Title: Development of “hunger neurons” and the unanticipated relationship between energy metabolism and mother-infant interactions

Short title: Linking the development of homeostasis and attachment

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Abstract

Over the course of a lifetime, the perinatal period plays an outsized role in the function of physiological systems. Here, we discuss how neurons that regulate energy metabolism contribute to the infant’s relationship with the mother. We focus our discussion on Agrp neurons, which are located in the arcuate nucleus of the hypothalamus. These neurons heavily regulate energy metabolism. Because offspring transition from a period of dependence on the caregiver to independence, we discuss the importance of the caregiver-offspring relationship for the function of Agrp neurons. We present evidence that, in the adult, Agrp neurons motivate the animal to eat, while, in the neonate, they motivate the offspring to seek the proximity of the caregiver. We specifically highlight the peculiarities in the development of Agrp neurons and how they relate to the regulation of metabolism and behavior over the course of a lifetime. In sum, this review considers the unique insights that ontogenetic studies can offer toward our understanding of complex biological systems, such as the regulation of energy metabolism and mother-infant attachment.
Life as an infant

Compared to adults, infants deal with distinct physiological disturbances, and, thus, they need regulatory processes that are specific to each stage of development. For example, due to their small body size, limited fat resources, and greater surface area to volume ratio—which increases heat loss—neonates are particularly vulnerable to cold exposure. As an adaptation to this vulnerability, neonates can tolerate substantial drops in body temperature that are otherwise lethal in adults. In addition to regulatory processes that maintain body homeostasis for survival and growth, infants also need to prepare for the next stage of their development. Every aspect of the infant’s physiology seems to serve a purpose later in life. For example, small respiratory movements in utero, which move amniotic fluid to the lungs, expand respiratory capacity. This helps the lungs grow and prepares the fetus for the postnatal world. Similarly, the ingestion of amniotic fluid and swallowing movements promote the development of the palate and the gastrointestinal tract, which enable the fetus to breastfeed. In sum, since early in prenatal life, the physiological and behavioral challenges of the developing animal provide the means to become an adult. This aspect of animal development is important to consider as we discuss the development of the neuronal circuitries that regulate energy metabolism and their involvement in mother-infant attachment.

The central regulators of energy metabolism

Studies in humans and rodents have identified the melanocortin system, composed of neurons that synthesize agouti-related peptide (Agrp neurons) and proopiomelanocortin (hereafter, POMC neurons) and their projection targets, as critical for metabolic control (1, 2). Agrp
neurons produce neuropeptide Y (NPY) and gamma-aminobutyric acid (GABA), whereas POMC neurons produce a number of POMC-derived peptides, including alpha-melanocyte-stimulating hormone (α-MSH). AGRP and α-MSH bind to melanocortin receptors in the brain with α-MSH acting as an agonist and AGRP as a functional antagonist (in fact, an inverse agonist) of these receptors (1). In rodents and nonhuman primates, Agrp neurons are activated by food deprivation (3, 4). In mice, the sensory detection of food is sufficient to inhibit Agrp neurons (5-7). In addition to the sensory detection of food, the ingestion of calories further reduces the activity of Agrp neurons (8, 9), supporting the model in which a negative feedback signal inhibits Agrp neurons upon food ingestion to suppress hunger. The chemogenetic and optogenetic overactivation of Agrp neurons, in which this negative feedback signal is bypassed, causes voracious food intake, even in well-fed mice (10-12). Moreover, the overactivation of Agrp neurons, if sustained over a period of days, weeks, or months, increases weight gain and adiposity (13-15). Therefore, at least in adult animals, Agrp neurons are positioned as central regulators in the control of energy metabolism.

