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Developmental influences on circuits programming susceptibility to obesity

Lori M. Zeltser

Naomi Berrie Diabetes Center and Department of Pathology and Cell Biology, Columbia University, 1150 St Nicholas Ave, New York, NY 10032, USA

Abstract

Suboptimal maternal nutrition exerts lasting impacts on obesity risk in offspring, but the direction of the effect is determined by the timing of exposure. While maternal undernutrition in early pregnancy is associated with increased body mass index, in later pregnancy it can be protective. The importance of the timing of maternal undernutrition is also observed in rodents, however, many of the processes that occur in the last trimester of human gestation are delayed to the postnatal period. Neonatal leptin administration exerts lasting impacts on susceptibility to obesity in rodents. Although leptin can influence the formation of hypothalamic circuits involved in homeostatic control of feeding during the postnatal period, these effects are too late to account for its ability to reverse adverse metabolic programming due to early gestational exposure to maternal undernutrition. This review presents an alternative framework for understanding the effects of neonatal leptin through influences on developing thermoregulatory circuits.

Keywords

maternal programming; undernutrition; catch-up growth; obesity; leptin; brown adipose tissue; thermogenesis

Introduction

The rapid increase in the prevalence of childhood obesity and the concomitant rise in type 2 diabetes/obesity-related medical morbidities and costs, lend urgency to the need for new insights into the causes and potential preventive measures for this disease. Because the trajectory of this increase is very steep- as much as 60% between 1988 and 2000 in some populations - it is unlikely that genetic and conventional environmental factors are sufficient to explain these trends [1]. There is a growing appreciation that maternal nutritional and metabolic status during gestation can exert lasting effects on susceptibility to obesity in offspring. In their “thrifty phenotype hypothesis”, Hales and Barker propose that maternal

Correspondence: Lori M. Zeltser, PhD, Naomi Berrie Diabetes Center, Columbia University, 1150 St Nicholas Ave, New York, NY 10032, USA, Phone: +1 (212) 851-5314, Fax: +1 (212) -851-6306, lz146@cumc.columbia.edu.

influences on the developing hypothalamus, pancreatic islets, adipose tissue and liver result in metabolic adaptations in the progeny that promote survival under conditions of limited nutrient availability, but render them vulnerable to nutritional excess later in life [2].

In rodents, the nutritional environment during lactation (roughly equivalent to the third trimester of human gestation) has lasting impacts on body weight and susceptibility to diet-induced weight gain [3,4]. As the amount of milk consumed during lactation determines the level of voluntary food intake after weaning [5], efforts to elucidate the mechanism of maternal programming of obesity have often focused on hypothalamic feeding circuits [6]. This review will explore the possibility that susceptibility to obesity due to suboptimal nutrition during development is mediated via effects on thermoregulatory circuits.

1. Association between suboptimal fetal growth and susceptibility to obesity in humans

1.1. Gestational undernutrition followed by catch-up growth—Suboptimal nutrition during gestation, due to famine or other factors that reduce birth weight, has been associated with long-term impacts on body mass index (BMI). However, in some situations maternal undernutrition is linked to increased body weight in progeny, while in others it is associated with reduced body weight. The timing of developmental exposure to famine and the abundance of food in the postnatal environment appear to determine whether offspring are at increased or decreased risk of obesity. The 5-month period of extreme food shortage in the Dutch Winter Hunger of 1944-45 afforded the unique opportunity to parse the consequences of severe maternal undernutrition in early vs. late gestation on offspring outcomes. Whereas maternal exposure to famine in early gestation is associated with increased BMI, exposure late in gestation and early infancy appears to be protective with respect to obesity, but is linked to impaired glucose tolerance [7,8,9]. These observations support the idea that maternal programming of obesity and metabolic dysregulation are mediated via effects on distinct developmental processes. This review will focus on programming of obesity-related endpoints, while the Brüning review in this issue will focus on glucose tolerance.

Another important determinant of the impact of maternal undernutrition on offspring BMI is the abundance of food in the postnatal environment. Maternal programming of increased BMI is typically observed in situations when the period of famine is followed by relative nutritional abundance, as in the Dutch Winter Hunger. On the other hand, long-lasting famines involving exposure to undernutrition in both the gestational and postnatal periods, such as that caused by the Siege of Leningrad from 1941-5 [10], are not associated with increased BMI in offspring. The lasting impact of gestational undernutrition is not limited to famine conditions, but can also be observed in small for gestational age (SGA) babies that received suboptimal fetal nutrition but ample postnatal nutrition [2]. These observations are consistent with the idea that the undernourished fetus develops in anticipation of limited nutrient availability in later life [2]. While these adaptations promote survival under conditions of food scarcity, they are not well-suited to a nutrient-rich environment and thus increase susceptibility to diet-induced weight gain [2,11].

1.2. Rapid weight gain in infancy as a risk factor for obesity—One common feature of SGA babies and those exposed to the Dutch Winter Hunger early in gestation is that readily available food sources in the postnatal environment promote rapid "catch-up growth". Fast growth trajectories in early infancy are associated with increased prevalence of obesity, even in babies with normal birth weights [12,13,14,15,16]. It has been proposed that preferential deposition of fat mass in neonates as compared to older infants underlies this observation [17,18]. In support of this idea, rapid weight gain during the first three months of life is associated with a higher percentage of body fat and more central adiposity in early adulthood than weight gain that is distributed evenly throughout the entire first year [19]. Thus, constrained postnatal growth in infants born into famine conditions could underlie observations that these individuals have reduced BMI in adulthood [7,10]. Distinguishing between directs effects of maternal undernutrition on the development of circuits regulating energy balance and indirect effects due to increased risk of rapid growth in infancy could lead to more effective strategies to prevent obesity in at-risk SGA infants.

2. Rodent models of maternal undernutrition

Experimental animal models have been used to gain mechanistic insights into the fetal origins of adult obesity. Obesity-related outcomes in sheep models of maternal nutrient restriction depend on the timing of exposure, similar to observations from studies of the Dutch Winter Hunger (as discussed in section 1.1 of this paper and reviewed in [20]). Suboptimal nutrition during the first two-thirds of sheep gestation leads to increased adiposity that persists to adulthood [21], while restriction in late gestation results in reduced adiposity [22]. While the formation of neural circuits that regulate food intake and energy expenditure is largely completed at parturition in precocial newborns, such as sheep and humans, these processes continue into the suckling period in altricial newborns, such as mice and rats [23]. Because distinct developmental events occur in the gestational and postnatal periods in the rodent, they can be used to distinguish which periods, and therefore processes, are developmentally sensitive to maternal influences. At the same time, it is important to keep in mind that situations in which the early and late gestational environments in humans are discordant are the exception, rather than the rule. This review will focus on rodent models of maternal programming, although corresponding periods in precocial species will be discussed in section 9.

