CHAPTER ELEVEN

POSTNATAL DEVELOPMENT OF HYPOTHALAMIC LEPTIN RECEPTORS

Elizabeth C. Cottrell,*1 Julian G. Mercer,† and Susan E. Ozanne*

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Abstract
The hormone, leptin, plays a key role in the regulation of energy balance and neuroendocrine function, as well as modulating a range of other physiological systems from immunity to cognition. In the adult brain, leptin regulates food intake and energy expenditure primarily via the hypothalamus. In addition to these well-defined actions in adult life, there is increasing evidence for a role of leptin during development. Leptin receptors are widely expressed in the developing brain from an early stage, and leptin is known to have profound effects on...
the proliferation, maintenance, and differentiation of neuronal and glial cells. During the early postnatal period, in both rats and mice, there is a surge in circulating leptin concentrations. Despite this elevation in leptin, neonates maintain a high level of food intake, and both feeding behavior and metabolic responses to exogenous leptin administration are absent until around the time of weaning. However, it is during this period that direct neurotrophic actions of leptin have been demonstrated, with leptin promoting neurite outgrowth and the establishment of hypothalamic circuitry. Exactly how leptin exerts these effects remains unknown, but changes in the distribution of hypothalamic leptin receptors during this period may, at least in part, underlie these age-specific effects of leptin. © 2010 Elsevier Inc.

I. Introduction

Leptin, a hormone derived predominantly from adipocytes, is critically involved in the regulation of energy homeostasis. Discovered in 1994 (Zhang et al., 1994), leptin was initially thought to act only as a satiety factor, signaling to the brain the repletion of body fat stores. Since this time, however, leptin receptors (ObRs) have been identified in essentially every tissue, and leptin has been shown to play a role in a diverse range of physiological systems, including reproduction, immunity, cardiovascular function, and cognition (Ahima and Flier, 2000; Harvey et al., 2005; La Cava and Matarrese, 2004; Tune and Considine, 2007). In terms of body weight regulation, leptin promotes negative energy balance by inhibiting feeding and stimulating energy expenditure, acting primarily through central nervous system (CNS) ObRs. Thus, the most apparent phenotype in those individuals lacking either leptin or functional ObR is severe obesity, driven by extreme hyperphagia and unabated adipose tissue accumulation. Numerous other metabolic abnormalities result from a lack of leptin signaling, as well as impairments in brain development, bone formation, and immune function.

In addition, a developmental role for leptin has been increasingly recognized. In line with these findings, it has been established that there are restricted periods in early life in which leptin replacement (in leptin-deficient ob/ob mice) or supplementation (in leptin-replete animals) can exert long-term effects on tissue structure and organization, as well as influencing the metabolic phenotype of the adult. These age-specific effects of leptin may be related to developmental changes in receptor expression, as recent evidence has shown that there are dynamic changes in the distribution of ObR and leptin actions during the early postnatal period in the rodent.
II. THE LEPTIN SYSTEM

A. Sources and regulation of leptin

Leptin is the protein product of the \( ob \) gene, which encodes a 4.5-kb mRNA and is translated to produce a circulating protein of 16 kDa (Zhang et al., 1994). Leptin is mainly expressed in adipose tissue and circulating concentrations are, in the fed adult, highly correlated with the degree of adiposity (Maffei et al., 1995). Additional tissues have been shown to produce leptin, including the stomach, placenta, mammary epithelium, pituitary, and hypothalamus (Bado et al., 1998; Hoggard et al., 2001; Morash et al., 1999; Smith-Kirwin et al., 1998). Over any relatively extended period of time, leptin concentrations are reflective of total body fat mass; however, leptin concentrations are acutely modulated by nutritional state. In both humans and adult rats, leptin concentrations are decreased in response to fasting, correlating with a reduction in blood glucose and insulin levels (Ahren et al., 1997a,b). On fasting, the fall in leptin concentrations mediates a number of other physiological adaptations to this disruption in energy homeostasis (reducing thyroid hormone concentrations and altering gonadal hormones), with administration of leptin during fasting preventing the changes in these axes (Ahima et al., 1996). These adaptations presumably function to promote feeding behavior, in order that body fat does not become overly depleted, and to minimize energy expended and delay reproduction until such time that body energy stores are replaced. In vitro studies investigating the molecular regulation of leptin have shown that incubation of isolated rat adipocytes with glucose and insulin increases both the production and secretion of leptin, with the rate of secretion being proportional to the degree of insulin-stimulated glucose uptake (Barr et al., 1997; Mueller et al., 1998). In addition, a number of other factors are also involved in the regulation of leptin expression, including glucocorticoids, catecholamines, and cytokines.