Sensing ingested calories

In adults, the cranial nerve X—also known as the vagus nerve—and splanchnic nerves sense ingested calories in the gastrointestinal tract and in the hepatic portal vein, inhibiting Agrp neurons (16). The developmental aspects of these peripheral-brain circuits, however, remain poorly understood. As we will discuss below, several lines of evidence suggest that, in early development, the inhibitory signals following the ingestion of calories do not reach the arcuate neurons in the hypothalamus.
In 10-day-old mice deprived of the lactating mother for 90 minutes or 8 hours, the activity of Agrp neurons increases as measured by the early gene Fos (17). These findings resemble earlier experiments performed in neonatal rats, in which significant periods of maternal deprivation (24h or more) increase the expression of Npy and Agrp in the arcuate nucleus (18, 19). These experiments in the rat were interpreted as evidence that nutrient (breastmilk) deprivation activates Agrp neurons in neonates in a way somewhat similar to adults (18, 19). The most recent work in mice, however, provides evidence for alternative interpretations. For example, in 10-day-old mice, if breastmilk (from mice) or whole milk (from cows) is delivered into the posterior part of the mouth of the deprived pups—thus, providing calories for the pups deprived of the mother—the number of Fos positive Agrp neurons remains elevated to the same extent as animals that did not receive any milk infusion (17). A way of interpreting these findings is that at this young age, the ingestion of calories does not suppress the electrical activity of Agrp neurons.

Other lines of evidence support the idea that peripheral sensing of caloric intake does not recruit the same peripheral-brain circuits in neonatal mice and rats as it does in adult animals. For example, the gut-hormone cholecystokinin (CCK), which inhibits food intake in adult animals by activating the peripheral terminals of the vagus nerve, does not affect milk intake in 5- and 10-day-old rats (20). Moreover, when rat pups deprived of milk for 8 hours were allowed to ingest an unlimited amount of milk delivered through an oral cannula, while attached to the nipple of the anesthetized mother, 5- to 10-day-old rats consumed an excessive amount of
milk, which impairs locomotion. Pups terminated milk intake only after extreme gastric distension (21).

Other behavior studies also provide evidence for the development of the homeostatic systems that regulate ingestion. For example, adult animals rapidly and strongly learn about food sources. When 24-hr milk deprived rat pups are trained to choose between suckling two different anesthetized mothers, however, they do not show a preference for the “lactating nipple” over the “non-lactating nipple” until they are two weeks old (22). Similarly, allowing 15-day-old rats to suckle a non-nutritive nipple from a mother whose nipples were ligated during 8 hours of milk deprivation does not cause a change in the ingestion of deprived pups (23).

Overall, it appears that sensing ingested calories and caloric deprivation, at least in the way that we understand how it occurs in adult animals, is a process that slowly matures after birth, in preparation for weaning.

The dynamics of Agrp neurons in neonates

The fact that neonatal rats consume excessive amounts of milk that is delivered to their mouth (21) illuminates how the dyad of mother and offspring regulates the ingestion of breastmilk. During breastfeeding, stimulation of the breast sends a signal to oxytocin-producing neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. The activation of the oxytocin neurons releases oxytocin in the posterior part of the pituitary. This oxytocin then enters circulation and, through the blood, reaches the breast, causing the release and, consequently, the ingestion of milk. An important aspect of this neuro-humoral reflex is that
the release of oxytocin occurs at random periods during breastfeeding (24, 25). Even though
the offspring remains attached to the nipple for many hours a day (26), milk release is not
constant, which prevents overconsumption. This aspect of the physiology of breastfeeding is
important to contemplate as it implies the necessity of close proximity of mother and offspring
for frequent suckling. As we will discuss below, this proximity seems to be a critical feature of
early development that modulates the activity of Agrp neurons.

In 2005, the laboratory of Richard Palmiter ablated the Agrp neurons of adult mice and
demonstrated that within a few days, mice succumbed to death from aphagia (27). [A less
pronounced phenotype was reported by other researchers using technical approaches that did
not lead to complete ablation of Agrp neurons (28, 29).] In contrast to ablation of Agrp neurons
in adults, the same group reported that ablation of Agrp neurons in neonates (up to 8 days old)
had little or no effect on body weight gain during development (27). This result and the series
of findings showing that Agrp neurons are immature after birth (see more below) suggested
that the functional properties of these neurons are also slow to mature.