2.1. Gestational undernutrition followed by catch-up growth programs sensitivity to diet-induced obesity—Rodent models of maternal undernutrition recapitulate observations that the timing of developmental exposure and postnatal dietary factors determine whether the offspring exhibit susceptibility or resistance to diet-induced weight gain. Maternal nutrient restriction throughout gestation and lactation has little effect on offspring fed a chow diet, but leads to increased adiposity when challenged with high fat diet (HFD) in adulthood [24,25,26]. A rapid increase in the postnatal growth trajectory in rodents, whether or not it was preceded by growth retardation, can lead to increased body weight and adiposity on chow and susceptibility to HFD-induced weight gain [4,24,27,28,29].

2.2. Postnatal undernutrition can be protective against DIO—Models involving maternal dietary restriction during lactation and suckling in a large litter have been used to study the impacts of undernutrition in the suckling period. While postnatal undernutrition is consistently associated with reduced body weight at weaning [3,30], these effects do not always persist into adulthood [27,31]. Protective effects of reduced nutrition during lactation are more pronounced in mice with genetically- or diet-induced obesity (DIO) [32,33].

In summary, rodent models recapitulate fundamental observations in precocial species that maternal undernutrition early in gestation programs increased susceptibility to obesity, while late exposure programs resistance to HFD-induced weight gain. Consistent with delayed maturation of circuits regulating energy balance in altricial newborns, impacts associated with exposure in late human gestation are shifted to the suckling period in rodents. In both precocial and altricial species, the long-term impact of maternal undernutrition on obesity is most clearly observed when progeny are challenged with a calorically dense diet in adulthood.

3. Developmental influences on hypothalamic feeding circuits in rodents

Pioneering studies by Widdowson and McCance demonstrated that manipulations of litter size could be used to assess the long-term impact of changes in caloric intake during the suckling period [3]. As maternal milk supply is finite, the primary determinant of food intake in species with large litter sizes is the number of suckling pups [37]. Postnatal undernutrition (UN) by lactation in a large litter leads to persistent reductions in body weight [3]. Observations that large litter size programms reduced food intake [5] fostered interest in elucidating developmental influences on brain circuits regulating food intake.

3.1. Ontogeny of circuits regulating food intake—Feeding behavior is controlled by sensorimotor, neuroendocrine and cognitive systems that process and integrate signals from the external environment in the context of internal neuronal and humoral signals of energy availability [38]. Circuits regulating distinct aspects of feeding behavior are formed in different periods of development. The most basic type of control over food intake, meal initiation and termination, develops earliest. Autonomic circuits linking the stomach and feeding circuits in the hypothalamus and brainstem are observed at birth and expand rapidly within the first week of lactation [39,40]. Gastric distension can suppress food intake as early as postnatal day 1 (P1), while postabsorptive nutritional signals from the gut operate after P9-11 [41,42](reviewed in [40]). Homeostatic regulation of food intake in response to information about the availability of short- and long-term energy stores emerges in the peri-weaning period [43,44,45,46]. Projections from neurons in the arcuate nucleus of the hypothalamus that can sense nutrient (i.e. glucose, fatty acids) and hormonal (i.e. leptin, ghrelin and insulin) signals of energy status are first detected in preautonomic components of the feeding circuitry at P15-16 [47]. However, leptin's ability to suppress food intake does not emerge until after weaning at P28 [44]. Finally, cognitive processes that control motivated aspects of feeding behavior are not developed until post-ingestive consequences can be reinforced by the action of corticolimbic circuits, which mature in the post-weaning period [48,49].

Lactation is an important period for the establishment of post-weaning levels of food intake [5] and the formation of circuits regulating homeostatic influences on feeding behavior [47,50]. These observations raise the possibility that maternal programming of susceptibility to obesity is mediated, in part, via effects on developing interoceptive neurons in the mediobasal hypothalamus. Efforts to study maternal influences on developing feeding circuits have centered on two neuronal populations in the arcuate nucleus of the hypothalamus (ARH) that have been implicated in homeostatic regulation of energy balance, NAG neurons co-expressing neuropeptide Y (NPY), agouti-related peptide (AgRP) and gamma-aminobutyric acid (GABA) and another population that expresses pro-opiomelanocortin (POMC).

NAG neurons are activated by signals of negative energy balance (i.e. ghrelin) and are inhibited by signals of an energy replete state (i.e. leptin) [51,52,53]. Central injection of NPY or AgRP [54,55,56] or stimulation of NAG neuronal activity is sufficient to drive acute and robust feeding behavior [57,58]. As functionally distinct sets of POMC neurons sense signals such as leptin, insulin and serotonin [59,60], dissecting the roles of POMC-expressing neurons in regulating food intake is more complicated. While POMC neurons mediate the effects of serotoninergic compounds on food intake [61], there is little evidence to support the idea that leptin- or insulin-sensing POMC neurons directly control food intake [62]. The failure of pharmacological and optogenetic regulation of POMC neuronal activity to acutely impact food intake [57,58] supports the idea that effects of POMC neurons on feeding are likely secondary to impacts on energy expenditure and/or glucose homeostasis.

3.2. Maternal influences on the ontogeny of hypothalamic circuits regulating energy balance—The development of NAG and POMC neurons spans gestation and lactation in the rodent (Figure 1), and maternal nutrient status is reported to impact several stages of neuronal differentiation and maturation. Most ARH neurons are born at embryonic day 11-12 (E11-12) and differentiate from a *Pomc*-expressing progenitor [63,64]. After E14, some neurons switch off *Pomc* expression and begin to express *Npy*; the number of NAG neurons reaches stable levels by P15 [64]. POMC vs. NAG cell fate decisions can be influenced by maternal signals during gestation [65], although these differences often do not persist to adulthood.

