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Wired for eating: how is an active feeding circuitry established in the postnatal brain?

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Abstract

From birth, mammals have to find food and maximize caloric intake to ensure growth and survival. Suckling must be initiated quickly after birth and then maintained and controlled until weaning. It is a complex process involving interactions between sensory and motor neuronal pathways. Meanwhile, the control of food intake and energy homeostasis is progressively established via the development of hypothalamic circuits. The development of these circuits is influenced by hormonal and nutritional signals and can be disturbed in a variety of developmental disorders leading to long-term metabolic, behavioral and cognitive dysfunctions. This review summarizes our current knowledge of the neuronal circuits involved in early postnatal feeding processes.

Introduction

During adulthood, feeding behavior is controlled by a complex and distributed neuronal network involving the hypothalamus, brainstem and limbic system [1••]. In addition, this feeding circuitry integrates stimuli from different neural networks [1••], allowing a central control to maintain energy homeostasis [2]. In a newborn, feeding involves active sensory and motor functions controlled by different brain structures to trigger and maintain suckling [3]. Then, the brains of neonates have to establish a circuitry to maintain energy homeostasis by monitoring energy expenditure, nutritional status and induce corresponding changes in metabolism, behavior and food intake [4••]. Despite the recent development of advanced tools in neuroscience, it is still very challenging to deconstruct the structure and function of neural circuits involved in early feeding behavior. For example, it is not trivial to experimentally establish a causal link between neuronal activity and motivation for suckling, suckling and satiety in a newborn.

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Conflict of interests

Nothing declared.

In this review, we will discuss our current knowledge of brain circuits involved in the onset of feeding and of the hormonal mechanisms underlying the development of hypothalamic circuitry controlling food intake and energy homeostasis.

Sensory and motor functions implicated in the onset of feeding

From birth, mammals have to find food to survive. Rodents are born blind, deaf and bald with limited muscle strength and coordination. Nevertheless, neonates have to find their mother's nipples and suckle by themselves in the first hours after birth [5]. Suckling involves an awakened state, a tactile and olfactory functional system to locate the mother's nipples [6], a rooting reflex, a rhythmic suckling reflex and swallowing [7]. Thus, several sensory inputs and motor outputs involving different brain structures and muscles are required to trigger and maintain a suckling [3]. Studies involving mouse genetic mutations and lesion experiments in rodents have indicated that sensory systems, motor systems and the hypothalamus are involved in the initiation of suckling (Table 1).

Sensory inputs and the onset of suckling

It has been shown that the perinatal sequence of experiences associated with labor and delivery is required to allow a successful transition from *in utero to extra utero* life and, in particular, for the first nipple attachment of a newborn pup [5]. Toda *et al.* showed that birth regulates the initiation of sensory maps, such as the barrel formation in the somatosensory cortex through serotonin signaling. He also showed that suckling behavior requires somatosensory inputs from the infraorbital nerve and proposed that birth *per se* actively regulates the functional maturation of this sensory system [8]. Interestingly in the polydactyly/arhinencephaly (disruption of the *Gli3* gene) mouse model, pups die on the first day of life (P1) due to a lack of suckling caused by defects in the olfactory system. Mutant pups lost their olfactory ability to locate the nipple caused by a failure in the olfactory nerve projections to the central nervous system [9].

Tactile stimulation

At birth, newborns receive various type of mechanical and tactile stimulations. This perinatal sequence includes *in utero* compressions linked to female contractions during labor [10]. Then at birth, the dam assists each pup with intensive licking of the entire body, intensive rotation of the pup' body leading to vestibular stimulation and gentle tugging [5,10]. Finally, after all the pups are delivered, the dam turns her attention to the newborns, which she gathers into a clump in the nest and settles over them, heating the nest. Noticeably, during this period, their body surface temperature also changes significantly (cooling after birth and rewarming in the nest) [10]. Interestingly, Abel *et al.* [11••] developed a 'simulated birth' paradigm to reproduce some of these stimuli. They showed that prenatal compression simulating uterine contractions is necessary for newborn pups to attach to the nipples and allow the first suckling, when they are exposed to a postnatal temperature regime. Should this compression inducing mechanical and cutaneous effects on the offspring be considered as a tactile or nociceptive activity? To assess the effect of the normal maternal licking (i.e., cutaneous stimulation) just after birth, cesaeran delivered pups were stroked with a soft

brush. 100% of stroked pups survived whereas only 25% of pups that were not stroked survived, supporting a strong role of sensory stimulation. What are the consequences of those stimuli on brain activation?

