

Minireview: Leptin and Development of Hypothalamic Feeding Circuits

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The arcuate nucleus of the hypothalamus (ARH) is a critical component of the forebrain pathways that regulate energy homeostasis, and it plays a particularly important role in relaying leptin signal to other part of the hypothalamus. However, until recently, little was known about the development of these critical pathways. Recent work investigating the development of leptin-sensitive hypothalamic pathways suggests possible developmental mechanisms that may contribute to obesity later in life. Anatomic findings indicate that ARH circuits are structurally and functionally immature until the third week of postnatal life in mice. Recent data also sug-

gest that leptin is required for normal development of ARH pathways and that this developmental activity of leptin is restricted to a neonatal window of maximum sensitivity that corresponds to a period of elevated leptin secretion. Thus, leptin may function to organize formation of hypothalamic circuitry in much the same way that sex steroids act on sexually dimorphic circuits. Perturbations in perinatal nutrition that alter leptin levels may, therefore, have enduring consequences for the formation and function of circuits regulating food intake and body weight. (*Endocrinology* 145: 2621–2626, 2004)

DURING THE PAST 30 yr, we have witnessed a 7-fold increase in the incidence of childhood obesity with accompanying increases in type II diabetes and other pathological conditions associated with obesity (1). In addition to adversely affecting quality of life for affected patients, epidemiological studies indicate that such rates of obesity will have a dramatic impact on life expectancy (2). Although there are some obvious sociological factors that contribute to this alarming rise in obesity, we know relatively little about biological processes that promote obesity in children. There appears to be a genetic basis for a small percentage of obese patients, and in nearly all these cases symptoms arise during childhood. However, alterations in prenatal nutrition have also been implicated in the development of obesity (see Refs. 3–6). Children born with low birth weights tend to become obese later in life with an increased risk of developing type II diabetes (7, 8). Similarly, mice born to obese dams display a propensity for obesity in adulthood and give birth to offspring that also tend to become obese (9). At least one determinant for these patterns of obesity appears to be maternal diet because dams raised on a high-fat diet develop diet-induced obesity and have greater numbers of offspring that become obese (9). Circulating hormones that act on the brain represent important signals that reflect peripheral energy status and may, therefore, influence development of central mechanisms that regulate food intake and body weight. This

review will focus on the development of hypothalamic circuits regulating feeding, paying particular attention to the development of projection pathways from the arcuate nucleus of the hypothalamus, a key region regulating neuroendocrine function that also plays a critical role in mediating the actions of leptin on food intake and body weight.

The Arcuate Nucleus of the Hypothalamus (ARH) as a Major Site of Leptin's Actions

It has been accepted for decades that the hypothalamus plays a critical role in the regulation of feeding, and recent work has defined a core circuitry in the hypothalamus that appears to mediate many of the effects of leptin on feeding and energy balance. The effectiveness of the adipocyte-derived hormone leptin in regulating energy stores is due to its direct access to hypothalamic neurons that control feeding behavior and other aspects of energy metabolism (see Refs. 10–14 for reviews). Distinct subsets of hypothalamic neurons may respond to leptin by virtue of their location in regions where the blood-brain barrier is compromised, or through neural connections with circumventricular organs. The ARH meets both of these requirements because it resides above the median eminence and shares connections with regions such as the subfornical organ (15). The ARH has long been associated with obesity (16). Its cells express leptin receptors (17–19) and exhibit signal transducer and activator of transcription 3 phosphorylation in response to central and peripheral injections of leptin, which is generally viewed as a molecular signature of leptin signaling (20–22). Moreover the projections of the ARH to other hypothalamic sites implicated in the control of feeding such as the periventricular (PVH) and dorsomedial (DMH) hypothalamic nuclei, as well as to the lateral hypothalamic area (LHA) (23), suggest that the ARH is a principal monitor of leptin signaling in the brain (Fig. 1). Importantly, the distribution of ARH projections

Abbreviations: AgRP, Agouti-related protein; ARH, arcuate nucleus of the hypothalamus; BSTp, principal nucleus of the bed nuclei of the stria terminalis; DMH, dorsomedial nucleus of the hypothalamus; Lep^{ob}/Lep^{ob}, leptin-deficient mice; LHA, lateral hypothalamic area; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVH, paraventricular nucleus of the hypothalamus; WT, wild-type.