While many intra-hypothalamic projections are formed before P6 [50], those implicated in regulating food intake develop in the latter half of the suckling period. Projections from ARH neurons to the paraventricular nucleus of the hypothalamus (PVH) are first detected at P8-10 [47,50]. However, they do not innervate the origin of pre-autonomic projections that regulate feeding in the caudal PVH [66,67] until P15-16 [47]. Projections from NAG neurons to the lateral hypothalamic area (LHA), which can also stimulate feeding [68], are first detected at P12 [50]. As projections from ARH neurons that regulate food intake are formed during the suckling period, it raises the possibility that maternal influences on obesity are conveyed via effects on this process [6]. Exposure to undernutrition during lactation is associated with increases in the percent of NAG neurons in the ARH, the number of AgRP+ projections to the PVH and release of NPY/AgRP in the PVH at 3-4 weeks [30,33,69,70], This increase in NPY/AgRP tone could promote survival by stimulating food intake in undernourished animals. However, it cannot explain the protective effect of

postnatal undernutrition against diet-induced obesity [32,33]. As the effects of postnatal undernutrition on the NPY/AgRP system are transient [26,71], it is likely that impacts of postnatal undernutrition on other determinants of energy balance underlie the long-lasting susceptibility to DIO.

4. Leptin in the neonatal period programs susceptibility to diet-induced obesity

Exposure to leptin in the early postnatal period imparts lasting effects on susceptibility to obesity, although the direction of the outcome is dependent on the nutritional status of the dam during gestation. Daily leptin treatment in wild-type rodents raised in average-sized litters results in elevated *Npy* expression in the PVH and increased weight gain and adiposity on a HFD [25,72], similar to consequences of exposure to early restriction (as discussed in section 2.1). On the other hand, neonatal leptin treatment can reverse sensitivity to DIO programmed by exposure to UN during gestation [73]. To elucidate what is driving the differential effects of neonatal leptin administration, it is important to identify the developmental processes that are impacted. There is an endogenous surge in plasma leptin levels at the end of the first postnatal week in rodents, although there is some variability in the precise timing of the peak [25,43,74](Green arrow in Figure 2). Since leptin does not affect food intake at this time [45], understanding how leptin is regulated and what it is doing during this period can provide critical insights into the mechanism underlying its persistent effects on susceptibility to DIO.

4.1. Ontogeny and function of leptin signaling in homeostatic/hypothalamic feeding circuits—

Leptin receptor (*Lepr)* expression and pSTAT3-mediated leptin signaling are first detected in the parenchyma of the ARH at P5 and markedly increase during lactation [74,75](Pink “v” shapes in Figure 2). The onset of leptin signaling in other hypothalamic nuclei is delayed relative to the ARH; P9 in the dorsomedial nucleus of the hypothalamus (DMH) and P13 in the ventromedial nucleus of the hypothalamus (VMH) [75].

Pioneering studies by Bouret and Simerly demonstrated that leptin administration from P4-P12 promotes axonal outgrowth from ARH neurons [76]. Follow-up studies reported that neonatal leptin preferentially impacts projections from NAG neurons to the autonomic compartment of PVH [67], which have been implicated in regulating food intake [66]. The preferential effect of neonatal leptin administration on NAG neurons is likely explained by the fact that the majority of leptin-sensing neurons in the neonatal ARH express *Npy* and not *Pomc* [77](Figure 1). The excitatory effect of leptin on neonatal NAG neurons [77] would be predicted to support axonal outgrowth. Finally, as NAG projections to the caudal PVH form between P10-15 [47](Figure 1), they would be maximally exposed to the growth-promoting effects of leptin treatment from P4-12.

During the transition to solid food at weaning, leptin’s effect on neuronal responses in NAG neurons switches from excitation to inhibition, which is the response elicited in mature NAG neurons [77,78,79](red arrow, Figure 2). The timing of the switch in NAG neuronal responsiveness to leptin coincides with the onset of leptin’s effects on food intake in the fourth postnatal week [44], raising the possibility that they are mechanistically linked.

4.2. Effect of neonatal leptin on ARH neurons is likely independent of processes that program susceptibility to obesity—While the data are compelling that leptin signals during the neonatal period promote outgrowth of NAG projections to pre-autonomic neurons in the PVH that regulate feeding [67,76], there are several reasons why leptin's effects on feeding circuits cannot explain the lasting impact of neonatal leptin on obesity-related outcomes [25,73]. First, the effect of leptin treatment in wild-type mice raised in average-sized litters to increase susceptibility to HFD-induced weight gain does not involve changes in food intake [25,72]. Second, it is not clear how rescuing orexigenic NAG projections in leptin-deficient *ob/ob* mice could contribute to the long-lasting protective effects of leptin treatment in *ob/ob* neonates [67]. Finally, reduced ARH projections in *ob/ob* mice [76] do not impair the ability of leptin to normalize food intake in these animals [80,81].

To begin to elucidate how neonatal leptin programs susceptibility to obesity, it is critical to consider what is known about the source(s) and target(s) of leptin in the neonatal period. While milk-derived leptin is detected in pups and likely contributes to neonatal physiology [82], serum leptin levels during the postnatal surge do not correlate with milk levels [83]. In addition, litter size manipulations that alter fatty acid composition and insulin levels in milk do not impact leptin [83,84]. Finally, the absence of plasma leptin in *ob/ob* offspring of *ob/+* dams provides strong evidence that it is pup-derived [85]. While white adipose tissue (WAT) is the major source of circulating leptin in the adult [86], there is very little WAT at the time of the neonatal leptin surge. Leptin is produced by the stomach, although this activity is less apparent in first half of the lactation period [87].

Studies from Zhang et al. provide compelling evidence that the main determinant of plasma leptin at P10 is leptin produced in brown adipose tissue (BAT) [88]. The earliest detectable impairments in LepR-deficient *fa/fa* rats are in BAT structure and function, consistent with the possibility that BAT is both a primary source and target for neonatal leptin action. BAT is the main site of non-shivering and adaptive thermogenesis in the rodent [89]. Thus, factors that establish baselines of BAT activity in the suckling period are well-positioned to exert a lasting impact on energy expenditure. To begin to evaluate whether effects of neonatal leptin on developing BAT and thermoregulatory circuits underlie its lasting effects on susceptibly to obesity, the timing of critical steps in the maturation of thermoregulatory circuits will be outlined below.