A series of recent findings, however, suggest that Agrp neurons are functional in neonates in
previously unanticipated ways. As alluded to above, the separation of 10-day-old mice from
their dam and litter activates Agrp neurons (17). Infusion (and ingestion) of milk during the
period of separation does not suppress the activity of Agrp neurons; close contact of the pup
with a foster dam, however, does. Among the different foster dams tested, foster dams without
protruded nipples (thus, preventing nipple attachment) have less effect on suppressing the
activity of Agrp neurons. In contrast, foster dams with protruded nipples strongly suppressed
the activity of Agrp neurons (17). This was equally true for both lactating and non-lactating
dams. These experiments suggest that the availability of milk had negligible significance for the
activity of Agrp neurons in 10-day-old mice.

Other variables, such as nipple attachment and warmth, present primary significance. (In Box 1,
we discuss key studies in monkeys on the importance of maternal variables for infant
attachment). In these experiments, immunohistochemistry for Fos was used as a readout of
neuronal activity, which lacks temporal resolution. The temporal dynamic of Agrp neurons in
neonatal mice was obtained using fiber photometry and genetically encoded calcium sensors
(17). In 13-day-old mice, separation of the dam activated Agrp neurons within seconds.
Conversely, reunion suppressed the activity of these neurons to pre-separation levels, also
within seconds. An interpretation of these experiments is that, in neonates, the electrical
activity of Agrp neurons reflects the proximity of the dam.

Using chemogenetics, overactivation of Agrp neurons in 10-day-old mice increases the
likelihood that pups attach to the nipples of an anesthetized dam, but does not affect the
latency to attach, milk consumption (17), or nipple-shifting behavior, a behavior that occurs
when mice and rats develop a homeostatic sensitivity to caloric deprivation (30). It is only in 15-
day-old mice that the chemogenetic overactivation of Agrp neurons increased nipple-shifting
behavior and milk consumption (17). Interestingly, the same chemogenetic overactivation of
Agrp neurons increased the emission of separation-induced ultrasonic vocalizations, a form of
vocal behavior that functions to attract the dam back to the nest and induce maternal care (31).

Thus, as opposed to adult mice, in neonates, the motivation induced by Agrp neurons seems to be for the mother and not for the milk itself. It remains unknown, however, how these different motivations are controlled by Agrp neurons. Below, we review several characteristics of the development of Agrp neurons that provide insights into how these neurons can control different motivations at different periods of life.

Box 1: Primary significance of contact comfort for the affectional response of the infant mammal

Work performed in monkeys more than half a century ago provides strong evidence for the significance that different maternal variables have for the infant.

With the goal of testing the factors that bond an infant primate to its mother, the experimental psychologist Harry Harlow studied the development of the rhesus monkey [for reference, see (70-73)] with the goal of testing the variables that affect the bonding of an infant primate to its mother. Harlow first noticed—as had Gertrude van Wagenen 15 years before him (74)—that rhesus monkeys raised in the laboratory would cling to diapers left on the floor of the cage, and they would display intense protest followed by despair behavior when the diapers were removed. Harlow realized that orphan monkeys bond to inanimate objects in ways similar to what was commonly observed in humans.

Harlow then raised orphan monkeys with two different types of surrogate (artificial) mothers present in the infant’s cage. These artificial mothers were a wired mother with a bottle that delivered milk and a wired mother wrapped in cloth, which mimicked the tactile stimulation that infants receive from their biological mothers. When the orphan monkeys were given the choice between these two artificial mothers, they overwhelmingly chose to stay in contact with the cloth mother as opposed to the wired mother with a nursing bottle. These results were the first to experimentally suggest that components of maternal care, such as skin stimulation, are of primary significance for the emotional attachment between infant mammals and their mothers, with nursing being a factor of much lower importance.