The exploration of tactile processing in the newborn brains of rodents has been poorly investigated, and most of what we know about brain activation has been inferred from studies of human infants. The tactile-kinesthetic stimulation of preterm infants has fairly specific effects on the secretion of epinephrine/norepinephrine and maturation and/or activity of the sympathetic nervous system [12]. Using electroencephalogram recordings, Fabrizi *et al.* [13] mapped the maturation of tactile and nociceptive activity in the developing brain and suggested that the neural circuits necessary for discrimination between touch and nociception emerge following 35–37 weeks gestation in the human brain. At this developmental stage, touch and noxious evoke characteristic somatosensory potentials. fMRI studies confirmed that a mechanical skin stimulation (brush stimulation on the sole of the foot) activates distinct brain regions in the newborn, including the somatosensory cortex, occipital and frontal cortex, thalamus and the contralateral insula [14]. This is similar, but not the same, as the pattern of brush activation in adults where the somatosensory cortex, the contralateral mid-insula and posterior insula, the temporoparietal junction and the ipsilateral cerebellum are activated. These studies show that tactile and noxious stimulations activate distinct brain regions, notably the somatosensory cortex, in the human neonates at term and even before birth. These data show that a functional maturation stage of cortical circuits occurs around birth in human allowing discrimination between sensory and noxious stimulations.

Olfactory stimuli allow the newborn to locate and grasp the nipples

Mammalian females emit odor cues and signals (pheromones) located on their nipples and ventrum that direct their inexperienced newborns to the nipple and optimize their first suckling [9,15••]. When these odor/pheromones cues are removed by washing the nipples, suckling is eliminated but can be reinstated by brushing nipples with amniotic fluid or maternal saliva [16,17]. The effect produced by amniotic fluid raises the hypothesis that olfactory control of suckling could be determined by the experience of the perinatal pup. Further experiments showed that odors learned prenatally and reinforced both with birth stimuli and postnatally become conditioned stimuli for nipple attachment [5,18]. Neural and behavioral responses to the natural maternal odor and neonatal learned odors are similar, suggesting that both types of odors use similar neural networks to control pups' behavior. These neural systems involve the olfactory bulb for neural plasticity and the hyperfunctioning noradrenergic locus coeruleus flooding the olfactory bulb with norepinephrine [19].This circuit is different from the mechanism of odor learning developed at adulthood. Importantly, odors can stimulate the sensory system using different pathways. For instance, the olfactory and trigeminal systems interact, and odorants stimulate the olfactory bulb, but the trigeminal nerve also controls the strength of masseters in suckling [20].

Motor outputs

Effective suckling requires the coordination of muscles and hindbrain cranial nerve systems such as the trigeminal (V), the glossopharyngea (IX) and the vagus (X) nuclei and in particular the hypoglossal (XII) nerve that controls the tongue [21] and the facial (VII) nerve innervating the buccolabial musculature [22,23]. In newborn rats, resection of the XII nerve results in the death due to a failure to suckle milk [24]. How are these motor nuclei controlled at birth?