5. Ontogeny of BAT thermoregulatory circuits in rodents

5.1. Perinatal period – BAT recruitment—The brown adipose depot is formed during gestation [90], but the first few days after birth is a critical period for the recruitment of BAT in altricial newborns [89]. Uncoupling protein 1 (UCP1), the critical mitochondrial protein needed to produce heat in brown adipose tissue, is expressed in the final days of gestation [90](Figure 3), but neonates do not have the capacity to thermoregulate at birth [91]. There is a dramatic increase in *Ucp1* expression in BAT within the first few hours after birth [91]. High levels of catecholamines [92], glucocorticoids [93] and prolactin [94] at parturition could all contribute to this process, either by direct effects on BAT or by activating autocrine factors in BAT (i.e. IGF2) [94](Figure 3). After birth, the transition to

lactation exposes the neonates to fatty acids and ketone bodies [95], factors that promote the expression of *Fibroblast growth factor 21* (*Fgf21*) by the liver [96]. FGF21 can be detected in plasma within 2 days of birth and is maximal at P6 [97](Figure 3). FGF21 treatment in neonates is sufficient to increase thermogenic genes and core body temperature [97]. The initial phase of BAT recruitment at parturition is likely independent of sympathetic inputs because there are very few autonomic projections to BAT that can be detected at birth [98]. Thus, the collective action of neuroendocrine, cold-induced and dietary factors within first 2 days of birth likely explain the onset of cold-induced thermogenesis at P2-5 [91,99], a behavior that is critical for survival.

5.2. Early lactation period – increased sympathetic input and capacity for cold-induced thermogenesis—Neonatal responses to cold are much weaker than those exhibited by adults. In the adult, input from the sympathetic nervous system (SNS) to BAT is the major driver of cold-induced thermogenesis [89]. Sympathetic nerves innervate BAT by P6, and the dramatic increase in the capacity for cold-induced thermogenesis between P10-15 [99] coincides with an expansion in the catecholaminergic innervation of the BAT parenchyma [98](Figure 3). *Ucp1*, a molecular indicator of BAT activity, reaches adult levels by P16 [100]. Together these observations are consistent with the idea that factors driving autonomic innervation of BAT between P5-15 (such as cold) are major determinants of thermogenic activity.

5.3. Peri-weaning period – critical period of development for baselines of activity in thermogenic circuits—Baselines of activity in thermoregulatory circuits appear to be established in the peri-weaning period. The transition from a ketogenic diet during lactation to a carbohydrate–based diet is likely responsible for reduced circulating levels of FGF21 in weanlings, as this decrease can be prevented if animals are weaned onto a HFD [97]. Maintenance of elevated levels of this BAT-activating factor could underlie observations that weaning onto a HFD results in increased thermogenic capacity and protection from DIO [101]. Exposure to cold in the peri-weaning period is also associated with lasting increases in thermogenic capacity [102,103]. While HFD-feeding at weaning is protective against diet-induced weight gain [101], cold-rearing leads to increased susceptibility [103]. Observations that early cold exposure leads to increased catecholaminergic innervation of BAT [103,104] raise the possibility that early elevations of sympathetic tone lead to the establishment of high thresholds for activity – a phenomenon also described as norepinephrine (NE) resistance [105,106].

6. Leptin influences BAT development and activity

6.1 Stages of BAT development—There at least four stages of BAT development (Figure 3). The gestational phase is characterized by the formation of the tissue depot and production of key components of the thermogenic machinery (i.e. UCP1). Hormones secreted at parturition (i.e. glucocorticoids, prolactin) and following the transition to a milk-based diet (i.e. FGF21) are likely responsible for “unmasking” BAT activity in the neonatal phase (P0-10). The mid-lactation phase (P10-17) is characterized by the establishment of sympathetic projections and SNS-dependent stimulation of BAT activity. Environmental factors in the peri-weaning period, including diet and temperature, influence baselines of

activity in thermogenic circuits. Gain- and loss-of-function studies provide insight into leptin's influence on these processes.

6.1.1. Gestational Phase: Total mitochondrial protein and UCP1 levels are not altered in leptin signaling-deficient *fa/fa* rats and *ob/ob* mice [107,108], arguing against a major role for leptin in the earliest phase of brown adipocyte proliferation and differentiation.

6.1.2. Neonatal Phase: Impairments in BAT mitochondrial function and reduced energy expenditure at thermoneutrality have been detected in LepR-deficient rats as early as P2 [109,110]. Because deficits in energy expenditure are not associated with a decrease in total mitochondrial protein or UCP1 [107,108], perinatal leptin signals may promote the "unmasking" of BAT activity. By P7-8, leptin-deficient models exhibit increased lipid deposition [111,112,113] and modest reductions in thermoregulatory thermogenesis [109,110,112]. Leptin administration to lean rats from P1 reduces adiposity by P7 [114,115], but does not increase energy expenditure [44]. These observations support the idea that leptin plays a role in "unmasking" BAT after birth and maintaining baseline thermogenic activity of BAT. In principle, leptin could mediate these effects via direct effects on BAT to promote lipolysis [116] and/or indirect stimulation of the earliest sympathetic projections to BAT [98].

6.1.3. Mid-Lactation Phase: The period from P10-17 is characterized by an expansion of sympathetic projections onto BAT and a marked increase in thermogenic capacity and activity. At P10, *leptin* mRNA expression in BAT and circulating protein levels in plasma are elevated in LepR-deficient rats [117]. Exposure to NE, but not cold, can restore lower levels of leptin expression in BAT of *fa/fa* rats at this age, consistent with the idea that leptin conveys a cold-induced negative feedback signal via sympathetic neurons [88]. Increased lipid accumulation in *fa/fa* and *ob/ob* mutants is accompanied by impaired BAT mitochondrial structure at this stage [99,118], although it is not clear whether the two are causally related.

