDa protein secreted from white adipose tissue that acts as a crucial signal for body energy stores. It is found in the blood circulation in proportion to fat mass and functions to blunt feeding behavior and promote energy expenditure. It is now widely recognized that leptin primarily acts on the brain to mediate its effects on feeding and energy balance. The observation that central nervous system-specific deletion of leptin receptors results in a phenotype that is a virtual carbon copy of whole-body leptin receptor-deficient ($\text{Lepr}^{\text{db/db}}$) mice strongly supports this idea [15]. The hypothalamus has traditionally been the focus of studies on obesity, owing not only to its central role in neuroendocrine functions and feeding behavior, but also to the fact that it contains the highest density of leptin receptors of any brain region [13,22]. Accordingly, leptin acts directly on neurons located in various parts of the hypothalamus, including the ARH, the VMH, and the LHA, to induce its effects on feeding and energy balance regulation in mature animals [3,16,21,38]. An emerging concept in the field of leptin neurobiology also implicates other non-hypothalamic brain regions in mediating the central effects of leptin. These regions include, but are not limited to, the midbrain [23,30], the hippocampus [40], and the hindbrain [26].

It is broadly recognized that hormones can produce pleiotropic effects, especially in the brain, on functions that are well outside those they have traditionally been thought to regulate. Consistent with this idea, although the effects of leptin in the brain were previously

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thought to be limited to the neural control of feeding behavior in mature animals, it is now becoming increasingly clear that leptin can also influence a variety of developmental processes in the immature brain. This review summarizes the neurodevelopmental changes that have been observed in response to alterations in leptin levels during critical periods of development.

Leptin Secretion during Important Periods of Brain Development

Leptin is one of the first major metabolic hormones to appear during development. White adipose tissue (the main source of leptin production in adult animals) is minimal at early ages, yet mouse fetuses do contain significant leptin levels in their blood as early as E12.5 [52] (Ishii and Bouret, unpublished data). Various tissues produce leptin during embryonic development. On embryonic day 13.5, high levels of leptin gene expression are found in the fetal liver and cartilage-bone structures, followed by cardiac expression between E16.5 and 18.5 [28,29]. In addition to being produced by the embryo itself, dams also contain high levels of leptin during pregnancy, but whether maternal leptin crosses the placenta and reaches the embryo during early-mid gestation (i.e. when brain development is initiated) remains unclear. Circulating leptin levels increase markedly during the postnatal period and exhibit a “surge” [2]. These significantly higher levels of postnatal circulating leptin are associated with greater production of leptin mRNA in both white (abdominal) and brown (interscapular) adipose tissue [20]. The mechanisms that underlie these transcriptional changes are largely unknown. The ingestion of fat contained in the mother's milk represents a plausible cause for the increase in leptin expression during the first weeks of postnatal life. Dietary fat can influence leptin expression [44], and fat is abundant in rodent milk ranging from 22% in colostrum to 9% in late milk [41]. After weaning, there is a coordinated decrease in levels of leptin mRNA and leptin peptide [2,20] when pups switch from maternal milk to an adult diet. Leptin transport across the blood-brain barrier (BBB) also appears to be developmentally regulated [7]. The short form of the leptin receptor, LepRa, which is considered to be one of the main transporters for leptin across the BBB [27,33], is expressed in brain microvessels at birth [47]. Analysis of leptin transport across the BBB also reveals that the hormone can reach the brain at early ages [47].