In the obese adult \( ob/ob \) mouse, there is no detectable leptin in the circulation, as the mutation responsible for this genetic obesity causes the production of a truncated protein that is not secreted (Zhang et al., 1994). In accordance with this defective secretion, \( ob/ob \) mice have markedly elevated adipose tissue leptin mRNA, approximately 20-fold that of wild-type mice. Administration of leptin to \( ob/ob \) animals results in a normalization of body weight, due to a curbing of the extreme hyperphagia exhibited by these animals and a concurrent stimulation of metabolic rate (Campfield et al., 1995; Halaas et al., 1995; Pelleymounter et al., 1995).
B. Leptin receptors

The ObRs are members of the class I cytokine receptor family, and to date there are at least six alternatively spliced isoforms (ObRa–f; reviewed in Fruhbeck, 2006). Each of these isoforms share common extracellular and transmembrane domains, but differ in their intracellular sequence. ObRa, c, d, and f possess relatively short cytoplasmic domains whereas ObRb, the so-called “long” isoform, has an extended C-terminal region and is the only variant capable of complete intracellular signal transduction (Baumann et al., 1996). However, a degree of intracellular signaling has been demonstrated for the ObRa isoform (Bjorbaek et al., 1997). ObRe is a truncated form of the receptor, which is secreted into the circulation and thought to play a role as a binding protein, regulating leptin bioavailability. In addition, recent studies have implicated ObRe in the regulation of leptin transport at the blood–brain barrier (BBB) by antagonizing the uptake of leptin and inhibiting transport into the CNS (Tu et al., 2008).

Binding of leptin to ObRb results in autophosphorylation of JAK2 and subsequent activation of the janus kinase/signal transducer and activator of transcription (JAK/STAT-3) pathway (Banks et al., 2000). Parallel signaling pathways are also activated, including the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways. Suppressor of cytokine signaling-3 (SOCS3) is robustly induced in response to leptin (Bjorbaek et al., 1998), and acts as a negative regulator of this signaling pathway. As such, SOCS3 has been used extensively as a marker of ObR activation by leptin (Cottrell et al., 2009; Proulx et al., 2002). Furthermore, SOCS3 is also implicated as a key molecule in the development of central leptin resistance and progression to obesity in mice fed a high-fat diet (HFD; Enriori et al., 2007). Mice with either a complete lack of SOCS3 in the brain (Mori et al., 2004) or whole body haploinsufficiency of SOCS3 (Howard et al., 2004) have both increased leptin sensitivity and are relatively resistant to the obesity-inducing effects of high-fat feeding.

C. Central regulation of energy balance by leptin

Leptin was initially thought to act solely as a regulator of energy balance through hypothalamic sites. However, as mentioned previously, leptin has wide-ranging effects in the body and acts on many tissues. For the purposes of this review, we focus on the central actions of leptin and its role in development.

Within the CNS, leptin acts to inhibit feeding and stimulate energy expenditure. The arcuate nucleus (ARC) of the hypothalamus is considered to be the primary site of leptin action (Satoh et al., 1997). Recent evidence has also shown that a population of ARC/ObR–expressing neurons extend
processes into the median eminence and are, therefore, in direct contact with the circulation (Faouzi et al., 2007). Leptin receptors are widely expressed within this brain region, and are colocalized within orexigenic neurons expressing neuropeptide Y (NPY) and agouti-related protein (AgRP) as well as within the anorexigenic proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)-expressing neurons (Schwartz et al., 2000). These neurons are responsive to changes in circulating leptin and insulin (indicative of body energy stores) and send projections to downstream nuclei, including the paraventricular nucleus (PVN) where integration of inputs from hypothalamic and other sites, including brainstem and higher cortical centers, occurs. Disruption of projections from the ARC to these downstream nuclei is associated with an inability to regulate energy balance appropriately (Bell et al., 2000; Bouret et al., 2004a; Dawson et al., 1997), indicating a key role for this region in energy homeostasis.

