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Feeding circuit development and early life influences on future feeding behavior

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Abstract

A wide range of maternal exposures– undernutrition, obesity, diabetes, stress and infection – are associated with increased risk of metabolic disease in offspring. Developmental influences can cause persistent structural changes in hypothalamic circuits regulating food intake in the service of energy balance. The physiological relevance of these alterations has been called into question because maternal impacts on daily caloric intake do not persist to adulthood. Recent behavioral and epidemiological studies in humans provide evidence that the relative contribution of appetitive traits related to satiety, reward and emotional aspects of food intake regulation changes across the lifespan. This article outlines a neurodevelopmental framework to explore the possibility that cross-talk between developing circuits regulating different modalities of food intake shapes future behavioral responses to environmental challenges.

Introduction

A thorough understanding of the mechanisms that regulate food intake is important because of the increasing incidence of obesity and metabolic disorders. Moreover, the consumption of ‘highly palatable foods’, is becoming more widespread; these foods are usually calorie dense and highly processed, and dysregulate the normal regulation of energy balance and can lead to weight gain. Although most high-profile studies have focused on acute factors influencing energy balance in adult humans and other animals, there is also evidence for developmental influences on energy balance regulation later in life. Indeed, a large body of epidemiological evidence indicates that intrauterine exposure to adverse maternal metabolic conditions such as undernutrition, obesity and psychological stress increases susceptibility of offspring to obesity[1,2].

The prevailing theory to explain these observations, the Barker hypothesis, is that maternal influences on the developing brain and peripheral organs produce metabolic adaptations in their progeny that render them vulnerable to nutritional-intake excess later in life[3,4]. In animal models, manipulations of maternal nutritional status or hormonal status during gestation or the neonatal period produce marked effects on caloric intake at weaning. Exposure to overnutrition leads to increased caloric intake, while exposure to undernutrition

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leads to decreased caloric intake[5,6]. This led many to hypothesize that maternal programming of obesity risk in offspring is possible, and is conveyed, in large part, through effects on the developing neuronal circuits regulating feeding behavior[3,7,8].

The discovery that the adipokine leptin promotes the formation of key components of circuits that control feeding behavior in the service of energy balance (i.e. homeostatic regulation)[9] ushered in a wave of studies of maternal influences on hypothalamic development. This research demonstrated that the neurons in the arcuate nucleus of the hypothalamus (ARH) directly sense circulating signals of metabolic status (i.e. leptin, ghrelin and insulin) and identified critical periods of development when maternal influences on their levels exert a lasting impact on the structure and function of key components of circuits that regulate homeostatic feeding behavior[7,8]. Given the robustness and persistence of these neuroanatomical effects, it was initially assumed that they underlie maternal programming of obesity risk.

More recently, however, there is a growing appreciation that this model of maternal influences on caloric intake in offspring is over simplistic: although alterations in maternal nutrition are closely correlated with early growth rates, they rarely persist to adulthood[10,11]. In fact, a recent meta-analysis of 35 rodent studies did not find evidence that maternal influences on susceptibility of offspring to diet-induced obesity are due to changes in caloric intake[12]. This indicates that the model in which maternal programming of obesity risk occurs by developmental alterations in hypothalamic feeding circuits needs to be reevaluated.

Epidemiological studies in humans and experiments in rodent models demonstrate that maternal influences can increase preferences for high fat foods, independent of caloric intake per se[13–15]. The mechanism by which information about maternal nutritional status is conveyed to mesolimbic dopamine reward circuits that regulate food choices and motivated feeding behavior is not known. A challenge to identifying conduits for maternal signals to reward circuits, which regulate the motivation to consume food, is that they do not function until the transition to independent feeding. Whereas links between early maternal influences and preferences for “junk food” in childhood are consistent, there are inconsistencies in the degree to which these effects persist and are associated with obesity risk in adults[13,15–17].

This article synthesizes data from clinical and epidemiological studies of feeding behavior in humans with neuroanatomical and behavioral studies in rodents to present a neurodevelopmental framework to evaluate the contribution of maternal influences on neuronal development to feeding behavior and obesity risk in adults – a framework that can reconcile the apparently conflicting data. This framework was developed around three core considerations. First, systems that provide orosensory, visceral, reward, homeostatic and emotional control of feeding behavior develop in the same step-wise progression spanning gestation through adolescence in humans and rodents. Second, population-based behavioral studies in humans demonstrate that the relative contributions of different types of feeding control to weight gain changes across the developmental continuum. Third, studies in rodent models show that developmental influences on one control system can produce compensatory adjustments in later-developing systems to maintain stable levels of caloric

intake over the long term. In this review, I will first introduce the main systems influencing feeding behaviors and describe current knowledge of the ontogeny of feeding circuit development in rodents and humans. I will then describe maternal influences on feeding circuit development and discuss how crosstalk during development of the different circuits regulating food intake could determine future behavior.

Circuits Regulating Feeding Behaviors

Feeding circuit development in rodents and humans follows loosely similar trajectories, making rodent models appropriate for gaining insight into regulation of human food intake. The ontogeny and developmental influences on many neurobiological and/or behavioral correlates of feeding behavior have been characterized in rodents, and are described in the following sections. Several excellent reviews provide detailed descriptions of circuits that regulate different aspects of feeding behavior[18–20]. The neurobiological processes that determine food intake can be classified into direct and indirect controls over the size and duration of an individual meal[21]; these two control systems are covered in detail below.

Direct Control Systems

Direct controls arise from contact between food and sensory receptors during the consummatory phase of ingestion. Orosensory stimuli arising from palatable food (i.e. sweet and fat) provide positive feedback to the brain that increases the rate and amount of food consumption during a single meal. Conversely, post-ingestive stimulation of the gastrointestinal tract stimulates vagal signals (visceral inputs) that provide negative feedback that promotes satiation and meal termination. Direct stimuli transmit information about the quantity and nutrient composition of a meal via direct projections to the dorsal vagal complex in the hindbrain, where positive and negative feedback signals are processed and relayed to central pattern generators in the caudal pons and medulla that regulate somatomotor systems needed to consume food (i.e. swallowing and chewing) (black arrows in Figure 1)(reviewed in[22]).

Indirect Control Systems

Indirect control systems modulate the potency of direct positive and negative feedback control systems through connections between the forebrain and hindbrain. They permit the fine tuning of behavior in response to the energy density and palatability of food, anticipated need for energy, and likelihood of securing food.

Visceral Control Systems

In addition to direct (vagal) inputs, post-absorptive visceral inputs are relayed by neural signals and gut peptide factors released into the circulation upon ingestion of a meal that act on distributed sites in the CNS to promote satiation (i.e. meal termination) (green arrows in Figure 1). The nucleus of the solitary tract (NTS) is a key node in circuits regulating satiety. In addition to receiving direct control signals from the vagus, it receives indirect signals from blood-borne gut-derived factors. This information is relayed to nuclei in the rostral brainstem that promote meal termination – the lateral parabrachial nucleus (PB) and

periaqueductal gray (PAG). The PB relays visceral signals to reward circuits via the lateral hypothalamic area (LHA), ventral tegmental area (VTA) and nucleus accumbens (NAc)[23–25] and to cortico-limbic circuits via the central nucleus of the amygdala (CeA)[26–29]. The NTS also relays visceral cues to circuits regulating homeostatic feeding behavior via the paraventricular nucleus of the hypothalamus (PVH)[30].

Reward Control Systems

Rewards circuits regulate consummatory behaviors related to the "liking" of food (i.e. palatability) and appetitive behaviors relating to "wanting" of food (i.e. food seeking) to guide behavioral strategies to meet energy requirements in an efficient manner (light blue arrows in Figure 1). Information about the sensory properties of food that drive motivated intake is relayed from prefrontal and orbitofrontal cortices via the NAc to the LHA and VTA, critical nodes in the mesolimbic dopamine system. Reward-related signals are relayed to other feeding control systems via projections from the LHA to the PB and PVH[31,32].