The words of Harlow state their conclusions more precisely:
“We were not surprised to discover that contact comfort was an important basic affectional or love variable, but we did not expect it to overshadow so completely the variable of nursing; indeed, the disparity is so great as to suggest that the primary function of nursing as an affectional variable is that of insuring frequent and intimate body contact of the infant with the mother. Certainly, man cannot live by milk alone. Love is an emotion that does not need to be bottle- or spoon-fed, and we may be sure that there is nothing to be gained by giving lip service to love.” (70)

Since the middle of the twentieth century, the pioneering work of Harlow and many others has shifted the way that we understand the relationship between infants and their mothers. Instead of a simple drive-reduction model, the emotional attachment of the infant to the mother is now understood as a fundamental—and independent—process in early life that is not a derivative of more basic processes, such as the need for food.

Trophic signals for the development of arcuate neurons

Evidence in humans and rodents supports the thesis that Agrp (and POMC) neurons are slow to mature. Agrp neurons in mice, for example, do not complete their axonal projections until approximately the third postnatal week, which coincides with the end of the lactation period (32). Projections of the hypothalamus to the hindbrain are also slow to mature, even though the identity of these projecting neurons is mostly unknown [for more details, see the comprehensive review by Linda Rinaman (33)]. This delayed ontogeny of Agrp neurons correlates with the appearance of independent solid food ingestion in mice (34), which indicates that the transition from suckling to independent food ingestion represents a critical phase in the development of Agrp neurons.

Despite the delayed maturation of Agrp neurons, they are sensitive to hormones and metabolites during the first two postnatal weeks. For example, during the neonatal period, Agrp neurons respond to the injection of external ghrelin (which increases food intake in adults)
and leptin (which decreases food intake in adults) (35-38). In 6-day-old mice, the injection of ghrelin induces pERK (38) while in 10-day-old mice the injection of leptin induces pSTAT3 in Agrp neurons (39). Ghrelin and leptin, however, do not affect body weight gain in early development. In mice, the inhibition of ghrelin’s action does not affect body weight gain for the first two postnatal weeks (38). Likewise, the blockage of leptin does not affect body weight or milk intake during the first four postnatal weeks (40-42). Thus, the effects of ghrelin and leptin on ingestion seem to mature slowly during development, with their effect on ingestive behaviors beginning around weaning time, a period during which animals achieve their nutritional needs independently of the mother. In view of the results suggesting that Agrp neurons in neonates motivate the animal to seek the proximity of the mother, future studies should clarify whether hormones, such as ghrelin and leptin, affect the mother-infant relationship.

To add complexity to the study of Agrp neurons, there is a developmental switch in the way that leptin signals in these neurons. Early in development, leptin is an excitatory signal for Agrp neurons (i.e., leptin increases the electrical activity of Agrp neurons), but around the third postnatal week, leptin switches to an inhibitory signal (i.e., it suppresses the electrical activity of these neurons). Based on the electrophysiological properties of Agrp neurons, measured using recordings in slices, this switch appears to be caused by a lack of expression of functional ATP-sensitive potassium (K\textsubscript{ATP}) channels in Agrp neurons. In other words, the absence of K\textsubscript{ATP} channels makes leptin an excitatory signal (35).
The excitatory role of leptin coincides with the leptin surge, a period in neonatal development during which leptin levels increase several fold in circulation (40). Pioneering work by Richard Simerly and Sebastien Bouret provides a functional significance for the leptin surge. In mice, during the first two postnatal weeks, leptin acts as a growth factor for the sprouting of axons from Agrp and POMC neurons. During this period, a lack of leptin signaling impairs the proper development of these neuronal projections, contributing to obesity and metabolic dysregulation (32, 37). To investigate the closure of this critical phase for the trophic actions of leptin, leptin deficient ob/ob mice received treatment with leptin during different phases of development (39). Using this approach, leptin loses its trophic action over the sprouting of Agrp neurons around postnatal day 28 (39). Coincidently (or not), it is around this time that leptin starts to inhibit food intake when injected centrally in the brain (42, 43). The trophic actions of leptin, however, are not restricted to the development of Agrp and POMC neurons. In adult mice, leptin causes rapid synaptic rearrangement over the perikarya of Agrp and POMC neurons (44) and increases the growth of sympathetic nerve fibers over peripheral organs (45). These trophic actions of leptin resemble the trophic actions of gonadal steroids (first discovered by the pioneering work of Dominique Torran-Allerand) (46). For example, estrogen and leptin promote similar effects on the synaptic input organization of POMC neurons in adult mice (47). Thus, leptin—similar to gonadal steroids—functions as a trophic factor that promotes distinct forms of neuronal plasticity.