Within the ARC, leptin inhibits the activity of NPY/AgRP neurons, while activating POMC/CART containing neurons (Schwartz et al., 2000). Thus, in states of positive energy balance (where adipose stores are replete), raised leptin concentrations inhibit further feeding (reducing orexigenic and increasing anorexigenic signaling) and concurrently stimulate metabolic activity through increased sympathetic nervous system activation to peripheral tissues. Direct effects of leptin in ObR-expressing peripheral tissues have also been shown, including the mobilization of stored triglycerides in adipose tissue (Siegrist-Kaiser et al., 1997) and stimulation of skeletal muscle thermogenesis (Dulloo et al., 2002; Maroni et al., 2003; Minokoshi et al., 2002). Finally, leptin also plays a key role in preventing the lipotoxic effects of ectopically stored lipid in tissues such as pancreas and cardiomyocytes. Excess lipid, deposited in these tissues, can impair normal cellular physiology and contribute to the development of type 2 diabetes and cardiovascular disease (Unger, 2003). Thus, the effects of leptin to regulate whole body energy status are widespread.

III. DEVELOPMENTAL ROLES OF LEPTIN

A. Leptin and brain development

In addition to the metabolic effects of leptin in the adult, leptin plays a key role in brain development during early life. Several decades ago, ob/ob mice were found to have perturbed CNS development, including impaired myelination, structural abnormalities within the hypothalamus and altered expression of neuronal and glial cell markers (Bereiter and Jeanrenaud, 1979, 1980; Sena et al., 1985). More recently, studies have shown that the brain abnormalities in ob/ob mice are present even at embryonic ages.
In the developing rodent, ObRs are widely expressed throughout the CNS from early in mid-gestation (Hoggard et al., 1997; Matsuda et al., 1999; Udagawa et al., 2000) and leptin protein is detected in the circulation of fetal rodents (Udagawa et al., 2006). There is thus evidence for the presence of both ligand and the relevant receptor within the developing brain. Further direct evidence that leptin is involved during fetal life in brain growth and development was obtained recently, with the observation that ob/ob fetuses at E16 exhibit reductions in neuroepithelial cell number within the cortex and reduced proliferative capacity compared with wild-type animals (Udagawa et al., 2006). Administration of leptin to E14 embryos was able to increase cell number at E16, and there is some in vitro evidence that leptin can directly increase BrdU incorporation (a marker of proliferation) in cultured neurospheres (Udagawa et al., 2006).

Postnatally, the administration of leptin to ob/ob animals has been shown to increase brain size (Ahima et al., 1999; Steppan and Swick, 1999). However, restoration of brain weight to wild-type levels required leptin to be administered for 6 weeks, from 4 weeks of age. Administration of leptin for 2 weeks from 8 to 10 weeks of age was ineffective in the rescue of brain weight or protein content (Ahima et al., 1999), suggesting perhaps a critical period for leptin administration in the rescue of brain development during periods of greater plasticity at younger ages. Further evidence for restricted periods of leptin action in brain development is discussed in more detail below.

### B. Postnatal leptin surge

In both rats and mice, there is a transient increase in circulating leptin concentrations during the first 2 postnatal weeks (Ahima et al., 1998; Devaskar et al., 1997; Morash et al., 2001, 2003; Rayner et al., 1997; Yura et al., 2005). This rise in leptin is independent of body fat mass, and the regulation of this “surge” is at present unknown. Several studies have indicated that the source of postnatal leptin is likely to be the adipose tissue of neonatal rodents (Ahima et al., 1998; Devaskar et al., 1997), although alternative sites of production have been demonstrated. In one study, pituitary and cerebral cortex leptin expression was shown to correlate with the elevated circulating leptin concentrations, and it was suggested that this rise in leptin concentrations locally with the brain–pituitary axis may play a role in the development of these systems (Morash et al., 2001). If the leptin surge is generated by the developing adipose tissue, then the regulation of its production and secretion is clearly quite different to that in the adult. The rise in leptin appears to occur independently of circulating glucose or insulin (Cottrell et al., 2009; Srinivasan et al., 2008), key factors in the stimulation of leptin secretion in the adult (as discussed above). However, nutritional manipulations are able to alter leptin concentrations in the
neonatal rodent. Exposure to a reduced plane of nutrition during the postnatal period, through restriction of maternal food intake, was shown to lead to a significant reduction in circulating leptin concentrations in the offspring (Delahaye et al., 2008). Interestingly, the feeding of a high-carbohydrate diet during the first 2 postnatal weeks to rats, which leads to significant elevation of glucose and insulin concentrations, was also found to result in markedly reduced levels of circulating leptin in these animals (Srinivasan et al., 2008). This further suggests that glucose and insulin are not the key stimulators of leptin production in the early postnatal period.