Homeostatic Control Systems

Homeostatic systems assess nutritional requirements to maintain metabolic homeostasis, by sensing circulating levels of hormones reflecting energy stores (i.e. leptin, insulin and ghrelin)(pink arrows in Figure 1) in conjunction with endocrine and neural correlates of energetically costly processes, such as thermogenesis, growth and reproduction (dark blue arrows in Figure 1). Neurons in the ARH that express neuropeptide Y (NPY), agouti-related protein (AgRP) and γ-aminobutyric acid (GABA) (hereafter called AgRP neurons) are activated by nutrient, hormonal and neural signals of negative energy balance, and conversely, are inhibited by signals of the energetically replete state[33,34]. They transmit a potent inhibitory signal to many downstream targets to ensure that food-seeking behavior is prioritized over other potential activities. Targets of AgRP neurons include critical nodes in circuits regulating satiety (PVH, PB, PAG), reward (LHA) and emotional (bed nucleus of the stria terminalis (BNST), CeA) aspects of feeding behavior[35–37]. Over the long term, actions of AgRP neurons are opposed by the actions of proopiomelanocortin (POMC)-expressing neurons in the ARH. In addition to neural projections from the ARH, homeostatic information is conveyed by circulating signals of energy status (i.e. ghrelin, leptin) that act directly on neurons in key nodes in reward (LHA, VTA) and visceral circuits (NTS, PB) to modulate feeding behavior[38–43]. Homeostatic systems do not regulate food intake per se[44] but modulate the strength of reward and satiety circuits to favor motivated behavior in a manner that is appropriate for the situation. For example, food is less rewarding when it follows a meal or is likely poisonous, while it is more rewarding under conditions of negative energy balance, such as fasting or starvation. Functional images studies in humans demonstrate that ghrelin activates regions associated with reward and emotional feeding control systems (i.e. amygdala and orbitofrontal cortex) and that this response is correlated with hunger ratings[45].

Emotional Control Systems

Systems that relay information about behavioral emotional states arising from stimuli in the external environment, such as those that predict threats, can override other regulatory systems (red arrows in Figure 1). Sensory cues processed by the prefrontal cortex and

anterior cingulate cortex are transmitted to limbic circuits via projections to the basolateral amygdala; this information is then integrated by neurons in the CeA to regulate feeding behavior[46]. Threat-related stimuli are also conveyed to reward circuits via projections from the CeA to the LHA, VTA and NAC[47,48] and from the BNST to the LHA[49]. These circuits are relatively understudied from a developmental perspective, so will not be discussed further in this review. In the next section, I will discuss how the circuits underlying the direct and indirect systems controlling food intake develop in both rodents and humans.

Ontogeny of Feeding Circuits

To consider the possibility that maternal influences program later feeding behavior in offspring, it is necessary to appreciate the time frame over which different control systems develop. In humans and animal models, systems regulating distinct modalities of food intake develop asynchronously. The most basic types of feeding regulation - direct positive and negative feedback - are established shortly after birth, whereas the emergence of indirect control systems occurs gradually and extends into adolescence.

Feeding circuit development in rodents

The timing of key steps in the maturation of orosensory, visceral, reward and homeostatic feeding control systems in rodents has been characterized at both the behavioral and neuroanatomical levels. Studies of orosensory, visceral and reward circuits have largely utilized rats, whereas studies of homeostatic circuits have largely used mice. There are small (i.e. 1–3 days) differences in developmental timelines in rats vs. mice, but the timepoints corresponding to major developmental stages – gestation, lactation (0–3 weeks), post-weaning (>3 weeks) and pubertal transition (4–6 weeks) – is highly conserved. Thus, references in this review to a particular day in development are an approximation only. Figures 2–5 present an overview of when key neuroanatomical projections are formed within distinct control systems (dotted line), when they actively transmit signals (dashed line) and when their functional properties mature (solid line).

Orosensory Control Systems

Influences of maternal diet on infant responses to maternal breast milk[50,51] are likely mediated via effects on the development of orosensory control systems. In rodents, irect orosensory positive feedback (Figure 2) resulting from maternal milk stimuli can be detected shortly after birth[52,53], although intake in the first postnatal week is driven by thirst and not by nutritional content[54]. Orosensory systems develop the capability to drive dose-response increases in feeding in response to sweet between 1–2 weeks, with responses to fat maturing between 2–3 weeks[55]. The rewarding properties of olfactory stimuli associated with milk develop in rats by P6 and diminish after P12[56], whereas preferences conditioned by taste stimuli (i.e. sweet and fat) can persist after weaning[57,58]. These early positive sensory feedback systems depend on opioid signaling[59] and precede the development of the mesolimbic dopamine reward system (see below). Sensory stimuli are also transmitted to indirect control systems that regulate reward and emotional aspects of feeding behavior (see below).

Visceral Control Systems

Maternal influences on early patterns of caloric intake are major determinants of meal size and growth in the postnatal period[60,61]. These effects could, in theory, be mediated through influences on satiety-related control systems. At birth, the cytoarchitecture of the NTS in rodents (Figure 3) is largely mature[62] and the density and distribution of vagal sensory inputs to the NTS is established[63,64]. In neonates, direct negative feedback from gastric distension and gut-derived peptides (i.e. cholecystokinin) (visceral inputs) provide the only inhibitory control over feeding[54,65,66]. This direct negative feedback system does not require communication with forebrain circuits[67,68] and declines in strength after P14[69], concomitant with the development of indirect visceral control systems that engage forebrain circuits.

Transmission of visceral signals to indirect control systems in the brainstem (PB) and limbic regions (CeA, BNST) rapidly expand across the first two postnatal weeks[69]. Signaling to the PB, an important node in satiety circuits, continues to increase through 5–6 weeks[54,65,69–71]. Visceral signaling to limbic regions (CeA) declines markedly after P14, concomitant with extensive synaptic remodeling and pruning[72,73]. Although physical connectivity between the NTS and PVH is established at birth, there is a delay in the transmission of visceral signals until the second postnatal week[70,74]. Visceral signaling in the PVH reaches adult levels by 2 weeks[70], and there is no evidence of pruning or remodeling of these inputs[75]. The maturation of the electrophysiological properties of NTS neurons occurs at 3 weeks[76]. In summary, direct negative feedback systems promoting meal termination operate from birth, but indirect systems form and mature across lactation. More detailed information about the ontogeny of visceral inputs can be obtained from several excellent reviews[7,77].

Reward Control Systems

Maternal exposures that increase preference for high fat foods[13,14] are likely conveyed via effects on the developing mesolimbic dopamine reward circuits. Connectivity between the LHA and VTA is established by within the first week of life in rats (Figure 4)[78,79]. Projections from dopaminergic neurons in the VTA to the NAc are formed and remodeled through axon pruning by the end of gestation[80]. Varicosities on dopaminergic fibers are first detected at the end of gestation. The expansion of varicosities across the first two postnatal weeks is paralleled by the expression of dopamine and opioid receptors in the NAc[81–83]. Expression levels of the dopamine 2 receptor and opioid receptors declines after lactation (3–4 weeks), consistent with remodeling in these signaling pathways[84,85]. Synaptic connectivity between neurons in the VTA and their primary targets in the NAc, the medium spiny neurons, does not form until the end of the third postnatal week[82,86]. There is evidence of extensive pruning and remodeling within the dopaminergic system in the post-weaning period[87]. Thus, although reward circuits are physically formed by the end of lactation, processes that control learning-based aspects of feeding behavior are not developed until post-ingestive consequences can be reinforced by the action of cortico-limbic circuits, which mature in the post-weaning period[88]. More detailed information about the ontogeny of reward circuits can be obtained from[83].