Developmental Regulation of CNS Leptin Receptor Expression

The leptin receptor exists in multiple alternatively-spliced isoforms, of which only the long form (LepRb) associates with Janus kinase 2 (JAK2) to mediate intracellular signaling. Upon leptin binding, LepRb initiates multiple intracellular signal transduction pathways that result in the activation of STAT family transcription factors, extracellular signal-regulated kinases (ERK), and phosphoinositide-3 kinase. Leptin receptors, including LepRb, are detected in the mouse brain as early as embryonic day 10.5 [28,53]; however, during embryonic and early postnatal life, LepRb mRNA expression appears to be restricted to the ependymal cells of the third ventricle [12,17]. Remarkably, peripheral injection of leptin in P4 mice leads to strong induction of SOCS3 mRNA in the cells lining the third ventricle, suggesting that ependymal cells do contain functional leptin receptor during early life [17]. Only weak LepRb and leptin-induced SOCS3 expression is seen in the arcuate nucleus and other hypothalamic nuclei before P7. In sharp contrast, LepRb mRNA is abundant at P10 in various parts of the hypothalamus, including the ARH, VMH, DMH, and LHA [13] (Figure 1). Furthermore, peripheral leptin injection in P10 mice results in significant activation of STAT3 (a direct marker of LepRb activation) in these hypothalamic structures. LepRb mRNA is also transiently elevated in certain regions of the postnatal mouse brain such as the cortex, hippocampus, and laterodorsal nucleus of the thalamus [13] (Figure 1). However, these brain structures do not exhibit pSTAT3-immunoreactivity (IR) after peripheral leptin administration, suggesting that 1) they do not sense peripheral leptin, 2) leptin elicits the

activation of alternate signaling pathways such as MAPK or PI3K/Akt in brain sites that lack pSTAT3-IR following leptin administration, or 3) LepRb mRNA transcripts may not be translated into protein in these brain regions.

Early Studies of the Neurodevelopmental Actions of Leptin

Over 30 years ago, Bereiter and Jeanrenaud [4,5] reported that the brains of genetically obese and diabetic mice (Lep^{ob}/Lep^{ob} and Lepr^{db}/Lepr^{db} mice, respectively) were structurally different from those of control mice. They observed a reduction in cell density in various brain regions, including the hypothalamus, and found alterations in the dendritic orientation of hypothalamic neurons. These structural abnormalities of Lep^{ob}/Lep^{ob} and Lepr^{db}/Lepr^{db} mice were appreciated by Ahima and colleagues, who went on to show that the same mutants had reduced brain weight and an immature pattern of expression of synaptic and glial proteins [1]. Furthermore, these mutants showed elevated levels of growth-associated protein in the neocortex and hippocampus and a reduction in syntaxin-1, synaptosomal-associated protein-25, and synaptobrevin expression [1]. Ahima correctly predicted a role for leptin in brain development. The remarkable observation that leptin could restore normal brain weight in Lep^{ob}/Lep^{ob} only when the hormone was injected during early life [51] paved the way for the notion of critical periods for the developmental actions of leptin.

Hypothalamic Actions

The hypothalamus undergoes tremendous growth beginning early in gestation and continuing during the postnatal period (see [8] and [43] for review). During this developmental period, a variety of processes shape the hypothalamic nuclei involved in the control of feeding and energy balance. The cellular mechanisms proposed to explain how hypothalamic circuits are formed fall into five main categories: neurogenesis, neuronal migration, cell death, axon growth, and synapse formation. Hypothalamic neurogenesis and cell migration primarily occur during mid-gestation, whereas the organization of neural connections between various hypothalamic nuclei occurs during early postnatal life in rodents [8]. Thus, neurons composing the arcuate nucleus (ARH) are born between E12 and E14, and ARH neural projections do not fully develop until the first 3 weeks of postnatal life in mice [9]. Leptin represents a powerful neurotrophic agent that promotes the formation of ARH neural projections (Figure 2). Leptin treatment increases the density and length of axons from the ARH *in vitro* [10]. Moreover, in leptin-deficient (Lep^{ob}/Lep^{ob}) mice, the density of ARH axons innervating the PVH is approximately 10-fold lower than in wild type animals [10]. Remarkably, leptin treatment of Lep^{ob}/Lep^{ob} neonates restores a normal pattern of ARH connectivity; however, the same leptin treatment in adults does not reverse the abnormalities in ARH projections observed in Lep^{ob}/Lep^{ob} mice [10], suggesting that leptin acts primarily during a restricted neonatal period to exert its developmental effects on ARH neural projections. Nevertheless, the mature hypothalamus still appears sensitive to the neuroplastic actions of leptin, but both the degree and the nature of leptin's neuroplastic actions differ between adults and neonates. For example, whereas leptin administration to adult Lep^{ob}/Lep^{ob} mice does not have a significant impact on ARH axonal projections, it results in changes in ARH synaptic organization [48] (Figure 2). Taken together, these observations have had a significant impact on the field as they demonstrate that leptin can influence brain neurocircuitry and imply that leptin may program hypothalamic organization during early life.