Central pattern generators (CPGs) are underlying the rythmic movements of suckling and swallowing. They are composed of networks of local interneurons that activate groups of motoneurons (see for review [25••]). CPGs control the motoneuron bursts in response to central nervous system (CNS) (sensorymotor cortex) and peripheral sensory inputs [26]. Importantly, separate CPGs control the V, VII and XII motor activity; those CPGs are coupled together with an unknown mechanism to coordinate suckling [27]. However, those CPGs are capable of generating a basic swallow pattern in the absence of peripheral or descending cortical inputs [28] and swallowing is already observable in the developing fetus to regulate the amniotic fluid volume and composition [29]. The transition from suckling to chewing occurs gradually over a period that varies between species (e.g., around P12 in rats) [7], and it is unclear if the suckling CPG evolves to control mastication or if the mastication CPG emerges separately.

Endocannabinoid, oxytocin and vasopressin stimulate the motoneurons and suckling activity in newborns

Pharmaocological (CB1 receptor antagonist) and genetic (CB1R-KO) approaches have shown that the enocanna-binoid-CB1 receptor system plays an important role in the initiation and maintenance of suckling behavior in the first day of life in rats and mice during their first encounter with the nipple and milk [30,31]. Several data suggest that CB1 receptor blockade interferes with the modulation of glycinergic synaptic currents in hypoglossal motoneurons [32], and the hypoglosal nerve may fail to adequately activate tongue movement.

Oxytocin (OT) and vasopressin (AVP) are two similar amino acids (only 2 aa are different) neuropeptides produced by OT or AVP neurons located in the paraventricular (PVH) and supraoptic (SON) hypothalamic nuclei. In a mouse model of reduced OT release at birth (*Magel2*-KO mouse) or in wild-type mouse neonates that received administration of an OT-antagonist before the first suckling, there is a marked alteration in the initiation of suckling that can be reversed after an OT administration in *Magel2*-KO pups [33••]. Noticeably, Wrobel and colleagues [34] showed that in 5-day-old rats, OT and AVP receptors may function as neuromodulators of the hypoglossal (XII) nucleus responsible for tongue movements. AVPRs might directly or indirectly activate the motoneurons and OTR might indirectly inhibit the motoneurons. Interestingly, in rabbit pups, genital stroking induces an activation of the OT neurons [35]. Altogether, it is tempting to speculate that tactile stimulation might activate the OT-neurons that in turn stimulate the hindbrain motoneurons to trigger suckling.

Development of homeostatic circuits that regulate feeding

Energy homeostasis is achieved by the integration of peripheral metabolic signals by neural circuits. The organization and function of neural circuits regulating energy homeostasis has been a subject of intense investigation and led to definition of a core circuitry in the hypothalamus that interacts with other brain regions, such as the brain stem, that appear to mediate many of the effects of the metabolic hormones, such as leptin and ghrelin, on feeding and energy balance (Figure 1) [1••].

Classic neuroanatomical studies have defined the developmental periods during which patterns of hypothalamic connectivity are established. A systematic study utilizing axonal labeling showed that neural projections from the arcuate nucleus of the hypothalamus (ARH) are not formed at birth and remain structurally and functionally immature until three weeks of postnatal life [36]. Arcuate neurons first send axonal projections to the dorsomedial hypothalamic nucleus (DMH) at postnatal day 6 (P6), followed by inputs to the PVH between P8 and P10 and to the lateral hypothalamic area (LHA) at P12 [36]. The pattern of ARH axonal projections achieve a distribution resembling that seen in the adult at weaning. In contrast to the development of arcuate circuits, efferent projections from the DMH to the PVH and LHA are fully established by P6 [36]. Similarly, projections from the ventromedial hypothalamic nucleus (VMH) develop prior to those from the ARH. By P10, VMH fibers supply strong inputs to the LHA, whereas at this age, the LHA is almost devoid of fibers from the ARH [36]. In addition, neurohypophyseal projections from the PVH to the median eminence appear to be mostly developed at birth [37].