The above observations raise two important points. First, the lack of leptin signaling impairs the axonal development of Agrp (and POMC) neurons during a critical phase. Thus, these neurons
are subjected to extrinsic factors that control their morphological and functional ontogeny,

such as leptin. Second, leptin remains an inhibitory signal for Agrp neurons (i.e., it suppresses
the electrical activity of these neurons) in adult leptin deficient ob/ob mice, whose Agrp (and
POMC) neuronal projections are severely impaired (see more below). Thus, leptin’s actions on
Agrp neurons do not seem to be necessary for the developmental switch in the expression of
K\textsubscript{ATP} channels (35). This observation suggests that, independent of leptin signaling, there are
other extrinsic or intrinsic (i.e., cell autonomous) molecular mechanisms that guide the
development of Agrp neurons. [Several articles and reviews have discussed the molecular
mechanisms that are involved in the development of arcuate neurons and will not be discussed
(48-52)]. Based on the above observations, it will be important to study the causal relationship
between these developmental features of Agrp neurons in response to leptin and how they
affect the behavior of the growing infant towards the mother.

The transient innervation of target areas by arcuate neurons

Agrp neurons in mice also transiently innervate the ventral tegmental area of the midbrain,
where dopamine neurons are located, during the first postnatal week (53). In adults, this
specific axonal projection is substantially reduced (53, 54). Experiments using selective ablation
of Agrp neurons and, later, electrophysiological recordings of dopamine neurons provide
evidence for the importance of this temporary innervation. Using transgenic mice that express
diphtheria toxin receptor under the control of the Agrp promoter (27), it is possible to ablate
the population of Agrp neurons by the injection of diphtheria toxin at different ages (27). Using
this approach, injection of diphtheria toxin in 5-day-old mice facilitated synaptic plasticity in the
dopamine neurons when those same mice reached the age of 30 days old (53). These
electrophysiological findings correlate with an increased behavior response of adult animals to
novelty and cocaine, behavior responses that depend on midbrain dopamine neurons (53).
Thus, in mice, the window of development during which Agrp neurons temporarily project to
the ventral tegmental area affects the plasticity of dopamine neurons and cognate behaviors.

Another set of experiments from the laboratory of Serge Luquet further demonstrates that
neonatal ablation of Agrp neurons alters the way that adult animals express reward-related
behaviors. For example, ablation of Agrp neurons in neonates leads to obesity in adulthood.
The obesity phenotype starts to develop late in adulthood and, it is suggested, arises from
increased hedonic feeding (reward-based) (55, 56). Thus, Agrp neurons—and likely POMC
neurons, as they also project to the ventral tegmental area (54, 57)—modulate the way that
dopamine neurons in the midbrain mature, which has consequences for adult physiology and
behavior.

The temporary innervation of the ventral tegmental area by Agrp neurons (53, 54) points to the
existence of a critical phase during which Agrp neurons innervate specific target sites. In
support of this idea, maternal high-fat feeding during lactation impairs Agrp (and POMC)
neuron development and causes obesity in the offspring (58). Similarly, as alluded to above, in
leptin-deficient ob/ob mice, Agrp (and POMC) neurons show remarkably reduced axonal
projections, and the mice are morbidly obese (37). During the first two postnatal weeks, daily
injections of leptin can rescue Agrp (and POMC) neuron development in ob/ob mice and
improve metabolic homeostasis \(^{37}\). Hence, these results suggest that, by altering the development of arcuate neurons, the early postnatal period has lasting effects on metabolic control and reward-related behaviors.