Endocrinology is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

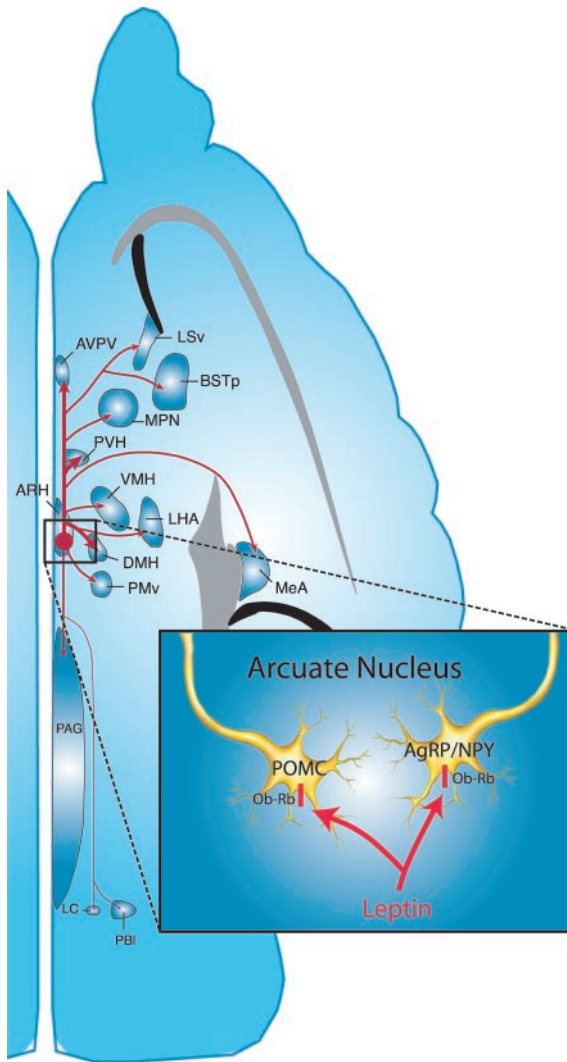


FIG. 1. Pathways for integration of feeding. Schematic representation (horizontal section) of the organization of major projections from the ARH. The relative size of each pathway is roughly proportional to the thickness of the lines associated with it. Inputs from the ARH that contain AgRP/NPY and α MSH and that project to the PVH, DMH, and LHA represent major routes for regulation of body weight and food intake by leptin. AVPV, Anteroventral periventricular nucleus; BST, bed nuclei of the stria terminalis; LC, locus coeruleus; LSv, ventral part of the lateral septum; MEA, medial nucleus of the amygdala; MPN, medial preoptic nucleus; NTS, nucleus of the solitary tract; Ob-Rb, long form of the leptin receptor; PAG, periaqueductal gray; PBI, parabrachial nucleus; PVa, anterior periventricular nucleus of the hypothalamus; PVpo, preoptic periventricular nucleus.

appears virtually identical in both rats and mice, and the organization of these pathways is quite similar in males and females (23).

The ARH contains two populations of neurons that play a particularly important role in distributing leptin signals centrally. Neuropeptide Y (NPY) and agouti-related protein (AgRP) are coexpressed within a subpopulation of arcuate neurons. A separate subpopulation of neurons in the ARH contains melanocortin peptides, such as α MSH, which are derived from proopiomelanocortin (POMC) (Fig. 1). These anatomically distinct populations of ARH neurons provide

overlapping projections to other key parts of the hypothalamus (23–27) and appear to exert opposing regulatory functions: NPY and AgRP are orexigenic, whereas melanocortins are anorexigenic (for reviews see Refs. 10, 12, and 28).

