The Role of Hypothalamic Neuropeptides in Neurogenesis and Neuritogenesis as potential Target on Cancer, and Metabolic disorders Treatment and Prevention (Part two)

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Abstract

Neurogenesis occurs in the adult brain in a constitutive manner under physiological circumstances within two regions: the dentate gyrus of the hippocampus and the sub-ventricular zone of the lateral ventricles.

Numerous studies, however, have also reported adult neurogenesis in the hypothalamus, a brain structure that serves as a central homeostatic regulator of numerous physiological and behavioral functions, such as feeding, metabolism, body temperature, thirst, fatigue, aggression, sleep, circadian rhythms, and sexual behavior.

Recent studies on hypothalamic neurogenesis have identified a progenitor population within a dedicated hypothalamic neurogenic zone. Furthermore, adult born hypothalamic neurons appear to play a role in the regulation of metabolism, weight, and energy balance.

Recently, low proliferative activity was reported in the hypothalamus and the cell layers surrounding the third ventricle.

In this article, I discuss The Role of Hypothalamic Neuropeptides in Neurogenesis and Role of Hypothalamic Neuropeptides in Neuritogenesis

Key Word: Hypothalamus, Neuropeptides, Neurogenesis, Metabolic disorders and Cancer

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1. Introduction

Understanding the functional consequences of this plasticity has been of great interest to the neuroscience field, and a variety of animal model studies have informed us that many of these newborn neurons survive and functionally integrate themselves into the working brain. Anatomical evidence for ongoing neurogenesis in the adult mammalian central nervous system (CNS) was first described by (1). However, the functional relevance of these findings was not clear at the time, and several decades passed before this finding aroused wide interest. Methodological advancements in electron microscopy techniques revealed that adult generated mammalian hippocampal neurons could survive for an extended period and receive synaptic inputs (2),(3). further suggesting that neurogenesis could modify neural circuits. Advances in immune-histochemistry combined with 3H-thymidine-labeling demonstrated that adult neurogenesis was a robust phenomenon (4). Immunohistochemical detection of neuronal markers and the introduction of bromodeoxyuridine (BrdU), a synthetic thymidine analog lineage tracer of DNA replication (5), further propelled the under-standing of adult neuro-genesis in the mammalian CNS by allowing for broader visualization and stereological quantification of newborn neurons (6). Given the critical role that hypothalamic neural circuitry plays in maintaining physiological homeostasis, functional integration of newborn neurons and/or their release of hormones/peptides may result in *disproportionately larger effects* in physiology and behavior relative to other brain regions. This review summarizes studies on the identification and characterization of neural stem/progenitor cells in the mammalian

hypothalamus, in what contexts these stem/progenitor cells engage in neurogenesis, and potential functions of postnatally generated hypothalamic neurons. Past studies mainly focused on two regions: the subgranular zone (SGZ) in hippocampus, and the subventricular zone (SVZ) (7). In SGZ, a subtype of astrocytes was considered to be neural stem cells, giving birth to new granule cells in the dentate gyrus (DG) (8). [2]. In the SVZ, both astrocytes and ependymal cells have been suggested to be the neural stem cells that produce neuroblasts migrating to the olfactory bulb (9). Newly born neurons were considered to be important in many aspects of brain function, and provided the therapeutic targets in treating brain diseases (10). In recent years, some other potential neurogenic areas have been discovered and multipotent neural precursors could be isolated from these regions under normal physio-logical conditions, including the hypothalamus, an important region for homeostasis and reproductive behaviors. Previous studies since 1990s suggested the generation of new neurons in the postnatal hypothalamic third ventricle wall (11),(12),(13). One of the earliest studies on adult generated cells in hypothalamus examined the effects of seasonal photoperiod on new neuron formation near the ventricle wall (14). The administration of trophic factors such as brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor into the ventricle can also induce or promote adult neurogenic processes in the hypothalamus (15),(16),(17),(18).

2. Origin and birthdate of neuroendocrine hypophysiotropic factors

The availability of genetically engineered mouse models has added a new dimension to studies of the ontogeny of parvicellular neuronal subtypes. In recent years, a clearer picture has emerged of the precise steps in development and the factors involved in the differentiation of and acquisition of function by cells that secrete hypothalamic releasing factors. Below we outline some of the key advances in this field.

2.1. GnRH

A total of 14 forms of GnRH have been described (19), with the physiologically most important form being GnRH-1 (referred to here as GnRH). GnRH is a central regulator in the hypo-thalamic–pituitary–gonadal axis and is produced by neurosecretory cells located throughout the basal hypothalamus including the preoptic nucleus and AH. The release of GnRH triggers the synthesis and release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which regulate gonadal steroidogenesis and gametogenesis (20). Unlike all other parvicellular neurons that arise from within the hypothalamic anlagen, GnRH neurons originate in the olfactory placode (19), and migrate through the ventral forebrain. In mice, GnRH neuron migration terminates in the medial septum, POA and anterior hypo-thalamic regions (21). Recent evidence indicates that the initial population of GnRH neurons (9.5-10.5 dpc) are generally located rostral to later-born (11.5-12.5 dpc) GnRH neurons and that the GnRH neurons located at different rostral-caudal positions may be functionally distinct (22). Several extracellular cues that direct the emergence and migration of nascent GnRH neurons have been identified which include Fibroblast Growth Factor 8 (23), hepatocyte growth factor (24), and secreted-class 3 semaphorins (25). Of particular interest is semaphorin-4D (Sema4D) which belongs to the semaphorin protein family group of axon/cell guidance proteins and is expressed along GnRH migratory route (26). The Sema4D receptor, PlexB1, is expressed in migratory cells that are exiting the olfactory placode (27). *PlexB1* deficient mice exhibit aberrant migration of the principal GnRH fibers that project to the ME (28), confirming the importance of

