Review

Role of hypothalamic neurogenesis in feeding regulation

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The recently described generation of new neurons in the adult hypothalamus, the center for energy regulation, suggests that hypothalamic neurogenesis is a crucial part of the mechanisms that regulate food intake. Accordingly, neurogenesis in both the adult and embryonic hypothalamus is affected by nutritional cues and metabolic disorders such as obesity, with consequent effects on energy-balance. This review critically discusses recent findings on the contribution of adult hypothalamic neurogenesis to feeding regulation, the impact of energy-balance disorders on adult hypothalamic neurogenesis, and the influence of embryonic hypothalamic neurogenesis upon feeding regulation in the adult. Understanding how hypothalamic neurogenesis contributes to food intake control will change the paradigm on how we perceive energy-balance regulation.

Neurogenesis in the adult brain

Neurogenesis is a complex and highly regulated process that results in the production of new neurons (see Glossary). Neurogenesis occurs at high rates during the embryonic period when substantial quantities of new cells are generated by the proliferation of neuroprogenitor cells (NPCs), and subsequently migrate to the developing tissue [1]. In the adult, neurogenesis occurs at low rates in discrete regions of the brain such as the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampus [2]. NPCs from these regions proliferate and migrate to their final destination, the olfactory bulb and the granule cell layer of the dentate gyrus, respectively, where they differentiate to form new neurons and integrate into pre-existing circuits [3]. Importantly, neurogenesis is not simply a restorative mechanism; it represents a functional response of the organism to daily challenges imposed by environmental and internal states [2]. Moreover, the new neurons produced through the adult life seem to contribute to behavioral functions such as learning, memory consolidation, and mood regulation [3].

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A new neural stem/progenitor cell niche has recently been described to reside in the adult hypothalamus, a brain region that functions as the central regulator of homeostasis by controlling food intake, metabolism, and

Glossary

Arcuate nucleus (ARC): a region of the hypothalamus where the nutrient-sensing neurons are located.
Ependymal cells: cubic ciliated cells that line the ventricles (cavities) of the brain. In addition to barrier functions, ependymal cells are involved in the production and circulation of the CSF. In the hypothalamus, ependymal cells are the interface between the third ventricle (3V) and hypothalamus parenchyma.
Feeding regulation: a complex mechanism that includes central processes that take place in the hypothalamus. In brief, ARC neurons receive peripheral signals regarding the energy status of the organism and synthesize neuropeptides in response to those signals. The neuropeptides help in integrating and translating those signals into motivated behavior. Usually, hypothalamic responses counteract the nutritional signals to re-establish energy homeostasis.
Growth factors: molecules that increase the generation and/or survival of progenitor neuronal cells in neurogenic areas of the adult brain.
Hypothalamus: a brain area responsible for feeding regulation and metabolism. It consists of several regions (nuclei) with different neuronal populations that express specific neuropeptides. The hypothalamus is located in close proximity to the 3V.
Hypothalamic neurogenesis: the generation of new neurons in the adult or embryonic hypothalamus that arise from the proliferation and differentiation of hypothalamic NPCs.
Leptin: an anorexigenic hormone released from adipocytes into the circulation as a function of body fat content. High levels of fat storage raise the concentrations of leptin, and leptin suppresses food intake by inhibiting NPY/AgRP neurons and activating POMC neurons.
Neurogenesis: the set of events leading to the production of new neurons from NPCs. This process includes division (proliferation) of NPCs, migration, maturation (differentiation to a specific neuronal type), and functional integration of the new neurons into existing neuronal circuits.
Neurogenic niche: the zone(s) in the adult brain where NPCs are retained after embryonic development. The microenvironment in the neurogenic niche, including cell–cell interactions, can retain the NPCs in the undifferentiated state and regulate the proliferation and differentiation of NPCs [66].
Neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons: a group of neurons located in the ARC that express NPY and AgRP; these neuropeptides have orexigenic actions (increase food intake) and are activated during energy deficiency.
Neuroprogenitor cells (NPC): the population of cells with proliferative and self-renewal capacity that can differentiate to different neural phenotypes.
Paraventricular nucleus (PVN): region of the hypothalamus that receives most of the neuronal projections from the ARC neurons.
Proopiomelanocortin (POMC) neurons: a group of neurons located in the ARC that express POMC; neuropeptides resulting from processing and cleavage of the POMC gene product have anorexigenic actions (decrease food intake) and are increased in situations of energy excess.
Subependymal astrocytes: glial cells located beneath the ependymal layer of the 3V wall that present features of neural stem cells, including expression of glial fibrillary acidic protein (GFAP) and proliferation upon growth factor stimulation. Therefore, subependymal astrocytes are identified as adult hypothalamic NPCs.
Tanycytes: specialized non-ciliated ependymal cells characterized by a long basal process that penetrates into the hypothalamic parenchyma. Tanycytes are considered to be adult hypothalamic NPCs because they are proliferative in basal conditions and upon stimulation with growth factors, and express the neuroprogenitor markers vimentin and nestin.

body temperature, among other functions. Emerging evidence discussed in detail below suggests that these adult-born hypothalamic neurons play a crucial role in feeding regulation, underscoring their significance in the central control of energy-balance.