A key factor in controlling the development of hypothalamic circuits is the expression of LepRb by ARH neurons. As noted above, the ARH contains a high density of neurons that express LepRb, and the administration of leptin to mouse neonates results in the activation

of major LepRb signaling pathways, including pSTAT3 [13]. The fact that leptin induces neurite outgrowth from isolated ARH explants supports the idea that leptin acts directly on LepRb-containing ARH neurons to promote axonal growth. A clear role for ARH LepRb signaling pathways in ARH axon growth is lacking; however, it is interesting to note that ARH neural projections are also disrupted in leptin receptor-deficient Zucker (fa/fa) rats [6]. Still, not all regions that express LepRb respond to the trophic action of leptin. The DMH contains a substantial density of neurons that express leptin receptors during postnatal life [13], but its projections to the PVH appear to be normal in Lep^{ob}/Lep^{ob} mice [10].

Nutritional Manipulations of Perinatal Leptin: Impact on Hypothalamic Development

The majority of research on nutritional manipulations of perinatal leptin levels has been focused on metabolic abnormalities, a natural bias given the obvious importance of leptin in metabolic regulation. There is also a growing appreciation that nutritional alterations in leptin levels during early life may have structural consequences on hypothalamic feeding circuits. For instance, maternal obesity increases leptin levels throughout postnatal life and reduces the hypothalamic response to leptin during critical periods of development [34]. The same obesogenic/hyperleptinemic intrauterine environment also impacts hypothalamic neural connectivity: animals born to obese dams display abnormal development of neural projections containing AgRP [34]. The detrimental effects of maternal obesity on hypothalamic development are not restricted to alterations of neural projections during postnatal development, however. Hypothalamic neurogenesis during embryonic life is also influenced by maternal high-fat feeding. Offspring born to obese mothers display increased proliferation of hypothalamic neuronal precursors during embryonic development, resulting in an increased number of orexigenic neurons in the mature hypothalamus [14].

Interest in maternal malnutrition is also particularly high given its high prevalence worldwide and the evidence regarding its disease-promoting potential in offspring. In rodents, maternal food restriction during pregnancy and lactation blunts the naturally occurring postnatal leptin surge [57], yet similar metabolic and structural defects are observed between maternal undernutrition and maternal obesity. The neurostructural abnormalities observed in the offspring of food-restricted dams include disrupted organization of the hypothalamic projections containing POMC-derived peptides [19]. We also know from recent work by Coupe et al. [18] that proteins in the maternal diet are important determinants of hypothalamic development as the offspring of dams fed a low-protein diet recapitulate the metabolic and hypothalamic phenotypes of animals born to underfed animals, including the disruption of ARH neural projections. Remarkably, exposure of undernourished pups to leptin during the early postnatal period reverses this metabolic dysregulation [56]. Whether the beneficial effects of leptin exposure on neonatally undernourished pups are at least partially caused by changes in hypothalamic development remains to be determined. Together, these studies provide a likely neurobiological mechanism to explain the well-established relationship between under/overnutrition during development and subsequent metabolic impairments.

Although it is clear that environmental factors influence the degree to which the hypothalamic nuclei, including the ARH, develop, it is also evident that the architecture of various hypothalamic pathways can be entirely determined by genetic background. Rats that have obesity inherited as a polygenic trait (diet-induced obese, DIO rats) represent a valuable tool for studying the influence of genetic background on the development of hypothalamic feeding circuits. Interestingly, these animals display reduced central leptin sensitivity as early as P10, i.e., before they develop obesity [11]. The plausible cause of this relative leptin insensitivity likely involves alterations in hypothalamic leptin binding [31] as