Homeostatic Control Systems

Subpopulations of neurons in the ARH directly sense a wide range of circulating factors and thus serve as a conduit for transmitting maternal signals to feeding circuits in the brain. The majority of newly-born ARH neurons initially express pro-opiomelancortin (POMC) (Figure 5)[89]. The transmitters and neuropeptides that comprise the signaling outputs in adults (NPY, GABA and AgRP) are progressively turned on in the latter half of gestation and the early postnatal period[89]. During the early postnatal period, AgRP neurons that project to pre-autonomic neurons in the PVH that regulate feeding transiently express leptin receptor (LepR); the onset of expression in other AgRP neurons takes an additional two weeks to complete[37,90–92]. Throughout lactation, leptin activates and ghrelin inhibits AgRP neurons to regulate axonal outgrowth to downstream targets that control food intake[75,92–95]. In the latter half of lactation, AgRP neurons are also activated by excitatory inputs, but inhibitory inputs do not arrive until the post-weaning period[96]. Projections from AgRP neurons reach pre-autonomic components of the feeding circuitry in the PVH between at P14 in mice[75,93,94] and P15–16 in rats[93]. AgRP→PVH projections reach adult levels by weaning (at P21), with no evidence of pruning[75]. In mice, AgRP projections to the reward circuits via the LHA appear at P12, while projections to cortico-limbic circuits via the BNST appear at P16[75]. Intrinsic (ion channels) and extrinsic (synaptic inputs) inhibitory regulation of AgRP neurons emerges in post-weaning period[92,97]. Less is known about the onset of homeostatic modulation of visceral and reward systems by direct signaling via leptin and ghrelin in these circuits. Leptin receptor expression and signaling in the rat VTA emerges in the second week[78,79]. In summary, although connectivity with homeostatic circuits is established by the second half of lactation, regulation of feeding behaviors in response to the availability of short- and long-term energy stores does not emerge until one week after weaning (P28)[92,98–101]. Before this stage, food intake is primarily driven by energetic requirements for temperature regulation and growth[102]. Thus, genetic disruptions in homeostatic circuits in the hypothalamus lead to increased growth[103–105]. More detailed information about the ontogeny of homeostatic circuits can be obtained from[7,106].

Feeding circuit development in humans

As mentioned above, the ontogeny of human feeding circuit development has parallels with rodents. Human neonates have the ability to respond to maternal odors, mediated by olfactory control systems. At birth they exhibit a preference for amniotic fluid, but within the first week, this transitions to a preference for breast odor[107]. Tactile and social bonding are sufficient to positively reinforce the preference for breast odor, but orosensory reward likely contributes as well[108,109]. Infants are also capable of basic reactions to sweet or bitter taste. These responses are generated within the brainstem and do not require connectivity to higher brain structures[110].

The ontogeny of indirect control systems in humans can be approximated by the onset of appetitive traits that distinguish between satiety, reward, homeostatic and emotional aspects of feeding behavior. The validation of the Baby and Child Eating Behavior Questionnaires as standardized methods to quantify distinct appetitive traits in infants and children[111,112] made it possible to conduct prospective analyses of changes in their relative contributions to

feeding behavior across the developmental continuum, an issue that has not been assessed in rodent models.

Within the first six to eight weeks of life, infants regulate food intake in response to nutrient and hormonal cues to maintain consistent levels of caloric intake over a 24 hour period – which involves input to the brain from the viscera. They compensate for variation in the frequency of meals or in the caloric density of a milk-based formula by adjusting the amount they consume[113–116]. This precise regulation of caloric intake is maintained through one year of age and the initial introduction of solid foods with different caloric densities[113–116]. The emergence of basic feeding regulation systems as assessed in the laboratory, is also reflected by the acquisition of quantifiable traits related to “satiety responsiveness” and “food responsiveness” that are associated with specific patterns of food intake[117]. High “satiety responsiveness” scores are associated with a smaller meal size but not with meal frequency, while high “food responsiveness” scores are associated with more-frequent meals but not with meal size[118]. In the first year of life, regulation of feeding behavior is largely driven by control systems that modulate food seeking versus meal terminating behaviors[119], consistent with the maturation of orosensory and visceral control systems.

Basic patterns of connectivity are established within homeostatic circuits during gestation[120]. During the first year of life, there is no evidence of homeostatic regulation of food intake in response to signals of energy stores. Instead, nutrient intake is tightly correlated with and predictive of growth, not adiposity[121–123]. As observed in rodents, mutations that disrupt homeostatic systems exhibit increased growth in humans[124]. During the early childhood years, the association between intake and growth is gradually lost[125].

Similar to rodents, mesolimbic reward circuits are formed during gestation[126], but reward-based learning and motivation do not develop until the transition to independent feeding. As variety is increasingly introduced into the diet, toddlers learn to form associations between foods and post-ingestive consequences of eating and develop aversions to new foods[127,128]. These learned behaviors are strongly influenced by child-feeding practices and other environmental factors[115,127]. Between 1–4 years of age, compensatory reductions in portion sizes when consuming energy dense foods are progressively weakened, and individual differences in responsiveness to foods emerge[115,116,127,129]. Thus, circuits regulating reward-based aspects of feeding behavior develop in early childhood and gradually supersede regulation by orosensory and visceral systems.

Comparisons of rodent and human feeding circuits

Crucial to understanding how experimental manipulations of maternal nutrition in rat and mouse relate to humans is an appreciation for the comparative developmental biology of the species. The step-wise ontogeny of different feeding control systems progresses similarly in rodents and humans (Figure 6). Direct orosensory systems operate soon after birth in both species. During the period when milk or formula is the primary source of food, the balance between orosensory and visceral systems maintains a stable level of caloric intake. Although reward circuits are formed during gestation in rodents and humans, reward-based control of food intake is not a primary determinant of feeding behavior until more variety is introduced

into the diet and learned associations can be drawn. At this point, visceral satiety systems become less prominent. Connectivity with homeostatic feeding circuits is established within the second postnatal week in rodents and within the third trimester in humans. Initially the function of homeostatic circuits is tightly linked to requirements for thermogenesis and growth, and the regulation of feeding behavior in response to circulating signals of energy status emerges after puberty. As children enter adolescence, traits related to "emotional eating" emerge as the principal determinants of eating behavior[119,128,130,131]. Little is known about the ontogeny of emotional control systems in rodent models.

Maternal Programming of Feeding Behaviors

Studies in humans and animal models consistently find a link between maternal metabolic status and long-term impact on susceptibility to obesity. Experiments in animal models provide strong evidence of pronounced maternal influences on the formation of hypothalamic feeding circuits and on feeding behavior at weaning. However, more detailed analysis reveals a more complex picture, with two main areas of contention: whether maternal influences on feeding behaviors persist to adulthood; and whether influences on feeding behavior contribute to obesity risk, or whether effects on energy expenditure are responsible. Resolving these issues is critical to elucidating the underlying mechanism.

Maternal Influences in Humans

A large body of epidemiological evidence supports the idea that exposure to maternal undernutrition and obesity programs increased obesity risk (for excellent reviews of this literature, see[132–134]*). Because maternal nutritional and metabolic status are usually similar across all of human gestation, it is difficult to determine the time window for these effects. Two types of studies have been used to parse the contribution of early vs. late gestational influences to programming of obesity risk. Epidemiologists took advantage of the fact that famine conditions during the Dutch Hunger Winter of 1944–45 was limited in duration to evaluate the consequences of exposure to maternal undernutrition in the first vs. third trimester*[135]*. Temporal considerations were incorporated into studies of maternal obesity by comparing the influence of pre-gravid maternal BMI vs. gestational weight gain on later adiposity in offspring*[136]*. In both situations, the data point toward the first trimester as the critical period for programming susceptibility to obesity, while the third trimester is most important for birth weight. There is a growing appreciation that a rapid growth rate during infancy, and not initial birth weight, is the critical determinant of obesity risk*[137–141].