As well as endogenous production, maternal breast milk contains leptin both in the human (Miralles et al., 2006) and rodent (Stocker et al., 2004). In rat pups, ingested leptin has been shown to be taken up by the immature gastrointestinal tract and to enter the neonate’s circulation (Casabiell et al., 1997). It is to be expected that the circulation of a neonatal ob/ob mouse would have no detectable leptin. However, given the evidence for uptake of maternally derived leptin by the neonatal stomach, it is theoretically possible that ob/ob offspring may have a low level of circulating leptin, if hormone is transferred from the maternal milk. We recently investigated whether this was the case by measuring leptin concentrations in the serum of ob/ob mice and their wild-type littermates across a range of postnatal ages between birth and weaning. We also included measurement of heterozygous animals (ob/+ ) from these litters, to determine whether there was a gene–dosage effect in the production of a postnatal leptin surge. As shown in Fig. 11.1 (unpublished observations), wild-type animals exhibited the expected postnatal leptin surge, peaking around postnatal days 9–11 (P9–11). However, at no age did the serum of ob/ob offspring contain detectable leptin. Interestingly, ob/+ animals (those with a single functional copy of the leptin gene) exhibited lower leptin concentrations across the lactation period, and there also appeared to be a lack of evidence for a “surge,” as occurs in the wild-type animals. Whether or not this absence of a leptin surge might have long-term effects on adult phenotype in the ob/+ mice is not clear; however, it has been reported that although these animals are phenotypically normal, they are more susceptible to diet-induced obesity when fed a high-calorie diet, compared with wild-type animals (Begriche et al., 2008).

C. Leptin insensitivity in the early postnatal period

Despite the marked elevations in circulating leptin concentrations in the developing rodent, there is a lack of effect of these raised hormone levels on food intake in the early postnatal period (Mistry et al., 1999). This lack of sensitivity to leptin presumably allows neonates to maximize their food intake during a period of rapid growth. The acute administration of exogenous leptin to P10 rats was found to increase POMC and decrease NPY
in the ARC, as would occur in the adult; however, there was no effect on food intake or body weight in these pups (Proulx et al., 2002). This possibly reflects a lack of functional circuitry at such a young age at least in terms of feeding circuitry. However, it was found that leptin could reduce fat pad weight at this young age. Similarly, it was reported that in both wild-type and ob/ob mice, leptin was unable to reduce food intake or stimulate oxygen consumption in the first 2 postnatal weeks, but by P17 leptin administration was able to increase energy expenditure (Mistry et al., 1999). By 28 days of age, intracerebroventricular administration of leptin was able to inhibit food intake as well as stimulate oxygen consumption. Together, these findings indicate that there are different developmental trajectories for the circuits regulating feeding versus energy expenditure. In agreement with this, relatively recent studies indicated that indeed, downstream of ARC leptin actions, there is a divergence in melanocortin signaling pathways to regulate the feeding and expenditure arms of energy balance independently (Balthasar et al., 2005).

In humans, the body weights of leptin-deficient infants do not diverge until around the time of weaning (S. Farooqi, personal communication), suggesting that, as in the rodent, leptin does not act to regulate energy balance during the early postnatal period. Importantly, this divergence in

**Figure 11.1** Leptin concentrations in the serum of postnatal mice. Data are shown as mean ± SEM and were examined by two-way ANOVA followed by Fisher’s LSD post hoc tests. P values indicate significant differences in heterozygous (ob/+ ) offspring compared with wild-type littermates at each age. ***P < 0.001. n = 7–15 animals per group. Leptin was not detectable at any age in the serum of ob/ob offspring (ND).
body weight occurs in both breast- and bottle-fed infants, negating a role for breastmilk-derived leptin in the regulation of energy balance in early life.

D. Neurotrophic actions of leptin

Although the physiological function of the leptin surge remains incompletely understood, one of the roles for leptin in early life that has emerged in recent years is the establishment of hypothalamic neuroendocrine systems (Bouret and Simerly, 2007). Some of the most compelling evidence to date for a neurotrophic action of leptin during restricted periods of development is derived from the work of Bouret and colleagues. Using DiI tracing of neuronal projections in wild-type and \textit{ob/ob} mice, they showed that in the absence of leptin there is a failure to form projections from the ARC to the downstream PVN (Bouret \textit{et al.}, 2004a). \textit{ob/ob} mice have a reduction in fiber density within the PVN at P12, and this reduced innervation persists in the adult animal. However, administration of leptin during the period corresponding to the postnatal surge in wild-type mice was able to increase the density of ARC projections to the PVN at P12 in \textit{ob/ob} mice, whereas leptin treatment in adult life had no effect. Further to these tracing studies, a direct action of leptin on neurite outgrowth was shown in ARC explants taken from neonates at P6 (Bouret \textit{et al.}, 2004b). Thus, the current hypothesis is that leptin may play an active role in the establishment of the hypothalamic energy balance circuits it will later regulate (Bouret and Simerly, 2007).