Reduced sympathetic tone onto BAT is readily observed in leptin mutants at P15 [119]. Interestingly, this decrease is relatively specific to BAT, as rates of NE turnover in WAT, liver, and pancreas of *ob/ob* mice are similar to those in lean mice [119]. Thermogenic capacity of BAT in *fa/fa* rats can largely be restored by treatment with a β-agonist from P8-16 [120], consistent with the idea that this deficit is due to reduced sympathetic tone. The severity of the deficit in thermoregulatory thermogenesis in leptin mutants increases after P16-17, in parallel with the marked increase in sympathetic innervation of BAT [121,122,123]. P17 also represents the earliest age at which leptin injection is reported to acutely increase energy expenditure in lean or *ob/ob* mice [44]. Together, these observations support the idea that leptin plays a critical role in mediating sympathetic signals onto BAT that promote adaptive thermogenesis, which becomes more prominent in the transition to weaning.

6.1.4. Peri-weaning phase: Exposure to cold in the peri-weaning period leads to lasting increases in thermogenic capacity [102,103]. However, the influence of leptin on this process has not been explored. This is an important area for future research.

6.2. Sites mediating leptin's effects on BAT thermogenic circuits—The gradual emergence of impairments in BAT structure and activity across lactation in genetic mutants lacking leptin signals is consistent with the idea that leptin influences several distinct phases of the development of BAT thermoregulatory circuits. As the initiation of LepR signaling in the brain and periphery spans the period of gestation and lactation, temporal patterns of expression can point toward sites where leptin might act to influence a particular process. Leptin likely promotes the "unmasking" of BAT activity that occurs shortly after birth. LepR is not yet detected in the mediobasal hypothalamus at this time [74,75]. The observation that neonatal BAT does not receive catecholaminergic input at birth [98], argues against a role for leptin signaling in other brain regions in the initial phase of BAT recruitment. It is possible that early effects of leptin are mediated by direct signaling within BAT [116] or indirect actions on other endocrine organs.

The earliest deficit in mutant models that can be attributed to a central action of leptin is the suppression of *Leptin* expression in BAT at P7, which is mediated by sympathetic inputs to BAT [88]. Brain regions that project to BAT and express LepR by P10 include the median preoptic area (mPOA) and the nucleus of the solitary tract (NTS), but not the DMH [75,124,125,126]. While LepR is expressed in a subset of NAG neurons at P10 [77], projections to the autonomic compartment of the caudal PVH are not formed until P15-16 [47]. Recent studies support the idea that leptin can act directly on LepR-expressing sympathetic axons to promotes axonal outgrowth [127]. While this capability was not assessed in projections onto BAT, it raises the possibility that leptin secreted from BAT during the surge (P8-10) contributes to the dramatic increase in sympathetic innervation of the BAT parenchyma observed after this period [98]. If true, it could explain why the deficit in SNS tone in *ob/ob* at P14 is restricted to BAT and is not observed in other organs that receive sympathetic input [119].

In theory, two modes of leptin action could contribute to deficits in thermoregulatory thermogenesis observed in leptin mutants after P15 [99]. First, it is possible that reduced sympathetic innervation due to the loss of LepR in sympathetic axons causes lasting decreases in sympathetic tone onto BAT. Exploring this possibility is an important area for future research. Second, impaired LepR-dependent transmission of cold-induced signals in the DMH and/or mPOA, and possibly BAT-projecting neurons in the retrochiasmatic area, Edinger-Westphal nucleus or the NTS, could also impede adaptive thermogenic responses [126].

6.3. Role of leptin in developing thermoregulatory circuits—Several lines of evidence support the hypothesis that neonatal leptin administration programs susceptibility or resistance to obesity via effects on developing BAT thermoregulatory circuits. Lean mice raised in average-sized litters that received daily leptin injections from P3-13 [72] or P5-15 [25] have no detectable change in obesity-related endpoints under chow-feeding conditions, but develop increased adiposity in response to a HFD challenge. As enhanced sensitivity DIO in these mice is not accompanied by hyperphagia, it supports the idea that deficits in adaptive thermogenesis are responsible. Conversely, neonatal leptin administration (P4-14) to *ob/ob* mice is associated with long-lasting improvements in BAT morphology and enhanced thermogenic responses to nutritional and cold challenges [67].

In mature animals, leptin action in the CNS can promote thermogenesis by modulating sympathetic tone onto BAT [128]. However, this activity is not observed until P15, when the BAT parenchyma is densely innervated by sympathetic projections [44,99]. The consequences of leptin treatment in neonates are opposite from those observed in mature animals. Neonatal leptin administration in rats (P1-10) and sheep is reported to reduce BAT UCP1 protein and thyroid hormones that promote thermogenesis [129,130]. An inverse relationship between *Leptin* and *Ucp1* gene expression in BAT has also been noted in older (7 weeks) rats exposed to different temperatures [131]. These observations raise the possibility that BAT-derived leptin may act locally to suppress *Ucp1* and BAT thermogenesis, although this idea has not been directly tested.

What can explain the switch in leptin's effect on thermogenic endpoints in the last week of lactation? This transition is characterized by a gradual decrease in BAT-derived leptin, which had been acting to suppress thermogenesis, and a concomitant increase in LepR-mediated increases in sympathetic tone that promote BAT activity. As LepR signaling is weak in BAT-activating neurons of the DMH in neonates [75,124], the putative local inhibitory effect of leptin on *Ucp1* would be predicted to function unopposed. Sympathetic projections that form in the first postnatal week may provide weak negative feedback to leptin expression in BAT by P7 [88]. LepR-expressing neurons in the mPOA or NTS could mediate this signal, although this has not been examined directly [75,124]. The onset of LepR signaling in the DMH [75] and the dramatic increase in sympathetic inputs to BAT after P10 [98] may act to suppress leptin expression in BAT [88] and thus promote *Ucp1* expression and thermogenesis.

If BAT-derived leptin promotes innervation by sympathetic axons [127], it would accelerate the arrival of negative feedback signals to drive the sharp decline in plasma leptin that marks the end of the surge [43]. If true, this system would allow maximal activation of BAT in response to parturition/lactation-related signals, which is critical to promote survival. SNS-dependent down-regulation of BAT-derived leptin could then act to shut off the early phase of unopposed thermogenesis when the CNS-regulated phase is able to take over. Thus, the neonatal leptin surge could act to coordinate the transition between these phases of thermoregulatory thermogenesis. In theory, the high plasma levels of leptin in the neonatal surge could ensure that circuits driving food intake develop in time to meet the increased energetic needs driven by the action of circuits regulating energy expenditure.