Developmental Aspects of Leptin Signaling

Accumulating evidence suggests that there are physiological differences in the regulation of energy balance between adults and neonates. In sharp contrast to the effects of leptin on adults, several groups reported that exogenous leptin does not significantly inhibit growth, food intake, or energy expenditure during the first 2–3 postnatal weeks (29–32). More specifically, Mistry and colleagues (31) have shown that leptin does not alter significantly oxygen consumption (a marker of energy expenditure) or food intake in normal lean or obese leptin-deficient (Lep^{ob}/Lep^{ob}) mice until postnatal d 17 (P17) (31). Consistent with these data, neonatal Lep^{ob}/Lep^{ob} mice do not differ in body weight from wild-type (WT) littermates, but begin to diverge in weight during the second postnatal week (Ref. 31 and our unpublished data). The general thinking has been that the neonatal brain is relatively insensitive to leptin and may present leptin resistance (31). However, leptin receptors are expressed in the ARH of rats (33) and mice (Ref. 34 and our unpublished data) before development of ARH pathways, and recent findings suggest that this receptor can initiate cellular responses to leptin. For example, Proulx *et al.* (30) reported that acute peripheral leptin treatment modifies NPY and POMC mRNA expression in the ARH of postnatal rats. They also demonstrated an increase in suppressors-of-cytokine-signaling 3 gene expression (a marker of leptin receptor activity) in the ARH after leptin administration. In addition, leptin administration between P6 and P16 in mice resulted in elevated expression of the proto-oncogene *c-Fos* in arcuate POMC neurons as it does in adults (35). Collectively these results provide convincing evidence that leptin receptors are present and functional in the ARH during the postnatal period and suggest that the leptin insensitivity observed during this period may be due to a failure of these cells to relay leptin signals to other parts of the hypothalamus.

Development of Projection Pathways from the ARH

Methods for visualizing neuronal pathways during development have been available for some time yet have only recently been applied in the hypothalamus. In part because of its importance for the regulation of feeding, the first systematic study using axonal labeling defined the ontogeny of projection pathways from the ARH (35). The results indicate that ARH projections are immature at birth and develop mainly during the second week of life in mice. Interestingly, ARH projections to key sites known to mediate food intake and energy balance develop within distinct temporal domains with innervation of the DMH occurring first on P6, followed by innervation of the PVH on P8–P10 and innervation of the LHA on P12 (Fig. 2). Rostral projections, such as those to the preoptic region, reach their targets later and remain immature as late as P21. Similar results were found for development of AgRP containing fibers in rats (36), which