In addition to these actions in the hypothalamus, neurotrophic effects of leptin have also been demonstrated in extrahypothalamic sites. Leptin administration induces ERK1/2 signaling in the cortex of both neonatal and adult mice, and in cultured embryonic cortical neurons affects growth cone size and spreading (Valerio \textit{et al.}, 2006). Taken together, these actions of leptin indicate a widespread role for this hormone in neuronal development and circuit formation.

E. Developmental changes in leptin receptor

Although there is plentiful evidence that ObRs are expressed throughout embryonic development and early postnatal life, whether or not there might be changes in the distribution of these receptors over this period has only recently been addressed. In the rat, there is an increase in both ObRb mRNA expression and protein binding in the hypothalamus between E18 and early postnatal life (Carlo \textit{et al.}, 2007). We recently showed that, in the rat, there is a marked change in ObR distribution between birth and weaning (Cottrell \textit{et al.}, 2009). Specifically, there was dense ObR mRNA expression within the third ventricle (3V) of the hypothalamus, which progressively decreased and was completely absent by P19, and also was
not present in the adult brain. Conversely, ObR expression in the ARC and VMH increased over the period of suckling. Leptin administration at P4 was found to stimulate a robust induction of SOCS3 within the 3V, a response that was essentially absent by P14. By this later age, leptin-induced SOCS3 was prominent within both the ARC and VMH, reflecting a developmental change in leptin responses over a period in which endogenous leptin levels are raised, and during which time hypothalamic circuits are still developing. It is also interesting to note that the location of 3V leptin receptors may be relevant for the reported neurotrophic actions of leptin in the hypothalamic explants used by Bouret and colleagues (discussed above). A similar localization of leptin-induced signaling has been shown in mice, where between P5 and P13, leptin-induced P-STAT3 was detected in an unidentified population of cells within the subependymal region of the 3V (Frontini et al., 2008).

In terms of the leptin insensitivity in the postnatal mouse, we recently studied the ontogeny of hypothalamic ObRs in wild-type and ob/ob mice over the postnatal period. Given that (1) in the adult ob/ob mouse, ARC ObR mRNA is markedly upregulated in the absence of leptin and downregulated following exogenous leptin administration (Mercer et al., 1997); and (2) there is no significant effect of leptin administration during the early postnatal period on body weights of either wild-type or ob/ob neonates (Yura et al., 2008), we wanted to determine when hypothalamic leptin receptors become responsive to circulating endogenous leptin. We hypothesized that ob/ob and wild-type animals would have similar levels of ObR in the ARC up until the point at which responsiveness to circulating leptin occurs. Similar to previous observations in the neonatal rat, we determined that ObR increased progressively from P4 into adult life in both wild-type and ob/ob offspring (Fig. 11.2, unpublished observations). However, there were clear differences between wild-type and ob/ob animals, such that from P9 onward, ob/ob offspring exhibited an upregulation of ARC ObR compared with wild-type mice. Whether this divergence represents an onset of sensitivity to circulating leptin will require the administration of a leptin challenge to neonates across this period, to determine the timing of onset of activation of leptin signaling pathways in vivo in the hypothalamus.

IV. Developmental Programming: Role of Altered Neonatal Leptin Signaling

The field of development programming—encompassing the concept that an altered environment during critical periods of development can induce permanent changes in an individual’s physiology—continues to grow. There is now a wealth of evidence indicating that neonatal feeding
and growth trajectories can modulate predisposition to obesity, and as such, strategies that might be able to prevent such increased risks of adult disease are vital, as obesity rates continue to rise worldwide.