CNS leptin transport remains unaffected in DIO rats [39]. This early reduction in leptin sensitivity in DIO rats has profound consequences on the architecture of the hypothalamic neurocircuitry. DIO rats have a diminished density of ARH projections in the PVH, which appears to be caused by the inability of leptin to promote neurite outgrowth directly from ARH neurons [11]. The disruption of ARH neural projections is not the only structural abnormality observed in DIO rats as abnormal dendrite morphology has also been observed in the VMH of DIO rats [37]. Whether these defects are caused by reduced leptin sensitivity, however, remains to be established. Genetic background prevails over environmental factors to influence the formation of ARH projections. Thus, although maternal nutrition clearly influences the development of hypothalamic neural projections in non-genetically obese animals [34], it does not affect the architecture of ARH axonal projections in genetically obese DIO rats [11].

Extra-Hypothalamic Actions

The neurodevelopmental actions of leptin are not limited to hypothalamic development. Soon after the discovery that leptin influences the establishment of hypothalamic neural projections, various groups reported a role for leptin in hippocampal and cortical development (Figure 2). O'Malley and colleagues showed that exposure of hippocampal neurons to leptin enhances the motility and density of dendritic filopodia, with consequences on synapse morphology [46]. Furthermore, they showed that these structural effects of leptin on hippocampal synapses are mediated by the mitogen-activated protein kinase (MAPK) pathway. Moreover, in mature mice, leptin appears to increase the formation of new neurons in the hippocampus, a well-known neurogenic structure [58]. Peripheral administration of leptin to adult mice results in increased cell proliferation in the dentate gyrus, and many of these newborn cells do become neurons that functionally integrate into the hippocampal circuitry [24].

Work from Udagawa and others has also shown a role for leptin during cortical development [52]. LepRb is abundantly expressed in the cortex during perinatal life [13,53], and leptin deficiency results in a reduction in the number of cortical neurons born during embryonic life. Of the potential mechanisms underlying leptin's control of cell number during development, a significant alteration in neurogenesis has found the most experimental support. Indeed, neuronal birthdating studies using 5-bromodeoxyuridine (BrdU) labeling have provided evidence that leptin can influence cortical cell number by promoting neurogenesis [52]. Leptin also appears to influence axon growth in the developing cortex. In primary cultures of embryonic cortical neurons, leptin causes a three-fold increase in axonal growth cone expansion [55]. The LepRb-MAPK and LepRb-Akt signaling pathways appear to be involved in this induction of axon outgrowth. Leptin activates the MAPK and Akt signaling pathways in vitro, and suppression of either MAPK or Akt activation prevents leptin-induced axonal growth cone expansion [55]. In addition to neurotrophins, other proteins involved in axonal growth may participate in leptin-induced neurite outgrowth in the cortex. LepRb co-localizes with GAP-43 at the level of axonal growth cones [50], and the expression of GAP-43 is regulated by leptin in developing cortical neurons [55]. Recent evidence has also suggested that leptin is involved in the development of non-neuronal cells in the cortex and that leptin may influence the development of oligodendroglial cells [54].

There is little doubt that the rapidly expanding literature on the neurodevelopmental actions of leptin will involve many other brain regions. For example, the observation that LepRb is highly expressed and functional in the nucleus of the tractus solitarius (NTS) during early postnatal life [13] favors a role for leptin in the development and maturation of hindbrain pathways. Consistent with the idea that metabolic hormones influence hindbrain neural development, recent work has suggested that amylin, a hormone secreted by pancreatic beta

cells, is required for the normal outgrowth of neural projections from the area postrema to the NTS [42,49].