7. The importance of peri-weaning growth rates in programming susceptibility to obesity

It has been difficult to formulate a model to explain the contribution of changes in leptin signaling to the programming of obesity susceptibility because of the variability in the outcomes of studies using different experimental paradigms. For example, neonatal leptin administration improves deficits in BAT due to leptin deficiency in *ob/ob* mice [67] or severe intrauterine growth retardation (IUGR) [73]. However, the same treatment leads to impaired BAT thermogenesis and increased susceptibility to DIO when given to normally-nourished wild type mice [25,72].

There are also conflicting reports of the impact of maternal dietary restriction on the timing and size of the leptin surge. Some groups observed a premature leptin surge [25], while

other groups reported a delay [83]. These inconsistencies may stem from the fact that the plasma leptin surge is derived from the pup and not the dam [85], and thus variations in the timing, severity and nature of the maternal restriction could lead to different impacts on leptin production in pups. It is not clear what factors are driving leptin expression in neonatal BAT, but they may be independent of diet, as fasting does not impact leptin levels at this stage [43]. In light of these observations, influences of leptin on the formation of circuits regulating energy intake and expenditure are likely not the primary determinant of susceptibility vs. resistance to diet-induced weight gain in adulthood.

A recent paper provides compelling evidence to support the idea that the rate of growth in the peri-weaning period is predictive of responses to a HFD challenge [132]. In comparisons between experimental groups that were exposed to IUGR and/or neonatal leptin treatment, those that exhibited growth restriction in the peri-weaning period were protected from HFD-induced weight gain, while rapid growth in this period correlates with increased susceptibility [132]. Consistent with this theory, persistent improvements in BAT structure and capacity due to neonatal leptin treatment in *ob/ob* mice are also associated with restricted growth in the peri-weaning period [67]. The post-weaning period is characterized by a high rate of linear growth, a process that is energetically costly. Elucidation of the relationship between circuits regulating growth, adiposity and thermogenesis during development is an important area for future research.

8. Overview of the ontogeny of thermoregulatory circuits in rodents

A working model of the ontogeny of thermoregulatory circuits is presented below. While this formulation was informed by published information, many aspects of the model have not yet been examined directly. There are at least two phases of BAT thermogenesis, an immature phase that is critical for extrauterine survival and the transition to a fat-based diet, and a mature phase that is regulated by combined actions of sympathetic and circulating signals [89,133]. The immature phase is induced by hormones released at parturition (i.e. glucocorticoids, prolactin) and factors released in response to the ketogenic diet of lactation (i.e. FGF21) and does not appear to be impacted by maternal undernutrition [134]. It is possible that leptin works with these factors in the initial phase of BAT activity “unmasking” [109,110]. Some of these activating factors may drive expression of leptin in BAT, which may act locally to suppress *Ucp1* expression [129,130] and serves as the major source of plasma leptin in the neonate [88]. BAT-derived leptin may act locally to increase innervation by sympathetic projections [127] and via the circulation to promote axonal outgrowth in homeostatic feeding circuits [67,76]. Increased LepR expression in cold-activated neurons in the DMH [75] and sympathetic inputs to BAT after P17 [98], could act to robustly suppress leptin expression in BAT [88] and stimulate thermogenesis [126], providing for smooth transition to CNS-driven thermoregulation. Interactions between circuits regulating growth, adiposity and energy expenditure during the peri-weaning period likely impart significant and lasting effects on susceptibility to obesity [132]. However, little is known about the molecular and neuronal factors involved.

9. Translation to humans

Although the timing of developmental processes is different in rodents and humans, early nutritional restriction followed rapid growth is associated with increased susceptibility to obesity, while exposure that is limited to later developmental stages is associated with protection. Therefore, it is possible that effects of early suboptimal nutrition to depress BAT activity in rodents could underlie increased risk of obesity observed in precocial species as well. In support of this idea, reduced BAT function in children is associated with increased obesity [135,136,137].

9.1. Ontogeny of BAT in precocial species—Precocial newborns, including sheep, non-human primates and humans, exhibit active BAT from birth. Brown fat is first detected histologically in human fetuses at 20 weeks of gestation and is fully formed by 35 weeks of gestation [138]. As in rodents [134], BAT histology is not impacted by IUGR [138]. Serum leptin concentrations in humans are high at birth and rapidly decline [139,140]. Fetal leptin levels are elevated in growth-restricted humans [141] and sheep [142]. It is not clear whether there is a rodent correlate of this phenomenon; however, there are several reasons to think it may be similar to the leptin surge observed at the end of the first postnatal week in rodents. As in rodents, the peak of leptin at birth in sheep is followed by a rapid suppression of *Ucp1* expression such that the neonatal phase of declines after P7 [143]. Leptin treatment in neonatal sheep can drive a dramatic decrease in *Ucp1* [130], reminiscent of effects in rodents [129].

While it is tempting to speculate that the leptin surge in human births is analogous to the rodent surge at P8-10, there are some notable differences. For example, the leptin surge during parturition of precocial species is not likely to drive outgrowth of sympathetic innervation of BAT or AgRP projections to the autonomic compartment of the PVH, as these projections are established before birth in precocial species [144,145]. Gestational timing for influences on sympathetic innervation of BAT is supported by observations that reductions in catecholaminergic pathways in BAT due to intrauterine growth restriction are evident at birth in sheep [145]. Together, these observations support the idea that leptin signals in precocial newborns contribute to the process whereby the immature phase of BAT thermogenesis is extinguished, but do not influence axonal outgrowth or persistent patterns of BAT activity. This interpretation is consistent with reports that leptin levels at birth (i.e. cord blood) reflect birth weight [146,147], but do not predict later adiposity [148].

Several lines of evidence support the idea that the peak of BAT activity in humans occurs in infancy. Although the BAT depot is formed during gestation, it is likely activated by factors associated with parturition, as evidenced by lower UCP1 levels in BAT of pre-term and still-born infants than in older infants [149]. The maximal number of brown adipocytes detected histologically in infants [150,151] coincides with peaks of UCP1 protein levels in BAT [149] and plasma levels of FGF21 [152]. It has also been reported that *FGF21* is expressed in BAT and beige/BRITE adipocytes in human neonates and that *FGF21* levels are correlated with *UCP1* expression [153]. The peak of plasma FGF21 is observed at 6 months of age, with reduced levels detected by 12 months [152]. Finally, analyses of BAT histology

[150,151] and thermal imaging of the supraclavicular region [154] across the lifespan are consistent with the idea that BAT activity declines with age.