Many models used to study the long-term effects of neonatal nutrition have paid much attention to leptin and to the leptin surge itself in recent years. It has become apparent that not only a complete absence of leptin but also exposure to altered concentrations of this hormone during development can have long-term effects on adult physiology, and in particular can affect subsequent obesity susceptibility and a host of other metabolic complications. In the mouse, intrauterine growth restriction (IUGR) induced by maternal undernutrition (UN) leads to reduced birth weight and increased susceptibility to HFD-induced obesity in the UN offspring compared with normally nourished animals (Yura et al., 2005). In the postnatal period, these offspring exhibited a premature leptin surge, which was of greater amplitude than in control animals. By administering exogenous leptin to mimic this altered surge, it was shown that leptin-treated animals gained more weight on a HFD, implicating excess leptin exposure in early life as causal in the development of obesity susceptibility. Similarly, a recent study in rats demonstrated that maternal obesity during pregnancy is associated with an amplified and prolonged leptin surge in the offspring (Kirk et al., 2009). This increased leptin exposure was associated with subsequent

Figure 11.2  Leptin receptor expression in the postnatal hypothalamus. Leptin receptor expression in the ARC of wild-type and ob/ob mice, from neonatal to adult life. Data are shown as mean ± SEM and were examined by two-way ANOVA followed by Fisher’s LSD post hoc tests. P values indicate significant differences in ob/ob offspring compared with wild-type littermates at each age. *P < 0.05, ***P < 0.001. n = 7–12 animals per group.
leptin insensitivity, thought to drive the hyperphagia and increased adiposity in these animals. In contrast, the blocking of leptin action in neonatal rats, through administration of a ObR antagonist, was shown to predispose to later leptin resistance and increased body weight gain on a high-energy diet in adult life (Attig et al., 2008).

In a model of relatively severe maternal UN in the rat, there is again an adverse metabolic phenotype in the adult offspring (Vickers et al., 2000). However, in apparent contrast to the situation in mice, leptin treatment in early postnatal life was able to ameliorate these adverse programming effects in female offspring (Stocker et al., 2004; Vickers et al., 2005), but not in males (Vickers et al., 2008). Although female rats as adults have greater ObR expression relative to males, there is apparently no difference in hypothalamic receptor levels before puberty (Smith and Waddell, 2003), when differences in the effects of leptin administration between sexes have been reported. Thus, the biological basis of these observed sex differences remains to be determined.

Similar to the beneficial effects of leptin in the UN rat model, leptin administration during gestation and lactation to rat dams fed a low protein diet also prevents the adverse metabolic programming associated with this dietary manipulation (Stocker et al., 2004). Furthermore, this effect of leptin dosing to the mother protected offspring of normally nourished rat dams from the obesity-inducing effects of high-fat/high-energy feeding (Stocker et al., 2007). In another study looking at the effects of neonatal leptin supplementation, oral dosing with leptin within a physiological range during the lactation period was able to attenuate weight gain on a HFD postweaning (Pico et al., 2007). Although it is not yet clear how leptin supplementation during pregnancy and/or early life might impart long-term metabolic benefits, current data do suggest that early life leptin exposure can have lasting effects on energy homeostasis. However, the idea that leptin might be able to be used therapeutically in the prevention of obesity is still far from a reality.

V. CONCLUSIONS AND FUTURE DIRECTIONS

In contrast to the actions of leptin in adult life, numerous studies have shown that appetite and energy expenditure pathways in the rodent are relatively insensitive to leptin during the first postnatal weeks, a period of rapid growth. Leptin receptors are, however, present and functional in early life, and leptin has a clear role in brain development. It is established that there is an increase in ObR expression postnataally in both rats and mice, and more recently that there are clear differences in the sites of leptin action over the early postnatal period in the rodent. The precise function of the
transiently expressed ObRs in the 3V of the hypothalamus is not known, but the location and timing of this receptor expression may imply that they are involved in the early life establishment of hypothalamic circuitry. Changes in the actions of leptin with age might suggest distinct roles for this hormone at different stages of development (summarized in Fig. 11.3).

Clearly the interplay between ObR expression and dynamic changes in leptin production will be of importance in determining the ultimate signal that is transmitted to the developing system in question. The role of leptin in terms of metabolic programming is not yet clear, although there is growing evidence that perturbed leptin signaling or an altered leptin profile in the postnatal period can have long-lasting effects on adult physiology. The challenge now is to determine whether there may be realistic interventions to alter neonatal nutrition or hormone profiles, with the aim of improving adult metabolic health and reducing disease.

**Figure 11.3** Summary for the developmentally regulated actions of leptin during early life. Recent evidence has accumulated that leptin regulates the development of neuronal and glial cells during fetal life, and that during the early postnatal period leptin signaling plays a role in the establishment of neuronal circuitry. At around the time of weaning, when independent feeding is initiated, leptin begins to exert metabolic effects, presumably reflecting the maturation of circuitry that regulates feeding and energy expenditure. The precise timing of this switch in the actions of leptin is unclear but likely involves changes in the expression and distribution of functional leptin receptors during development.
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REFERENCES