After birth, there is strong evidence to support the idea that maternal factors influence the development of orosensory positive feedback systems regulating infant feeding behavior. The responsiveness of olfactory and gustatory sensory systems to maternal odors and flavors is positively reinforced by tactile stimuli and social bonding. Whereas preferences for sweet and avoidance of bitter flavors are strongly influenced by innate factors, exposure to certain volatile flavors in amniotic fluid as well as breast milk shapes flavor preferences later in life[142]. In addition, offspring preference for fat and protein at 10 years of age is correlated with maternal consumption of these macronutrients during gestation, but not with postnatal maternal diet or paternal diet[50]. Studies in non-human primates further support the idea that

maternal pre-gravid obesity and high fat diet consumption during pregnancy synergize to promote fat consumption in offspring at weaning, without effects on overall calorie intake[51].

Development of gustatory systems in pre-term infants exposed to severe IUGR may be delayed[143], but the ability to detect sweet or fat tastes is not impaired in adulthood[15,144]. Similar to observations with maternal obesity, exposure to maternal undernutrition or intrauterine growth restriction (IUGR) is also consistently associated with increased preference for palatable foods in the first few years of life, without effects on total caloric intake. However, there are differences between studies in the preferred macronutrient as well as the persistence of the effect. Some groups reported increased consumption of carbohydrates[144], while others observed increased fat consumption[15,17,145,146]. Some studies reported that the preference for palatable food is diminished with age[17], while others could detect effects in adults[15,144,146]. There also differences with regard to whether the primary impact is on females[144], males[145], or both genders[15]. Apparent inconsistencies between effects could stem from differences in the severity and duration of gestational restriction, as well as conditions in the postnatal environment.

The major limitation of epidemiological studies of maternal programming in the context of this article is that the main outcome measure is BMI, and rarely feeding behavior. Questionnaire-based quantification of appetitive traits has not yet been applied to investigate possible influences of maternal metabolic or nutritional status on specific appetitive traits. However, observations that satiety-related scores in infancy are more strongly correlated in monozygotic vs. dizygotic twins are consistent with the possibility that the gestational environment influences the development of visceral control systems[147].

Maternal effects on obesity risk?

Prospective studies of appetitive traits in two independent cohorts in Europe and Asia found that low “satiety-responsiveness” trait scores at 3 months are associated with increased meal size, and are the largest determinants of excess weight gain in the first two years of life[148–151,52]. Importantly, the inverse relationship between satiety-related appetite scores and weight gain in infancy is observed across the BMI spectrum and is independent of initial body weight. However, early appetitive traits do not continue as far as adolescence and the tight association with BMI is lost by 5–8 years of age[119,152]. This observation raises the possibility that maternal influences on orosensory and visceral control systems are not the primary determinants of obesity risk in adulthood.

The gradual shift in strength from satiety- to reward-based regulation of food intake that occurs during early childhood (1–5 years) is reflected in the relationship between appetitive traits and subsequent weight gain[115,116,119,127,128,130,153]. Satiety-related appetitive scores are no longer predictive of later weight gain, while scores related to emotional and motivated aspects of feeding are associated with higher BMI[119,152,154,155]. Prospective twin studies support the idea that feeding behavior in middle childhood is strongly influenced by environmental factors, including the quality and quantity of available food, parenting styles and psychosocial stress[128,131,156]. During adolescence, influences of environmental factors on feeding behavior decrease while genetic (and shared placental) contributions increase[156].

Emotional eating in the absence of hunger, but not deficits in satiety or homeostatic regulation, has been implicated as a primary driver of weight gain in adolescence[119,128].

In summary, studies in humans identified influences of gestational exposures on early appetitive traits that do not persist or predict weight gain in adulthood, yet long-lasting impacts on food preferences and obesity risk can be observed. To begin to understand the mechanism underlying these apparently paradoxical observations, I provide an overview of studies maternal influences on neurobiological and behavioral correlates of feeding control systems in rodents.

Maternal Influences in Rodents

A wide variety of developmental exposures have been used to investigate the timing and persistence of maternal influences on food intake in offspring. Despite some inconsistencies between findings in individual studies, there general principles that emerge from this body of research. These are discussed in the next section followed by a brief overview of impacts of maternal influences on reward and homeostatic circuits, where they are best characterized. For more comprehensive reviews of maternal influences on feeding circuits see[7,106,157–159].

Although in humans, the formation of circuits regulating basic feeding behaviors is largely complete during gestation, in rodents, connectivity is not established until the suckling period[160]. By targeting experimental manipulations to gestation and/or lactation, researchers identified periods, and therefore processes, that are sensitive to maternal influences. The most common strategies to study developmental programming of obesity risk involve manipulations of the maternal diet (i.e. caloric or macronutrient restriction or high fat diet (HFD)) or reducing or increasing postnatal litter size (to achieve over- or under-nutrition, respectively). These experimental paradigms consistently produce significant effects on offspring body weight and food intake at weaning. However, there are disagreements about the degree to which effects on feeding behavior are permanently “programmed”. A major limitation of studies in rodents is that caloric intake of a single diet provided ad libitum is usually examined over a period of 1 to 7 days, which does not distinguish between different types of feeding control systems. In addition, a major confound that has rarely been addressed in rodent studies is the effect of rearing below the thermoneutral zone, which leads to increased metabolism and food intake[161–164].

Impacts of Maternal Undernutrition

Reward Control Systems—Exposure to undernutrition exclusively during rodent gestation has been used to model maternal influences during the first trimester in humans, the time frame implicated in epidemiological studies of the Dutch Hunger Winter[135]. A meta-analysis of 89 effect sizes from 13 studies in 4 strains of mice and 40 studies in 3 strains of rats found weak, non-significant effects of gestational undernutrition on offspring caloric intake[12]. However, exposure to a low-protein diet during gestation (but not caloric restriction per se) is associated with mild hyperphagia in adult females (12 weeks), but not males[12]. Consistent with observations in humans[15,165], exposure to undernutrition during gestation is associated with an increased preference consumption of high fat foods in male

and female rats[13] and increased motivation for palatable food reward in male rats[166,167] and mice[168]. However, preferences for fat are only linked to increased adiposity in females, with no effect on body weight in either gender[13]. With age, effects on food preference are no longer apparent (30 weeks)[13].

Despite the robust link between gestational restriction and fat preference in rodents and humans, consistent neurobiological correlates have not been identified. Some groups reported increased responsiveness to a palatable food reward in the NAc of adult rats[166,167], but other groups did not[169,170]. Although several groups reported changes in the expression of key components of the dopamine signaling pathway in the NAc, findings were not consistent across the groups[168–171].

Homeostatic Control Systems—The most pronounced effects on growth and food intake are achieved by manipulations during the lactation period in rodents and the third trimester in humans[136]. Increasing litter sizes to cause undernutrition by limiting the milk supply to an individual pup results in marked reductions in caloric intake at weaning[60,61], but these often do not persist to adulthood. Exposure to postnatal undernutrition has been linked to increased weight gain and adiposity when challenged with a HFD. However, higher weight gain is not due to increased caloric intake[172–177]. The only large-scale study to study the impact of litter size across the spectrum revealed that the main determinant of HFD-induced weight gain in adulthood is post-weaning growth rate and adiposity, and not food intake[177].

The maturation of circuits that provide pre-synaptic and post-synaptic inhibitory signals to AgRP neurons is delayed by postnatal undernutrition in rodents[97]. The increased time window for leptin-induced activation of AgRP neurons likely underlies the persistent increase in orexigenic AgRP→PVH projections in models of undernutrition[97,178–181]. The delay in the onset of negative feedback from leptin signaling also promotes catch-up growth[97], a significant predictor of obesity risk[137–141].