9.2. Impacts of catch-up growth on BAT in humans—In rodent models and humans, rapid weight gain in the postnatal period is associated with increased deposition of fat and susceptibility to obesity, independent of birth weight [14,16,18,19,28,29,132,155]. The idea that increased fat deposition associated with catch-up growth [17,18] programs impaired BAT function is supported by the observation that malnourished toddlers that experience catch-up growth exhibit increased leptin and low FGF21 as compared to those who maintain a slow growth trajectory [156]. The early phase of BAT development is likely important, because failure to develop active BAT in children is correlated with increased BMI [135,136,137]. Thus, these observations are consistent with the hypothesis that increased fat deposition during rapid growth in infancy programs diminished BAT capacity and reduced ability to increase energy expenditure when confronted with a higher nutritional plane.

10. Summary

Increased risk of obesity programmed by early exposure to suboptimal maternal nutrition in humans is also observed in animal models with altricial (rats and mice) and precocial (sheep and non-human primates) newborns. Leptin administration to normally-nourished rodents in the neonatal period, roughly equivalent to the last trimester in humans, is sufficient to program increased susceptibility to diet-induced weight gain. The rodent neonate expresses high levels of leptin in BAT that acts locally to activate an immature phase of thermogenesis and may also promote innervation by sympathetic inputs. BAT-derived leptin is also released into the serum and acts to promote projections from NAG neurons to pre-autonomic neurons in the PVH that regulate food intake. Effects of neonatal leptin on developing circuits regulating energy intake and expenditure can be overridden by nutrient and external environment factors that influence growth rates in the peri-weaning period, which are predictive of susceptibility to diet-induced weight gain in adulthood.

The relationship between increased fat deposition during catch-up growth, decreased BAT activity and risk of obesity in human infants is strikingly similar to observations about the lasting impact of growth rates in the peri-weaning period on susceptibility to diet-induced weight gain in rodents. Since interventions in the peri-weaning period that enhance thermogenic capacity can be protective against obesity in rats, it is important to explore whether similar processes can be invoked in humans. In theory, observations that slow rates of infant growth associated with exposure to famine late in gestation/early infancy are protective against obesity could be mediated via impacts on BAT development during this critical period. If true, a better understanding of the relationship between growth in infancy, fat deposition, and thermoregulatory circuits in humans could lead to novel strategies to combat childhood obesity.

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Highlights

- Timing of exposure to maternal undernutrition programs susceptibility to obesity.
- Neonatal leptin programs susceptibility to diet-induced weight gain in rodents.
- Leptin's effects on hypothalamic neurons are too late to impact this process.
- Neonatal leptin impacts brown adipose structure and function.
- Influences on thermoregulatory circuits could program obesity susceptibility.

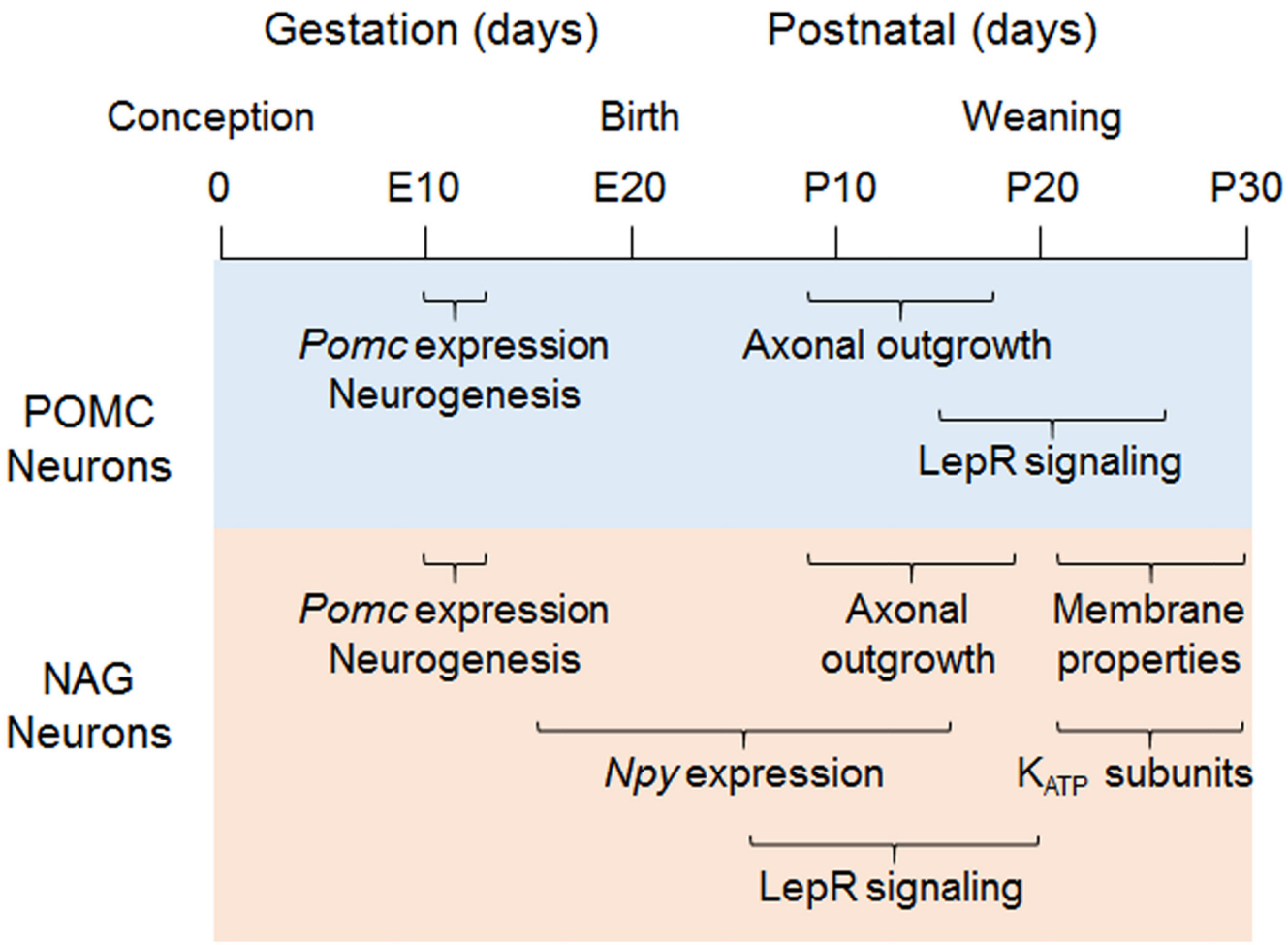

Figure 1. Ontogeny of leptin-sensing POMC and NAG neurons

Both neuronal populations are born at the same time during gestation and extend axons to target nuclei during the second week of lactation. However, the timing of terminal differentiation is divergent. LepR expression and signaling is observed earlier in NAG neurons than POMC neurons. In addition, the onset of K_{ATP} channel subunit expression in the peri-weaning period coincides with a switch from leptin-mediated activation to inhibition of NAG neurons.