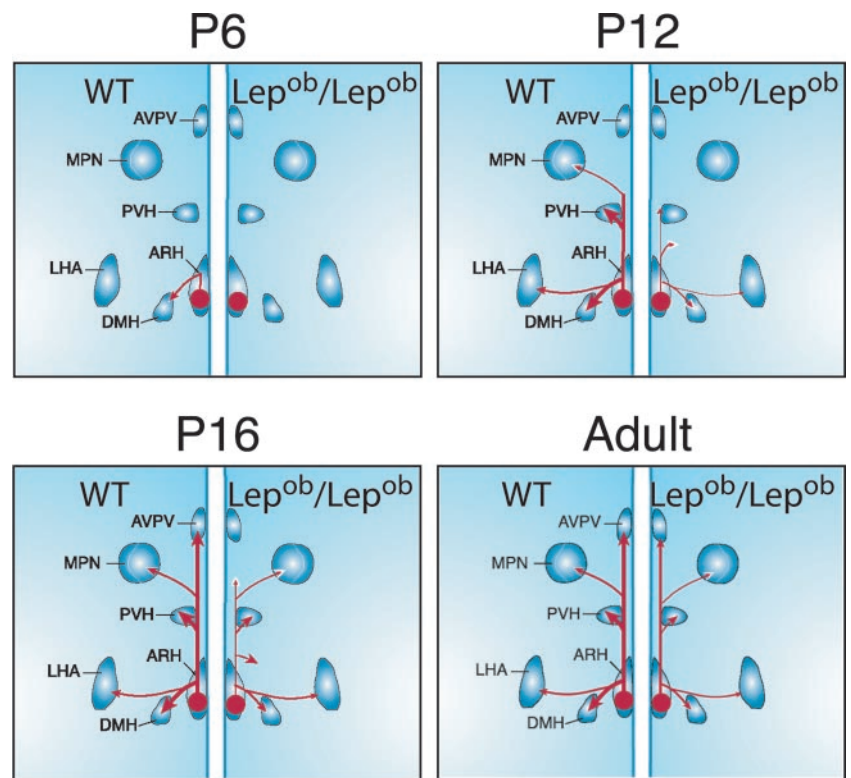


FIG. 2. Schematic diagrams (*horizontal sections*) that summarize the ontogeny of ARH projections through the hypothalamus in WT (*left panels*) and *Lep^{ob}/Lep^{ob}* (*right panels*) mice on P6, P12, P16, and adults (P60). Leptin deficiency permanently disrupts formation of projections from the arcuate nucleus to each major target nucleus. The relative size of each pathway is roughly proportional to the *thickness of the lines* associated with it. AVPV, Anteroventral periventricular nucleus; MPN, medial preoptic nucleus.

are generally believed to originate exclusively from NPY containing neurons in the ARH (24, 25).

The ability of circulating leptin to activate ARH neurons and their targets in adult rats has been known since Elmquist and colleagues (27, 37–39) demonstrated that peripheral injections of the hormone increased expression of c-Fos in the ARH, DMH, PVH, and LHA. The ontogeny and distribution of neurons that respond to leptin has recently been evaluated in neonatal mice. The results indicate that the ability of leptin to increase levels of c-Fos in the PVH and LHA appears to be age dependent and correlates with the arrival of ARH projections to each nucleus. Leptin administration to mice on P16 elevates c-Fos expression in a limited number of hypothalamic sites with particularly dense increases in c-Fos-immunoreactive nuclei in the ARH, and in its major target nuclei the DMH, PVH, and LHA (35). This pattern corresponds closely to that observed in adults; however, the pattern of c-Fos increased in ARH target nuclei is significantly different when leptin is administered to younger animals. In contrast to the ARH, where leptin causes significant inductions in c-Fos staining as early as P6, large elevations in c-Fos are not observed until P10 in the PVH, nor in the LHA until P16. Thus, activation of neurons in the PVH and LHA by leptin seems to occur only after they are innervated by ARH neurons, whereas leptin can cause elevated expression of c-Fos in ARH neurons of neonates before they have innervated other hypothalamic targets. Significant changes in c-Fos staining are generally taken to represent hormonal activation of signal transduction pathways through receptor-mediated events that lead to changes in gene expression, or through transynaptic activation of similar transduction pathways (40, 41). It would appear that both mechanisms are used

in the hypothalamus for regulation of feeding by leptin; receptor mediated cellular activation in the ARH and activation of neurons in the PVH and LHA that is mediated primarily by transynaptic stimulus transcriptional coupling. Taken together, these data suggest that immaturity of ARH projection pathways before P18 may at least partially underlie the insensitivity to leptin observed during the first weeks of postnatal development.