Several outstanding questions related to the temporary innervation of the ventral tegmental area by Agrp neurons, however, remain unanswered. For example: How do changes in Agrp neuronal activity during early developmental periods leave a long-lasting mark on midbrain dopamine neurons? Does the experience of the infant with the mother, which affects that activity of Agrp neurons, modulate the development of dopamine neurons? Do Agrp neurons directly affect the activity of midbrain dopamine neurons during the phase of life in which the relationship with the mother is more significant? Can the critical phase during which Agrp neurons affect the development of the midbrain dopamine neurons reopen later in life? These and other outstanding questions warrant further research.

Synapses onto Agrp neurons

The function of Agrp neurons, at least in the adult, is regulated by presynaptic neurons that provide excitatory and inhibitory inputs \(^{44, 54, 59-64}\). It is therefore important to understand the ontogeny of these pre-synaptic inputs and correlate it with the functional properties of Agrp neurons at different periods of life.

In the adult mice, the presynaptic inputs of Agrp neurons arise mostly from intrahypothalamic sites \(^{54, 60, 62, 64}\). A main source of excitatory inputs originates from neurons in the
paraventricular nucleus of the hypothalamus (PVH) (62) and a main source of inhibitory inputs originate from neurons in the dorsomedial hypothalamus (DMH) (62, 64). In the mouse, the inhibitory neurons in the DMH that project to Agrp neurons express leptin receptor and sit in the ventral portion of the DMH (DMH\textsuperscript{LepR} neurons). DMH\textsuperscript{LepR} neurons projecting to Agrp neurons do not collateralize to other brain regions, demonstrating a specific source of inhibition on Agrp neurons (64). Recordings of DMH\textsuperscript{LepR} neurons show that these cells are activated by the detection of food, and the artificial activation of these neurons inhibits food intake (64). More recent work from Bradford Lowell’s group expanded the understanding of the neuronal circuitry that mediates the inhibition of Agrp neurons upon detection of food: Glutamate neurons in the lateral hypothalamus activate DMH\textsuperscript{LepR} neurons—presumably those inhibiting Agrp neurons—upon the discovery of food (or exposure to sensory cues that predict food availability) (65). Whether this same circuit is functional in early life is unknown, but as we will review below, some evidence suggests it is not.

Using electrophysiology recordings in slices, it was shown that the maturation of inhibitory inputs onto Agrp neurons starts in the peri-weaning period, reaching mature levels in the fifth postnatal week (35, 66). In contrast to the delayed maturation of these inhibitory inputs, the maturation of excitatory inputs onto Agrp neurons reach mature levels in mice around the second postnatal week (around P13-15) (66). Thus, these results suggest the inhibitory feedback that suppresses the electrical activity of Agrp neurons matures slowly as mice age (15, 67, 68). In support of this idea, using Dil tracer—a chemical that labels axonal projections in postmortem tissue—Kevin Grove’s group found that projections from the DMH to the arcuate
nucleus begin to develop during the peri-weaning period (66). [Analysis of other intra-
hypothalamic projections, however, underscore the complexity of the development of this
brain region: In contrast with the delayed maturation of DMH projections to the arcuate
nucleus, for example, projections from the arcuate nucleus to other brain regions, such as the
PVH, mature much earlier (32)]. Together, the above findings suggest that the delayed
development of the inhibitory connections between the DMH and Agrp neurons mediate the
maturation of the negative feedback signal that inhibits Agrp neurons upon food consumption.
This possibility, however, still needs to be formally tested.

Interestingly, the delayed maturation of the inhibitory inputs onto Agrp neurons is not fixed.
Recent work from Lori Zeltser’s group, in collaboration with Grove’s group, showed that raising
mice in large litters, as a model of early life undernutrition, causes a delay in the maturation of
inhibitory synaptic inputs onto Agrp neurons as well as a delay in the switch in leptin’s action
from an excitatory signal to an inhibitory signal (68). These findings demonstrate that the
ontogeny of Agrp neuron function is susceptible to changes in environmental conditions,
further reinforcing the thesis that the early developmental phase is critical for the function of
these neurons in the lifelong regulation of energy homeostasis and behavior.