Impacts of Maternal Obesity

Reward Control Systems—Maternal intake of an obesogenic diet has been used to model developmental exposure to obesity. Exposure throughout gestation and lactation to maternal consumption of an obesogenic HFD is correlated with increases preference for fat in offspring in young adult rats (10–12 weeks)[14,182]. Although some groups report that this effect is permanent[194], others found that it diminished with age[14,182]. As reported in early childhood in humans[128,131,156], environmental influences in the rodent post-weaning period are important determinants of food preferences. Exposure to a low fat/sugar diet from 3–6 weeks can reverse food preferences associated with gestational exposure to high fat/sugar diets[183], and conversely, exposure to high fat/sugar diets from 3–4 weeks is sufficient to program persistent preferences for dietary fat in adulthood[16].

Several groups assessed the impact of exposure to an obesogenic maternal diet on the expression of opioid and dopamine pathway components in mesolimbic reward circuits. Among these studies, the most consistent finding is that mu opioid receptor (MOR) expression is elevated in the NAc[182,184–187]. Increased MOR expression is associated with

hypomethylation[184] and is reversed with methyl donor supplementation[188]. However, normalization of expression levels by treatment with a methyl donor[188] or naloxone[189] is not sufficient to reverse the preference for fat. Another complexity in transcriptional analyses of dopamine and opioid circuits is that they undergo extensive remodeling in the peri-weaning period. For example, MOR expression is positively correlated with fat intake in the post-weaning period (6 weeks)[183], but this relationship is reversed at 3 months[182]. This plasticity likely underlies observations that the post-weaning diet can override earlier exposures[183,16].

Homeostatic Control Systems—As seen with undernutrition, the largest impact of exposure to overnutrition on caloric intake and growth is observed during rodent lactation. Reductions in litter size to produce “overnutrition” due to less suckling competition or maternal HFD consumption during lactation lead to increased caloric intake and adiposity at weaning[60,61,190–194]. Although findings of programmed increases in body weight are consistent, observations about the impacts on offspring food intake are not. A meta-analysis of approximately 2500 unique individuals for food intake and body weight measurements from 53 studies in 8 laboratory strains of rats and mice identified the main source of variability in reported outcomes – whether food intake is scaled allometrically to body mass[194]. There are small and statistically non-significant difference in food intake, indicating that apparent increases in food intake likely reflect increased body mass of offspring. Notably, offspring diet did not interact with maternal HFD exposure to increase weight gain. Thus, overnutrition models in rodents recapitulate the observation that accelerated postnatal growth is the strongest predictor of obesity risk in humans[139,195]. However, the data support the idea that influences of early growth rates on later obesity risk are primarily mediated via effects on systems regulating energy expenditure and not food intake[106,177,196].

AgRP neuronal maturation extends from mid-gestation through the post-weaning period. Although maternal factors can alter the number of NPY^+ neurons during gestation and lactation, these differences rarely persist to adulthood[197,198]. Exposure to maternal obesity or over-nutrition during lactation can also reduce the number of neurons that express leptin receptors, with lasting decreases in responsiveness to negative homeostatic feedback by circulating leptin[199,200]. In parallel, genetic or nutritional manipulations that reduce leptin signaling during lactation (i.e. HFD, diabetes) are also associated with a permanent reduction in the number of orexigenic AgRP→PVH inputs[193,199,201,202]. These counterbalanced impacts of maternal obesity on the homeostatic system are reflected in the absence of persistent impact on caloric intake.

Maternal Programming: a framework

There are strong parallels between rodent and human studies with respect to the ontogeny of feeding control systems and key periods of susceptibility to maternal influences on feeding behaviors and obesity risk. Behavioral and epidemiological studies in humans provide insights into changes in the relative strength of different feeding control systems across the developmental continuum and the relative importance of environmental factors during each stage. Studies in rodent models identified critical periods of developmental when circuits regulating each type of control system are remodeled, and are thus sensitive to maternal

and/or environmental influences. In this section, I develop a generalizable framework for interpreting observations across a range of species and experimental manipulations by exploiting the strengths of each experimental system.

Orosensory and Visceral Control Systems

Maternal nutritional and metabolic status influences early patterns of food intake regulated by direct orosensory and visceral systems. These do not continue into adulthood and do not predict obesity risk, because reward and emotional control systems are the primary determinants of feeding behavior in the post-weaning period (early childhood).

Reward Control Systems

Exposure to maternal undernutrition[13,15,203] and consumption of high fat/sugar foods[14,50,51,182] are associated with increased preference for fat in the post-weaning period, but this behavior often diminishes with time. Across species, early gestation is a critical window for programming increased preference for high fat foods in response to maternal undernutrition[13,15,203]. However, in response to a maternal obesogenic diet, exposure during lactation is sufficient to program increased reward signaling in response to fat. Although the underlying neurobiology remains to be elucidated, it does not require changes in expression levels of critical components of the mesolimbic dopamine system[188,189,204]. Evidence from humans[115,127] and rodents[16,183] supports the idea that post-weaning diet and other environmental factors continue to influence pruning and remodeling in reward circuits during throughout childhood[87], which overrides earlier effects.

Homeostatic Control Systems

Physical connectivity within homeostatic control circuits forms later than other systems (Figure 6B) and across rodent species and experimental paradigms, maternal influences during lactation produce marked and persistent effects on the structure of homeostatic feeding circuits. The onset of homeostatic control of feeding occurs 3–4 weeks after the circuits can sense and transmit leptin and ghrelin signals. The function of homeostatic circuits during lactation and the peri-weaning period in humans and rodents is linked to growth rate and not food intake. Thus, maternal influences on homeostatic systems are well-positioned to mediate the impacts of catch-up growth on later obesity risk. Because the impact of catch-up growth is thought to be mediated via effects on energy expenditure and not on food intake[106,139,152], it would seem to contradict the idea that maternal influences on homeostatic circuits are responsible for persistent impacts on feeding behavior.

Homeostatic Circuits and Reward Systems

Recent studies present another possible avenue by which maternal influences on hypothalamic homeostatic circuits during lactation might program lasting impacts on feeding behavior – through indirect effects on the development of reward control systems[204]. Although the focus of neuroanatomical studies of homeostatic feeding circuits has been on projections to the PVH, innervation of key nodes mediating reward (LHA) is also reduced in mice exposed to an obesogenic diet during lactation[193]. During lactation, transient

projections from AgRP neurons to the VTA provide another means by which nascent homeostatic circuits can communicate with reward circuits[205]. Projections from AgRP neurons are well-positioned to influence the maturation of opioid and dopamine signaling systems that spans the second to fourth postnatal weeks[84,85] (Figure 6B).

Two different experimental paradigms that diminish the formation of AgRP projections to downstream targets in lactation – neonatal AgRP neuronal ablation and/or dysfunction[205,206] and exposure to overnutrition/obesogenic diet[193,199,201,202] – increase the strength function of reward control systems in response to high fat diet[184,191,204,207]. These effects do not require changes in the expression of dopamine pathway components[189,204], but are dependent on direct ghrelin signaling within the VTA[204]. Direct ghrelin signaling in dopamine neurons has also been linked to increased sensitivity of feeding behavior to social stress[204,208]. Thus, reductions in the function of neural homeostatic inputs during development may lead to an enhanced influence of the action of neuroendocrine signals of energy status (i.e. leptin and ghrelin) on the activity of reward systems.