Leptin and Brain Development

Despite evidence from a variety of sources that neonatal nutrition and maternal factors have long term effects on obesity (4–6, 42–44), we know relatively little about how the neonatal environment influences central mechanisms regulating food intake and energy balance. During neonatal development, food intake must be maximized to support growth, yet plasma leptin levels are relatively high (45, 46). These high levels of leptin during the postnatal period have been reported in both rats and mice (45–47). Moreover, as mentioned earlier, treatment of rodents with exogenous leptin does not increase milk intake or metabolic rates until after weaning (30, 31). The remarkable observation that there is a dramatic surge in circulating leptin levels during this period of apparent leptin insensitivity led Ahima and colleagues (45) to suggest that leptin itself may function as a developmental cue for brain development. That mice lacking leptin signaling (*Lep^{ob}/Lep^{ob}* and *Lepr^{db}/Lepr^{db}*) have reduced brain weight and morphological defects supports this notion (48–52). These same mutant mice also have deficiencies in expression of neuronal and glial proteins (52, 53). Furthermore, a recent report indicates that treatment of neonatal rats

with leptin increases expression of growth-associated protein-43 and synaptic proteins such as synaptophysin and synaptosomal-associated protein-25 in the hippocampus (54). Taken together, these data support a role for leptin in brain development and suggest that the postnatal surge in leptin may serve as a signal that promotes development of projection pathways from the ARH. That the postnatal surge in circulating leptin (P4 to P16) coincides with the development of ARH projections also supports this hypothesis.

Leptin Promotes Development of Projections from the ARH

The availability of leptin-deficient mice (Lep^{ob}/Lep^{ob}) makes possible the direct assessment of the impact of leptin on development of ARH projection pathways. Axonal labeling of ARH axons with the anterograde tracer DiI revealed that ARH projection pathways are severely reduced in Lep^{ob}/Lep^{ob} mice (Fig. 2) and that leptin deficiency causes a significant delay in formation of projections from the ARH to each major target nucleus (55). For example, whereas numerous fibers from the ARH innervate the PVH on P12 in WT animals, virtually no ARH axons were observed there in Lep^{ob}/Lep^{ob} littermates. Furthermore, the disruption of ARH pathways in Lep^{ob}/Lep^{ob} mice appears to be permanent because even on P60, a stage considered as mature regarding the regulation of energy homeostasis, there are fewer ARH fibers in each terminal field (Fig. 2).

The relative activity of NPY and POMC neurons in the ARH determines in large part whether animals increase food intake and body weight (see Ref. 12 for review). Given the profound perturbations in ARH projections visualized in Lep^{ob}/Lep^{ob} mice, it is not surprising that in the absence of leptin both AgRP/NPY and α MSH pathways are severely disrupted in adult Lep^{ob}/Lep^{ob} mice (Fig. 2). Interestingly, even though AgRP gene expression (56, 57) and protein (55) are increased in the ARH of Lep^{ob}/Lep^{ob} mice, there appears to be a dramatic decrease in AgRP-immunoreactive fiber density in the PVH, DMH, and LHA in these mice. The axon labeling experiments described above offer an explanation of this apparent paradox and demonstrate that AgRP/NPY containing projections from the ARH to the PVH, DMH, and LHA are only partially represented in leptin-deficient animals. However, it is not yet known whether AgRP and α MSH pathways are affected to the same extent in Lep^{ob}/Lep^{ob} mice. Hormonal signals that regulate development tend to act during restricted perinatal critical periods (for review see Refs. 4, 58, and 59). Leptin appears to function during the perinatal life to induce formation of ARH projections because peripheral leptin injections from P4 through P12 in Lep^{ob}/Lep^{ob} mice increased the density of ARH fibers innervating the PVH to a density that was comparable to that of WT littermates (55). In contrast, treatment of adult Lep^{ob}/Lep^{ob} mice with leptin for 20 d (P60–P80) was relatively ineffective because it did not restore the density of either α MSH or AgRP fibers in the PVH to levels that are characteristic of WT mice. Thus, the developmental activity of leptin on ARH projection pathways appears to be restricted to a neonatal window of maximum sensitivity that corresponds to a period of elevated leptin secretion (Fig. 2). In this regard, leptin functions sim-

ilarly to sex steroid hormones that act to organize sexually dimorphic limbic-hypothalamic pathways. For example, sexual differentiation of the central component of the medial preoptic nucleus is determined by sex steroids that act before the seventh day of life (60, 61). Sex steroids also impact the organization of limbic-hypothalamic projection pathways. The sexually dimorphic projections from the principal nucleus of the bed nuclei of the stria terminalis (BSTp) to the hypothalamus are determined by neonatal exposure to high levels of testosterone during the first week of life (62). However, the action of testosterone on BSTp projections is not the same for all terminal fields, suggesting that testosterone acts on the target regions during development to specify innervation patterns, and *in vitro* studies using explant cocultures support this interpretation (see Ref. 58 for review; and Ref. 63).