Metabolic hormones do not acutely regulate energy homeostasis during neonatal life

There are marked physiological differences in the regulation of energy homeostasis between adults and neonates. Indeed, the neonatal period is a critical stage of development, during which animals need to maximize caloric intake and maintain appropriate metabolic responses to ensure growth and survival. In light of this need for homeostatic regulation, the immaturity of hypothalamic circuits during neonatal life seems to contraindicate a role for the hypothalamus in relaying leptin's action on feeding and energy balance in neonates. Consistent with this idea, in sharp contrast to the effects of leptin in adults, several groups reported that acute leptin administration does not significantly inhibit growth, food intake, or energy expenditure during the first 2–3 postnatal weeks [38–41]. More specifically, Mistry and colleagues showed that exogenous leptin does not alter oxygen consumption or food intake in normal lean or obese leptin deficient (*ob/ob*) mice until P17 [40]. Similarly, ghrelin, which normally triggers a potent orexigenic response in adult animals, does not significantly promote milk intake or body weight in the first 2–3 postnatal weeks in rats and mice [42,43••]. A possible explanation for this lack of response is that the neonatal brain is relatively insensitive to leptin and ghrelin and may present hormonal resistance. However, both leptin and ghrelin receptors are found in the nuclei known to regulate feeding, including in the ARH, and acute peripheral leptin or ghrelin treatment activates hypothalamic neurons during early postnatal life [44,45].

Hormonal regulation in the development of hypothalamic circuits

Although leptin does not appear to inhibit food intake and body weight during neonatal life, rodents display a sharp surge in circulating leptin levels during the first 2 weeks of postnatal life [46•]. Ahima and colleagues hypothesized that in lieu of regulating feeding, leptin may function as a developmental factor for brain development [46•]. This hypothesis was further demonstrated experimentally by analyzing hypothalamic neural connectivity in *ob/ob* mouse neonates (Figure 1) [47••]. The density of projections from ARH neurons to other hypothalamic sites involved in the control of food intake were severely disrupted in postnatal *ob/ob* mice and remained diminished throughout life [47••]. Similar abnormalities in hypothalamic development were also found in leptin-receptor deficient Zucker rats [48]. However, not all components of feeding pathways seem to be altered in the absence of leptin. For example, neural circuits developing prior to the leptin surge, such as those from the DMH to the PVH [36], were similar in wild-type and *ob/ob* mice [47••]. As with many developmental factors, leptin exerts its neurotrophic effects during a restricted postnatal critical period: treatment of adult *ob/ob* mice with leptin did not restore ARH projections, but daily injections of leptin between P4 and P12 rescued them [47••]. The physiological relevance of postnatal leptin has been supported by several observations. Neonatal leptin treatment in *ob/ob* mice caused a long-term amelioration of body weight, food intake, and sympathetic stimuli [49]. In contrast, blunting the leptin surge in rats resulted in increased susceptibility to the development of diet- induced obesity during adulthood [50]. Not only the correct amplitude but also the correct timing of the postnatal leptin surge appears to be required for normal regulation of energy homeostasis in adult animals. For example, experimentally advancing the leptin surge caused various metabolic deficits, including higher predisposition to obesity during adult life [51].

In fact, a variety of metabolic hormones appear to be critical regulators of hypothalamic development (Figure 1). For example, intra-hypothalamic injection of insulin on postnatal day 8 is associated with morphological alterations of hypothalamic nuclei (including the ARH and VMH) and life-long metabolic disturbances [52,53]. Similarly, maternal hypoinsulinemia induced by strepto- zotocin injections is associated with a reduced density of arcuate projections in the offspring [43••]. In addition, genetic deletion of insulin receptors in POMC neurons improves ARH projections and glucose metabolism in mouse pups born to obese dams [54]. During neonatal life, ghrelin also appears to act as a developmental signal influencing ARH circuits. Mouse neonates injected with an anti-ghrelin compound between P4 and P22 display increased densities of ARH-containing axonal projections and these structural alterations are accompanied with long-term metabolic defects, including elevated body weight and fat mass [45]. Intriguingly, the density of ARH axonal projections is also elevated in *ghrelin*-KO mouse pups, but it is rescued in adult animals, indicating that arcuate circuits continue to be plastic not just early in development but even during the postweaning period in response to genetically programmed events [45].