Summary and Future Directions

Feeding behavior reflects the integrated output of orosensory, visceral, reward, homeostatic and emotional control systems. In adults, the balance between these system shifts in response to metabolic status (i.e. fasting vs. fed) and type of food (palatable vs. aversive). This review presents evidence that the balance between these systems changes across the developmental continuum as additional control systems emerge and mature. Studies in rodent models have provided insight into how maternal influences during the formation of reward and homeostatic circuits determine fat preference and growth. These effects are later overridden by environmental influences during the post-weaning period, a time of synaptic remodeling in reward circuits. Investigating how interactions between developing homeostatic and reward circuits regulate susceptibility to nutritional and environmental stressors in an important area for future research. In addition, we need to define neurobiological substrates of emotional control systems that emerge in adolescence as primary drivers of feeding behavior and weight gain. The application of advanced techniques to trace neuronal projections and synaptic architecture in the intact brain[209] and systems to record activation in genetically-defined subsets of neurons in free-behaving animals[210,211] will accelerate these efforts. To increase the likelihood that experimental paradigms in rodents are addressing physiologically relevant phenomena, studies to assess the influence of maternal factors on different types of feeding behavior across the developmental continuum in humans are critical.

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Glossary

Metabolic status

the sum of short-term energy availability and long-term energy stores; this information is transmitted by a combination of nutrient (i.e. glucose), hormonal (i.e. insulin) and neural (i.e. vagus-mediated gastric distension) signals.

Maternal undernutrition
insufficient food intake during pregnancy and/or lactation, usually resulting in growth restriction.

Pre-gravid
relating to the period before pregnancy

Emotional eating
eating to satisfy emotional needs rather than to satisfy hunger or homeostatic needs; a classic example is eating behavior in response to stress.

Dutch Hunger Winter
a famine that took place in the Netherlands near the end of World War II. Epidemiological studies of children of pregnant women exposed to this famine provided some of the earliest evidence of maternal programming of disease risk.

Orosensory inputs
information about food from sensory receptors in the oral cavity, such taste and texture

Intrauterine growth restriction
a condition when a baby is smaller than expected for its gestational age because it is not growing at the normal rate inside the uterus.

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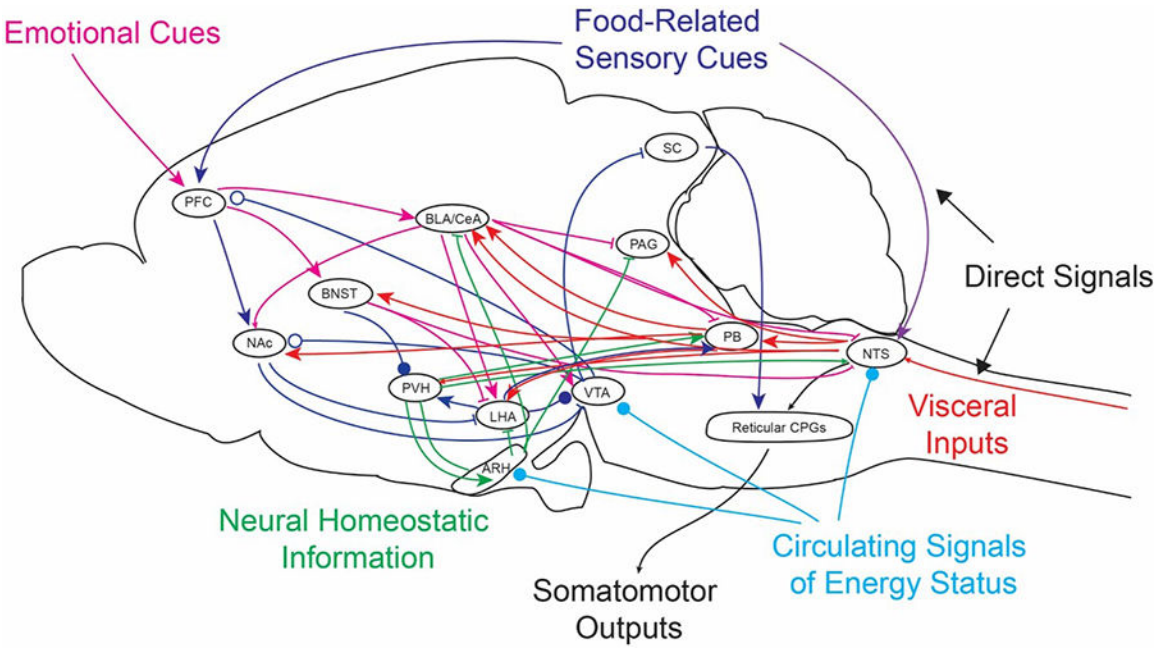

Figure 1. Summary diagram illustrating cross-talk between circuits regulating different aspects of feeding behavior.

Orosensory (purple) and vagal (red) signals are transmitted directly to the nucleus of the solitary tract (NTS) to promote and terminate feeding, respectively. Visceral signals are also transmitted directly or via the parabrachial nucleus (PB) to higher brain structures, where they converge with other feeding control systems (red arrows). Food-related sensory cues are transmitted from the prefrontal cortex (PFC) to reward circuits (green arrows). Information about metabolic status is transmitted via neural (green arrows) and circulating signals (light blue arrows). Emotional cues are related via the bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala (CeA) to regulate feeding behavior in response to anxiety and threats in the external environment (pink arrows). Cross-talk and competition between these inputs while they are still forming could impact the balance between circuits regulating different modalities of food intake. Arrowheads represent excitatory inputs, while lines represent inhibitory inputs. Open circles represent dopamine signaling, while closed circles can be inhibitory or excitatory.

Abbreviations: ARH, arcuate nucleus of the hypothalamus; BLA, basolateral nucleus of the amygdala; CPG, central pattern generator; LHA, lateral hypothalamic area; NAc, nucleus accumbens; PAG, periaqueductal gray; PVH, paraventricular nucleus of the hypothalamus; SC, superior colliculus; VTA, ventral tegmental area.

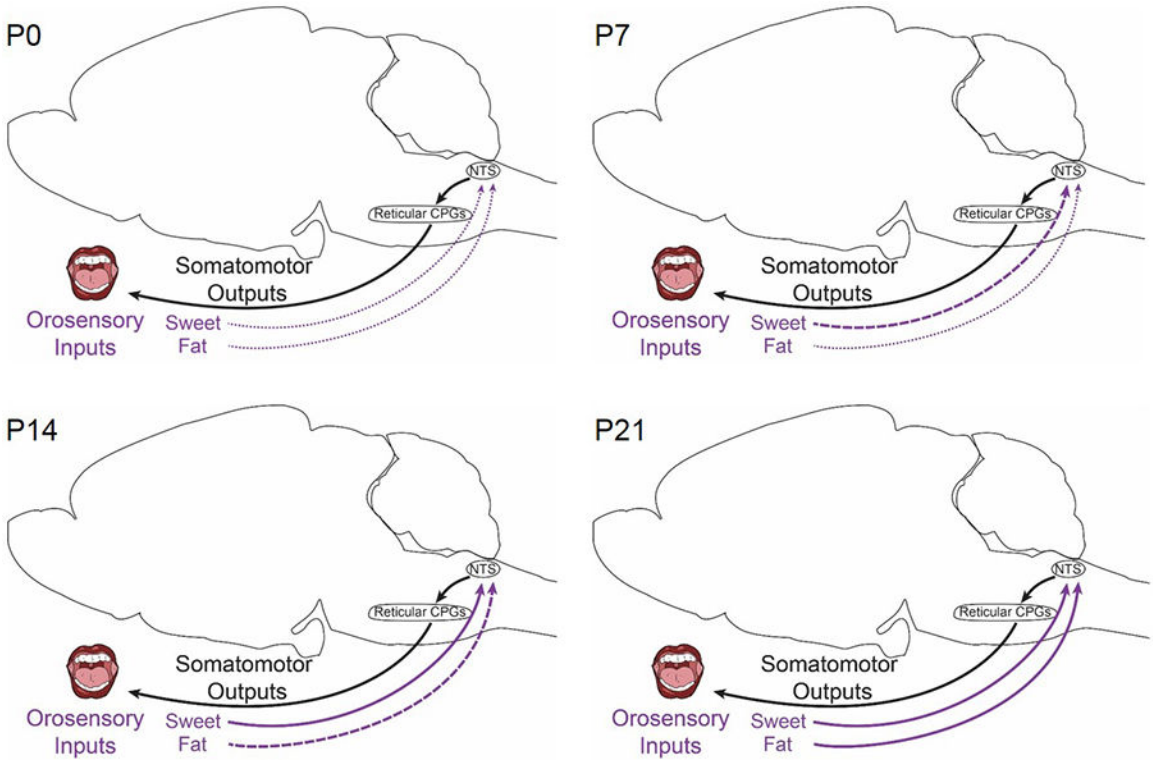

Figure 2. Ontogeny of orosensory inputs in rodents.