Hypothalamus and feeding regulation

Feeding behavior and energy-balance are regulated centrally by the hypothalamus. Distinct nuclei within the hypothalamus, including the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the ventromedial (VMH) and dorsomedial (DMH) hypothalamus, and the lateral hypothalamic area, share neuronal interconnections and together they maintain body homeostasis [4]. ARC neurons produce the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related protein (AgRP) that act to increase food intake, and the anorexigenic neuropeptide proopiomelanocortin (POMC), the product of which (α-MSH) acts to decrease food intake [5]. The activity of ARC neurons is regulated by metabolic peripheral signals including hormones and gastrointestinal peptides [4]. For example, the adipose-derived hormone leptin, which is produced in proportion to body fat content, can activate the leptin receptors present in ARC neurons [4] to increase the expression and release of POMC and reduce the expression and release of NPY, resulting in a decrease in food intake [5]. More recently, neurogenesis has been described in the hypothalamus and has been shown to participate in the response of hypothalamic neuronal circuits to metabolic signals [6–9].

Embryonic hypothalamic neurogenesis influences adult feeding regulation

Cell populations during embryonic hypothalamic neurogenesis

The development of hypothalamic feeding circuits starts during the embryonic period and, in rodents, continues through the first 2 weeks of postnatal life [10]. Recent studies show that hypothalamic NPCs are present in the embryonic hypothalamus; for example, in rodents, POMC and NPY neuroprecursors are identified as early as embryonic (E) days E10.5 and E14.5, respectively [11,12]. In agreement, NPCs isolated from fetal rat hypothalamus express neuropeptides NPY, AgRP, and POMC [13]. Importantly, the number of immature POMC neurons in the ARC triples and reaches its adult number during the fetal period [11]. Surprisingly, some POMC neuronal progenitors adopt a distinct fate, giving rise to antagonistic neuronal populations expressing NPY [11]. Therefore, NPY and POMC, which are expressed in mutually exclusive cell populations in the adult hypothalamus, colocalize in a subset of embryonic neuronal precursors [11].

Other hypothalamic cell populations are generated during the embryonic period including ependymal cells, cuboid ciliated cells that line the third ventricle (3V) wall of the hypothalamus, formed at E16–E18 [14]. Tanycytes are specialized ependymal cells that are located in the floor of the 3V. In rodents, a subpopulation of radial glial cells (NPCs of the embryonic brain) initiate their differentiation into tanycytes between E18 and the first postnatal days, and this process is completed by the first month of life [14]. Tanycyte functions are not clearly understood, but they seem to be involved in feeding behavior as chemosensory cells and adult NPCs that respond to diet alterations [14,15].

Impact of early nutritional and neurotrophic environment

The nutritional and neurotrophic environment during the embryonic period, when hypothalamic NPCs are developing, impacts upon the formation of an adequate NPC population [16–18]. For example, offspring of dams with higher body weight have a lower number of immature neurons in the ARC [19]. Accordingly, proliferation of hypothalamic NPCs in rodents during the perinatal period is influenced by maternal diet manipulation and hormone availability [16–18]. Specifically, offspring subjected to nutritional restriction during the gestational period present a reduced NPC population with decreased proliferative capacity [16]; this results in body weight and feeding deficits in newborns that persist after weaning [18,20]. By contrast, a maternal high-fat diet (HFD) regime promotes the proliferation, differentiation, and migration of orexigenic neuronal precursors in the hypothalamic PVN of rats, increasing the density of orexigenic neurons in newborns and leading to a higher risk of obesity [18].

A hypothesis has emerged from these findings that hypothalamic neurogenesis during the neurodevelopment period is crucial, and that conditions affecting neurogenesis during this period can modify the number of hypothalamic NPCs and thus affect satiety pathways. As a consequence, persistent changes on newborn homeostasis and, possibly, reduced capacity to adapt to metabolic challenges during adulthood may be observed. In accordance, this has been proposed as one possible mechanism responsible for the high incidence of obesity in our society [21].

Transcriptional regulation of embryonic hypothalamic neurogenesis

Several transcription factors have been identified as key regulators of hypothalamic neurogenesis during the embryonic period [22–29]. For example, the proneural transcription factor Mash1 (mammalian achaete-scute homolog 1) is required for the generation of hypothalamic neurons, and Mash1 null mice present severe hypoplasia of hypothalamic nuclei including the ARC [26]. In addition, Mash1 and neurogenin 3 (Ngn3) are involved in subtype specification of neurons that are important for feeding regulation [26,27]. Mash1 is required for the differentiation of NPY-expressing neurons and for the normal development of POMC neurons [26]. By contrast, Ngn3 inhibits the expansion of the NPY neuronal population and promotes the development of POMC-expressing neurons [27].

The transcription factors single-minded homolog 1 (Sim1), aryl hydrocarbon receptor nuclear translocator 2 (ARNT2), and orthopedia (Otp) control the terminal differentiation of neuroendocrine lineages within the PVN, including the specification of corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) neurons [22–25]. It has been reported that in mice null for either of these genes, TRH and CRH neuroprecursors fail to differentiate and produce hormones [22,24,25]. In addition, Sim1 heterozygous mice have a reduced total number of PVN