Future perspectives

Postnatal feeding difficulties, such as dysphagia, are present in 80% of infants with neurodevelopmental disorders [55••]. They may reflect a disruption in the development of neural circuits critical for feeding. However, how these circuits develop and particularly the relationships of the sensory inputs and motor outputs to the cortex, the hypothalamus and the hindbrain, remain poorly understood. Here, we summarized the current knowledge resulting from scattered and descriptive data. A better understanding of this circuitry and its regulation is important because it is a vital process and it would also help to identify novel therapeutic interventions to improve the quality of life of affected children.

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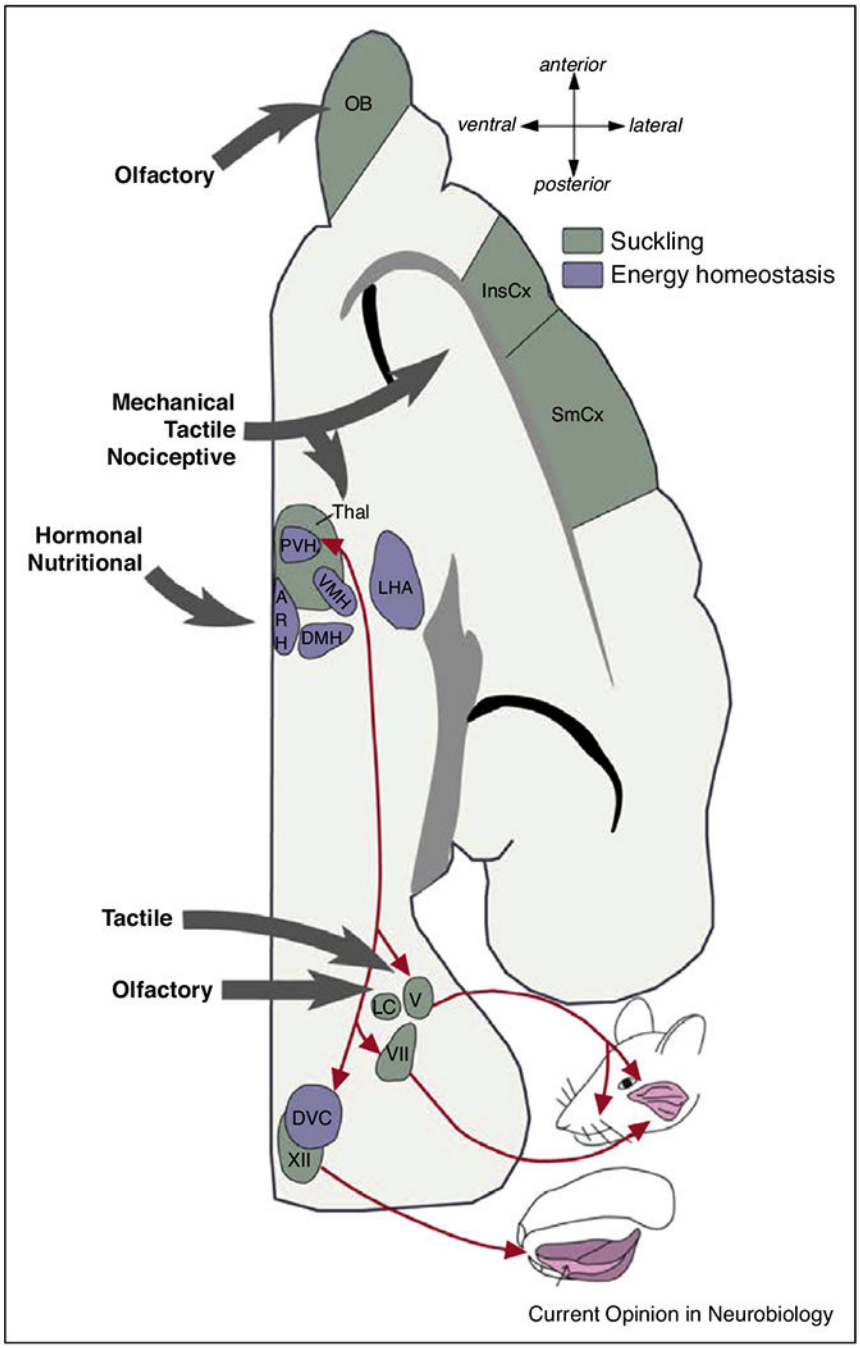

Figure 1.