Information about food during the consummatory phase is relayed from the mouth directly to the nucleus of the solitary tract (NTS) (gray arrows), where it is transmitted to reticular central pattern generators (CPGs) that drive motor outputs (red arrows). This direct control system operates within the hindbrain and does not require connections to forebrain circuits. Orosensory circuits are present at birth (postnatal day 0 (P0)) and are refined over the course of lactation (to P21). Projections relaying sweet tastes mature before those relaying fat. Thin dotted lines indicate that the presence of a physical connection, but weak or immature signal transmission. Bold dashed lines represent signal transmission that is robust, but immature. Solid lines represent mature connections.

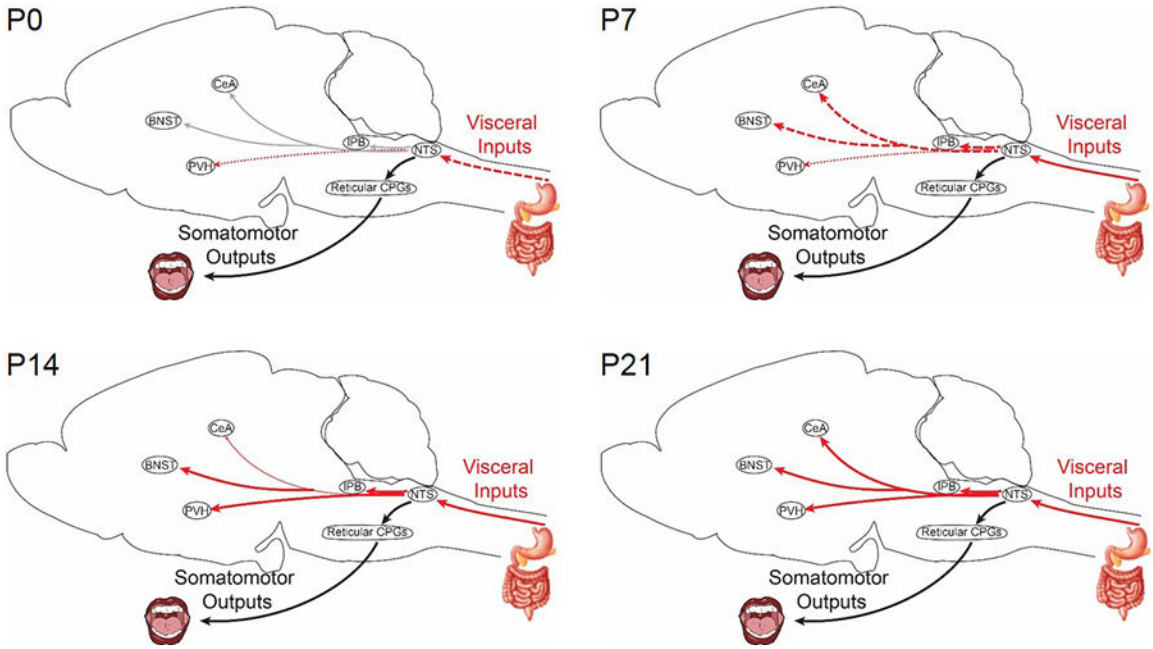

Figure 3. Ontogeny of visceral control systems in rodents

Visceral inputs are transmitted through direct and indirect control systems. Direct transmission via the vagus to the nucleus of the solitary tract (NTS) is sufficient to regulate meal termination and is present from birth (postnatal day 0, P0). Indirect control systems that transmit visceral signals from the NTS to higher brain centers develop across lactation (P7-P21). Projections from the NTS to the paraventricular nucleus of the hypothalamus (PVH) can be detected at birth. Visceral signals that are transmitted to key nodes in emotional control systems (bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala (CeA)) via the parabrachial nucleus (PB) are not fully functional until the end of lactation (P21). Thin dotted lines indicate the presence of a physical connection, but weak or immature signal transmission. Bold dashed lines represent signal transmission that is robust, but immature. Solid lines represent mature connections. Light gray lines represent projections for which developmental datapoints are missing.

Abbreviations: CPG, central pattern generator.

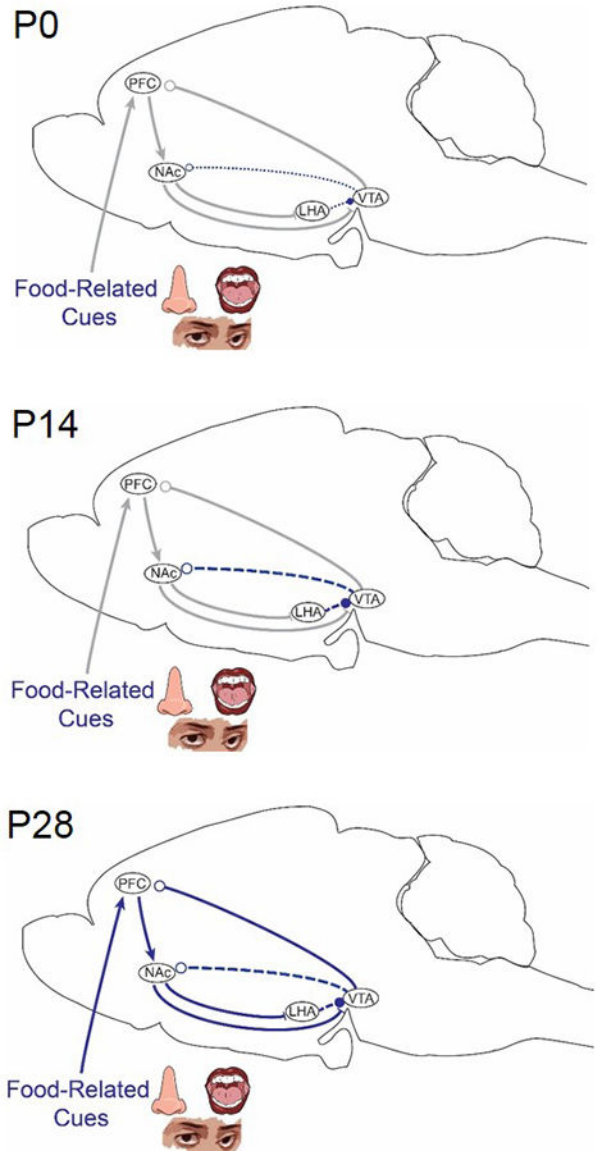

Figure 4. Ontogeny of reward control systems in rodents

Information about the sensory properties of food is relayed from the prefrontal cortex (PFC) to key nodes in circuits that regulate reward. Projections between some nodes in the mesolimbic dopamine system can be detected at birth (lateral hypothalamic area (LHA)→ ventral tegmental area (VTA) and VTA→ nucleus accumbens (NAc)). Dopamine and opioid signaling pathways develop across lactation and are not fully functional until a week after weaning (postnatal day 28 (P28)). Thin dotted red lines indicate the presence of a physical connection, but weak or immature signal transmission. Bold dashed blue lines represent signal transmission that is robust, but immature. Solid blue lines represent mature connections. Gray lines represent projections for which developmental datapoints are missing. Arrowheads represent excitatory inputs, whereas lines represent inhibitory inputs. Open circles represent dopamine signaling.