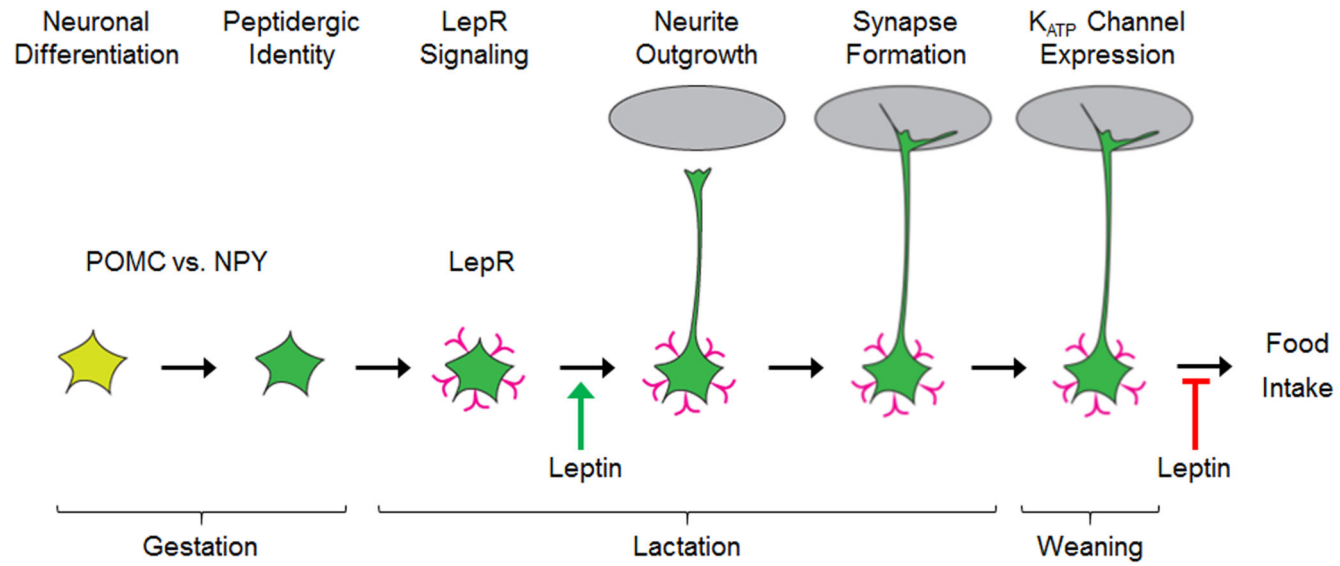

Figure 2. Ontogeny of leptin-sensing NAG neurons

Many NAG neurons are derived from a *Pomc*-expressing progenitor (yellow neuron); the decision to express *Npy* largely occurs during gestation and the early postnatal period (green neuron). LepR expression and signaling (pink "v" shape) is first observed at P5 and continues to increase throughout lactation. A leptin surge in the beginning of the second postnatal week (green arrow) activates NAG neurons and promotes neurite outgrowth. The expression of K_{ATP} channel subunits in the peri-weaning period coincides with leptin-mediated inhibition of NAG neurons (red stop arrow). The timing of NAG neuron maturation coincides with the onset of leptin's effects on food intake.

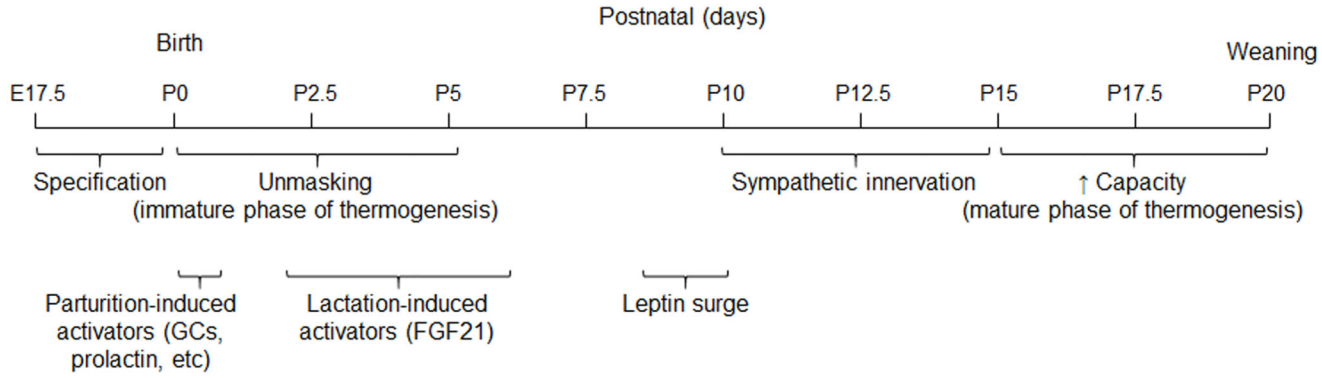

Figure 3. Stages of BAT development

The BAT depot is formed and produces thermogenic machinery by the end of gestation. Neuroendocrine factors produced at parturition and in response to the transition to a milk-based diet unmask BAT activity. This immature phase of BAT thermogenesis is critical to survival outside the womb and is largely unopposed. The surge of plasma leptin in the beginning of the second postnatal week immediately precedes the expansion of sympathetic projections onto BAT and a marked increase in thermogenic capacity and activity. The mature phase of thermogenesis is regulated, in large part, by sympathetic tone onto BAT.