Evidence in Humans

The majority of what we know about the influence of leptin on brain development and plasticity comes from rodent models, predominantly rats and mice. Nevertheless, there is increasing evidence suggesting that leptin may also influence neuroplastic events in the human brain. Much of our knowledge of the neural actions of leptin in humans has been inferred from non-invasive magnetic resonance imaging studies. Using voxel-based morphometry analysis, Matochick and colleagues reported that leptin replacement therapy in leptin-deficient patients has sustained effects on neural tissue composition in the human brain [45]. They found increases in the relative concentration of gray matter within the anterior cingulate gyrus, the inferior parietal lobule, and the cerebellum at 6 and 18 months after initiation of replacement therapy. Surprisingly, no changes in tissue concentration were observed in the hypothalamus. Voxel-based morphometry analysis can only provide information about gross changes in brain morphology, however, and more subtle alterations in neural architecture (e.g., changes in synaptic organization and axon growth) may not be detected by this approach. Moreover, it is important to note that the leptin treatment used in this study was done in adult patients, and we know from rodent studies that leptin has its maximal plasticity effects during neonatal life. The next challenge, therefore, is to determine if the neuroplastic actions of leptin on the human brain can be even more profound during early life and to confirm that leptin can influence brain development in humans, similar to what has already been observed in rodents. In this regard, it is interesting to note that leptin levels are elevated during pregnancy and embryonic development in humans [32], particularly during the period when the human hypothalamus undergoes tremendous growth [35,36]. Whether these elevated levels of leptin can influence brain development remains to be determined. Nevertheless, the observation that leptin levels at birth are correlated with head circumference [25] supports the hypothesis that leptin may influence brain development in humans.

Conclusion

Tremendous progress has been made in elucidating the effects of leptin on the developing brain and the cellular and molecular mechanisms by which those effects are achieved. There is still no evidence that leptin influences very early developmental events such as neural induction and the establishment of polarity; however, accumulating evidence indicates that leptin regulates later developmental processes such as neurogenesis, axon growth, dendrite proliferation, and synapse formation. Less attention has been paid to whether leptin influences neuronal migration. The perinatal period represents the period of maximal sensitivity to the neurotrophic actions of leptin. Nevertheless, it is also clear that the mature brain remains relatively sensitive to the neuroplastic actions of leptin, although both the degree and nature of the structural response appear to differ between neonates and adults. A better understanding of the mechanisms mediating leptin's neurodevelopmental actions and increased knowledge about the periods of maximal vulnerability of the brain to changes in leptin levels is clearly needed. Nevertheless, this relatively new area of research opens new avenues for understanding perinatally acquired predispositions to adult diseases.

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List of Abbreviations

AgRP	agouti-related peptide
αMSH	α -melanocyte-stimulating hormone
ARH	arcuate nucleus of the hypothalamus
BrdU	5-bromo-2-deoxyuridine
CNS	central nervous system
CNTF	ciliary neurotrophic factor
DIO	diet-induced obesity
DMH	dorsomedial nucleus of the hypothalamus
E	embryonic day
ERK	extracellular signal-regulated kinase
JAK	janus kinase
LepRa	short form of the leptin receptor
LepRb	long form of the leptin receptor
Lep^{ob}/Lep^{ob} mice	leptin-deficient mice
Lep^{db/db} mice	leptin receptor-deficient mice
LHA	lateral hypothalamic area
MAPK	mitogen-activated protein kinase
NPY	neuropeptide Y
NTS	nucleus of the tractus solitarius
P	postnatal day
POMC	proopiomelanocortin
pSTAT3	phosphorylated form of the signal transducer and activator of transcription 3
PVH	paraventricular nucleus of the hypothalamus
SOCS-3	suppressor of cytokine signaling 3
VMH	ventromedial nucleus of the hypothalamus

Figure 1. Leptin targets in the developing brain

Schematic drawing (horizontal section) of the distribution of leptin receptor-containing neurons in the postnatal and adult mouse brains. The staining found in the adult PMV was taken as a reference signal for the highest score, and the staining in the postnatal LHA was taken as a reference signal for the lowest score. Adapted from [13], with permission.

Figure 2. Developmental actions of leptin in the forebrain

Schematic illustration representing the neurodevelopmental effects of leptin. During pre- and postnatal life, leptin appears to be required for the normal development of forebrain pathways by regulating neurogenesis and circuit formation. In addition, leptin can still affect brain plasticity in adults by causing synaptic rearrangement of excitatory and inhibitory inputs on hypothalamic neurons and by influencing cell proliferation in the hippocampus. Images used with permission [10,46,55]