Some final remarks

While data on the functional properties of POMC neurons in neonatal animals is lacking, the
findings discussed above on Agrp neurons suggest a more general model in which Agrp (and
presumably POMC) neurons calculate the energy balance of the animal. A state of energy
deficit, due to fasting or due to increased metabolic demand (as it occurs when offspring separate from their caregivers), increases the activity of Agrp neurons. Conversely, food ingestion or decreased metabolic demand (as it occurs when mothers provide skin-to-skin contact to their offspring, providing warmth and insulation) suppresses the activity of Agrp neurons. This model seems to hold true in both infants and adults, which leads to some predictions. First, the function of Agrp neurons—which is, at the ultimate level (69), to restore homeostasis—does not change over the course of development. Second, what changes over the course of development are the ways by which the animal achieves this ultimate goal, using different physiological and behavioral strategies. In the adult, Agrp neurons motivate the animal to eat. In the neonate, they motivate the offspring to seek the proximity of the caregiver.

Based on the vast literature studying adult mice, it is fascinating to realize that ingested calories, at least in the form of breastmilk, do not appear to suppress the electrical activity of Agrp neurons. Rather, the proximity of the offspring to their caregiver appears to be a more salient and reliable way to make predictions about the restoration of energy homeostasis. Notably, it is during this early period of life that several unique developmental processes occur in Agrp neurons at cellular, circuit, and systems levels. Thus, it is tempting to imagine and speculate about the consequences that disruptions in the caregiver-offspring relationship can have on the development and function of physiological systems over the course of a lifetime. The breath of new technologies available for neuroscientists and physiologists provides the
means to test these predictions, creating the opportunity to link biological mechanisms to the outsized effects of the perinatal period on physiology and health across the lifespan.
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References


Legend for the Figures

Figure 1. Illustration of the rodent brain pointing to the location of the hypothalamus. In the coronal section, it is possible to observe the location of the hypothalamus. At the base of the hypothalamus is the arcuate nucleus where Agrp and POMC neurons reside. Agrp neurons reside in a more medial part of the arcuate nucleus, surrounding the medial eminence and the third ventricle. POMC neurons are intermingled with Agrp neurons and also reside more laterally in the arcuate nucleus.
Figure 2. Models of Agrp neuron activity in neonates and adults. (A) In neonates, deprivation of maternal cues, which generates a state of distress, activates Agrp neurons. The activation of Agrp neurons participates of a physiological response that increases crying and the proximity of the neonate to the mother (e.g., increasing maternal approach and care). Contact with the mother inhibits the activity of Agrp neurons. (B) Model with parallel degrees of analysis, but illustrating the modulation of Agrp neurons in adults. Caloric deprivation, which generates a state of hunger, activates Agrp neurons. Activation of Agrp neurons participates of a physiological response that increases food seeking behavior and ultimately food ingestion. Food ingestion inhibits the activity of Agrp neurons.
**Figure 3. Activity of Agrp neurons and their consequent proximal and ultimate causations.** In adults, the activity of Agrp neurons motivate the animal to eat to restore homeostasis. In this regard, food deprivation leads to activation of Agrp neurons and food consumption suppresses the activity of these neurons. Thus, the nutritional status of the animal and the availability of nutrients provide direct feedback to modulate the activity of Agrp neurons. In neonates, the direct feedback provided by the nutritional status of the animal and the current availability of nutrients do not seem to directly affect the activity of the Agrp neurons. It is the proximity of the mother, however, that modulates Agrp neuron activity. Separation of the mother increases, while reunion with the mother decreases the activity of Agrp neurons. An increase in the activity of Agrp neurons motivates the infant to seek proximity of the mother, which in turn will promote restoration of the homeostasis.