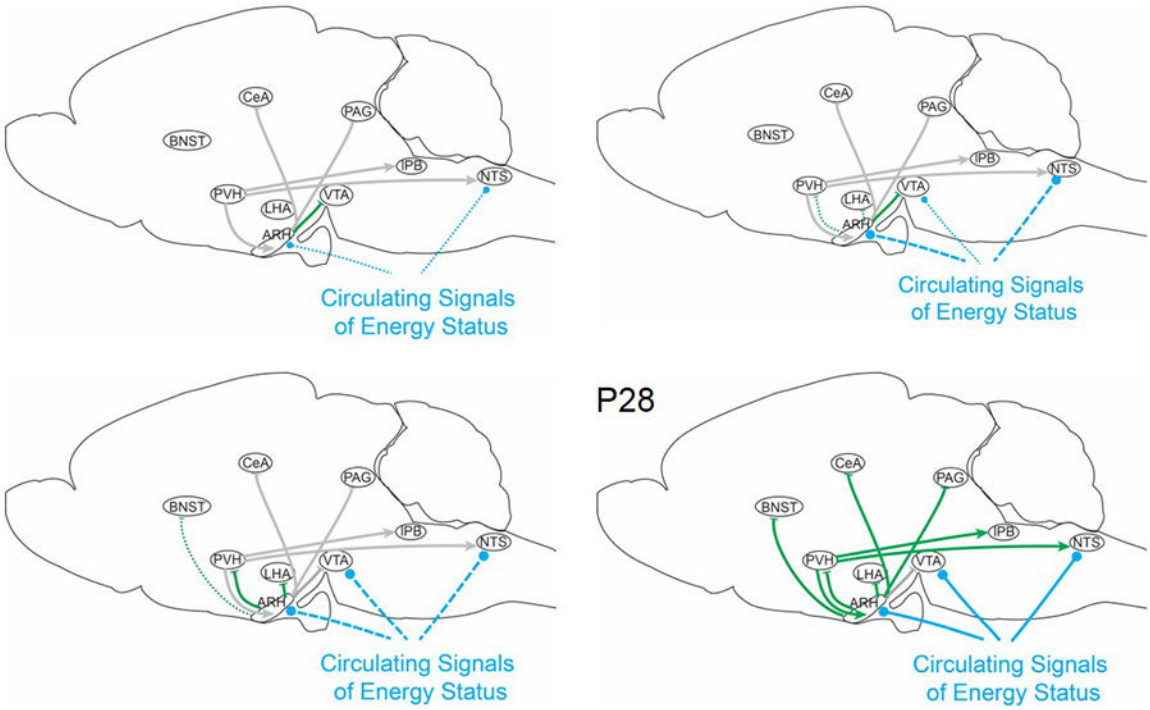

Figure 5. Ontogeny of homeostatic control systems in rodents

Interoceptive information about long-term energy stores is transmitted via neural projections from agouti-related peptide (AgRP) neurons (green arrows) and direct signaling via circulating factors (light blue arrows). Projections from AgRP neurons to downstream targets are not detected at birth. AgRP neuronal responsiveness to circulating leptin and ghrelin is observed within a week after birth; these signals regulate neurite outgrowth during lactation. A transient projection to the ventral tegmental area (VTA) is formed by postnatal day 7 (P7), and projections to the lateral hypothalamic area (LHA) and paraventricular nucleus of the hypothalamus (PVH) are fully formed by the end of lactation, AgRP circuits do not regulate homeostatic feeding behavior until P28. Thin dotted lines indicate the presence of a physical connection, but weak or immature signal transmission. Bold dashed lines represent signal transmission that is robust, but immature. Solid lines represent mature connections. Gray lines represent projections for which developmental datapoints are missing. Arrowheads represent excitatory inputs, while lines represent inhibitory inputs. Light blue circles represent sites that directly sense circulating signals of energy status (i.e. leptin and ghrelin).

Abbreviations: ARH, arcuate nucleus of the hypothalamus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; LHA,; NTS, nucleus of the solitary tract; P, postnatal day; PAG, periaqueductal gray; PB, parabrachial nucleus.

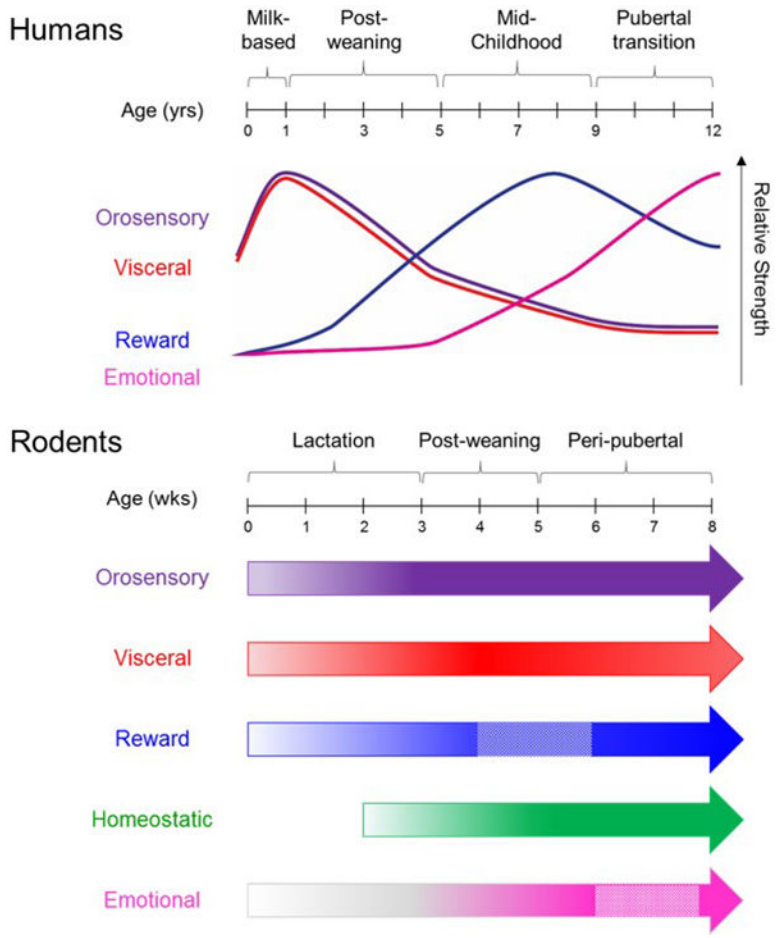

Figure 6. Step-wise progression of ontogeny of feeding control systems is conserved between humans and rodents.

In humans (top), population-based studies of feeding behavior demonstrate that the relative balance between different control systems changes across the developmental continuum. In rodents (bottom), the ontogeny of control systems has been defined at the neuroanatomical level. The start position of each arrow reflects the onset of a physical connection. Gradations of color intensity reflect increased maturation. Boxes outlined with dashed lines in reward and emotional systems represent periods of remodeling. Circuits are most sensitive to the effects of external influences during periods of maturation and remodeling.

While the absolute timing of developmental processes is necessarily different, the emergence of different control systems in relation to major developmental milestones is highly conserved. Orosensory (purple) and visceral (red) control systems are present at birth, but are superseded by other controls systems. Reward control systems (blue) gain in importance after weaning and are influenced by environmental factors. Emotional control systems (pink) are the primary driver of weight gain in adolescence. Homeostatic control systems (green) have not been assessed in studies in humans.