Highly simplified flat map showing brain regions involved in the perinatal regulation feeding. The regulation of feeding during early postnatal life involves a complex, distributed, and interconnected neuronal network involving neurons in the forebrain and hindbrain. Neurons in the olfactory bulb (OB), locus coeruleus (LC), thalamus (Thal), somatosensory (SmCx) and anterior insulate (InsCx) cortex as well as in the trigeminal (V), facial (VII), and hypoglossal (XII) nuclei play a critical role in the initiation and maintenance of suckling. Circuits emanating from these neuronal structures begin to develop before birth

and continue to be remodeled after birth upon olfactory, mechanical, and nociceptive stimulations. Neurons located in the arcuate (ARH), ventromedial (VMH), dorsomedial (DMH), paraventricular (PVH) nuclei of the hypothalamus, in the lateral hypothalamic area (LHA) and in the dorsal vagal complex (DVC) are involved in the homeostatic regulation of feeding. These neuronal systems are largely immature at birth and develop during the first three weeks of postnatal life in rodents under the influence of hormonal and nutritional signals.

Table 1

Mouse genetic mutations and lesion experiments in rodents that disturb the suckling activity

Animal model	Gene involved/gene product	Suckling phenotype	Structure involved	Phenotype
Olfactory phenotype				
Olfactory phenotype Genetic Arhinencephaly mouse [9]	*Gli3*/transcription factor mediator of Sonic hedgehog signaling	No suckling from birth due to loss of olfaction	Olfactory nerve	Death within one day after birth due to suckling deficit
Edg2-KO mouse [56]	*Edg2*/lysophosphatidic acid receptor	No or weak suckling from birth due to loss of olfaction	Olfactory bulb	50% of death within one day after birth due to suckling deficit
Hypothalamic phenotype				
Hap1-KO mouse [57]	*Hap1*/Huntingtin associated protein	No or weak suckling from birth due to a decrease level of GABA R in hypothalamus	Hypothalamus	Death within the 48 hours after birth due to suckling deficit
Magel2-KO+m/-p mouse [33••]	*Magel2* (hypothalamus, pons)	No or weak suckling from birth	Hypothalamus with oxytocin neurons	50% of death within one day after birth due to suckling deficit
Sensory/motor phenotype				
Hypoglossal/XII nerve injury in rat neonate [24]		Altered due to motor deficit	Hypoglossal motor nucleus unilateral nerve injury	More than 60% of death before P5 Decrease in body weight
Grin2b KO mouse [58]	*Grin2b*/NMDA receptor e-subunit	Altered due to sensory deficit	Trigeminal nucleus	Death within one day after birth due to suckling deficit
Facial/VII nerve injury in rat neonate [23]		Altered due to motor or sensory deficits	Facial motor nucleus unilateral nerve injury	No death Decrease in body weight
Cntfr KO mouse [59]	*Cntfr*/ receptor for ciliary neurotrophic factor	Altered due to motor deficit	Motoneuron deficit in the brainstem	Death within one day after birth due to suckling deficit
Gnasxl-KO+m/-p mouse [60]	*Gnasxl*	Weak at birth	Hypothalamus, orofacial motor nuclei (V,VII, XII)	50% of death within one day after birth
Cb1-R-KO mouse [61]	*Cb1-R*/Cannabinoid receptor 1	Altered the first postnatal day	Lack of CB1-Receptors in brain	No milk ingestion the first day of life
Reg2-KO mouse [62]	*Reg-2*/Member of family of growth neurotrophic factor	Altered due to	Cranial motoneurons	Reduction in milk ingestion after birth