The site of action for the developmental effects of leptin is unknown, but they appear to include a direct action on ARH neurons. In contrast to the target-specific pattern of development observed for BSTp projections, ARH projections to each major target region, including projections to extrahypothalamic regions known to be insensitive to leptin (64), appear to be reduced in Lep^{ob}/Lep^{ob} mice suggesting that leptin may act directly on the ARH to promote development of ARH projections. That leptin can induce neurite extension from isolated organotypic explants of the ARH supports this notion and illustrates the trophic activity of leptin on ARH neurons (55). However, not all regions that express leptin receptors appear respond to this trophic action of leptin. The DMH contains a substantial density of neurons that express leptin receptors, yet its projections to the PVH appear to be normal in Lep^{ob}/Lep^{ob} mice (55). Although the reason for its leptin independence is unknown, it is worth noting that this pathway develops before the peak of the leptin surge (35).

Together, these findings demonstrate that leptin is required for normal postnatal development of ARH projections and suggest that the postnatal leptin surge is indeed a key developmental signal affecting the architecture of hypothalamic circuits mediating feeding. Intriguingly, pharmacological doses of leptin can still reduce food intake in Lep^{ob}/Lep^{ob} mice even if ARH pathways are disrupted although the responses remain distinct (65). Presumably because of their importance to survival, hypothalamic circuits are remarkably plastic during development and may have built-in redundancy. Therefore, in the absence of ARH projections, leptin signaling in Lep^{ob}/Lep^{ob} mice may occur via different neural pathways, perhaps via projections from the DMH, which remain intact in Lep^{ob}/Lep^{ob} mice and therefore appear to be independent of the trophic actions of leptin during development. The hypothalamus displays a remarkable capacity for developmental plasticity and future work is required to resolve how leptin signaling occurs in the brains of Lep^{ob}/Lep^{ob} mice. Research toward this goal may improve our understanding of how leptin regulates hypothalamic circuits involved in modulation of food intake in normal individuals.

Conclusions

The past decade of research on leptin has provided fresh insight into how the hypothalamus responds to changing

energy demands by altering food intake and energy metabolism. It is now clear that in addition to its regulatory role in mature animals, leptin also acts as a trophic signal that directs key developmental events in the very hypothalamic pathways that convey leptin signals to brain regions regulating body weight. The findings reviewed here also imply that perturbations in the neonatal leptin surge may alter the impact of leptin on energy homeostasis throughout the life of an animal with enduring consequences for food intake and body weight. Because manipulations in neonatal nutrition can influence leptin levels, the developmental actions of leptin on brain development may provide clues about a link between nutrition and long-term abnormalities in body weight regulation.

The parallels between the trophic activity of leptin and the actions of sex steroids on brain development are striking. Hormones such as estradiol influence most major aspects of brain development including neurogenesis, cell death, morphogenesis, synaptic plasticity, and axon guidance. The possibility that the developmental actions of leptin may extend to an equally diverse array of neurobiological events is an exciting prospect that may open new avenues for understanding the biology of food intake and obesity.

Acknowledgments

The authors would like to thank Mrs. Shin Draper and Dr. Anda Cornea for their contributions to the studies described in this review.

Received February 21, 2004. Accepted March 17, 2004.

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The authors' research is supported National Institutes of Health Grants DK65900, DK055819, and NS37952 (to R.B.S.).

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Endocrinology is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.