Sema4D/PlexB1 interaction during GnRH cell migration. A number of transcription factors have been implicated in GnRH differentiation such as GATA-4 and Activator Protein-2α (AP-2α). GATA-4, a member of the GATA family of zinc finger-domain transcription factors, binds to the GnRH enhancer and regulates GnRH gene transcription (29). In the 13.5 dpc mouse brain, GnRH neurons express GATA-4 along their migration from the olfactory placode into the brain (30). The Activator Protein transcription factors are critical regulators of gene expression during embryogenesis. AP-2α has been detected in olfactory placode epithelium (31). It has been reported that GnRH neurons express AP-2α as they migrate into the forebrain (32).

2.2. GnIH

GnIH was recently discovered in the Japanese quail and acts directly on the pituitary to inhibit gonadotropin release (33),(34). The identification of GnIH arose when neurons immune-positive for the molluscan cardioexcitatory neuropeptide Phe-Met-Arg-Phe-NH2 (FMRFamide,(35), were found in the vertebrate nervous system to contain an unknown, but similar, neuropeptide (36). In the amphibian brain, some of these neurons were seen to project to the hypothalamic region close to the pituitary (36),(37). In turn, in the Japanese quail brain, clusters of these distinct neurons were seen localized in the PVN in the hypothalamus, with wide distribution in the diencephalic and mesencephalic regions and the most prominent fibers within the ME (33), (33). Recent studies have confirmed the effects of GnIH in rodents and sheep (38),(39),(40), (41). Birth-dating and neuronal migration, however, have yet to be examined.

2.3. DA

DA is a catecholamine neurotransmitter, which in the pituitary is primarily involved in the inhibition of prolactin (PRL) release. In order to detect DA and the cells that produce it, tyrosine hydroxylase (the rate-limiting enzyme in synthesis of dopamine) expression is used as a surrogate marker. Secretion of PRL is regulated by three populations of hypothalamic dopaminergic neurons, originally identified in rats (42). (1) the tuberoinfundibular (TIDA) dopaminergic neurons, arising from the dorsomedial ARC and project to the external zone of the median eminence (43), (2) tubero-hypophysial (THDA) dopaminergic neurons, arising from the rostral ARC and project into the hypothalamic-hypophysial tract and into the intermediate and neural lobes of the pituitary gland (44), and (3) the periventricular hypophysial (PHDA) dopaminergic neurons, arising from the more rostral PeVN and their axons terminate within the intermediate region of the pituitary gland (45). The PHDA neuronal populations control basal regulation of PRL secretion. Early immune-histochemical detection show the first appearance of dopaminergic neurons at 11.5 dpc in the rat (46). Insight into the role of specific transcription factors in the development and differentiation of dopamine neurons, specifically the THDA and PHDA subtypes is limited. The LIM-homeodomain transcription factor *Lmx1a* has been shown to play critical roles in the determination of midbrain dopaminergic neurons during brain development (47). More recently, it was identified that *Lmx1a* is expressed at high levels within the posterior hypothalamic area, ventral pre-mammillary nucleus, sub-thalamic nucleus, ventral tegmental area, compact part of the substantia nigra and parabrachial nucleus from birth to adulthood (48). However, the exact role of *Lmx1a* in the dopaminergic neurons that regulate secretion of prolactin is yet to be determined. *Otp* has also been found to be a key determinant of hypothalamic differentiation, including the DA neurons (49). Recent studies have begun to uncover the factors that regulate OTP expression and function. In zebrafish,(49),

have shown that *Otp* is transcriptionally regulated by the zinc finger-containing transcription factor Fezl. Furthermore, epistasis and cell culture experiments indicate that signaling via the G-protein-coupled receptor PAC1 increases the level of OTP protein by promoting OTP synthesis. Further research into the role of transcription factors, such as *Lmx1a* and *Otp*, on postnatal maturation, survival and/or function of midbrain dopaminergic neurons will help to provide a better understanding of the complexity of PRL inhibition and its regulation of secretion.

2.4. GHRH

GHRH stimulates the release of growth hormone (GH) from the pituitary. GHRH is expressed during the later stages of development and is essential for the expansion of somatotropes. Hypophysiotropic GHRH neurons are confined to the ventrolateral part of the ARC (50),(51), and first appear at 11.5 dpc in rat (52). The development and transcriptional control of GHRH neurons has been studied in mouse models using both gene disruption and transgenic approaches. One example of GHRH reduction has been identified using targeted disruption of *Gsh1*, a homeobox gene identified as a direct transcriptional activator of *Ghrh* (53). Targeted disruption of *Gsh1* leads to the complete absence of *Ghrh* expression resulting in severe attenuation of growth and an associated decrease in overall pituitary size (54). The haemato-poietic transcription factor Ikaros is also expressed in GHRH neurons and is required for *Ghrh* expression (55). In contrast, GHRH over-expression in a mouse model harboring the human GHRH gene coupled to the murine metallothionein I promoter (56), results in massive pituitary hyperplasia and an overabundance of somatotropes (57),(58). These transgenic mice also exhibit pituitary tumors, albeit with incomplete penetrance, indicating that sustained elevated GHRH exposure predisposes somatotropes to neoplastic transformation.

2.5. SS

SS acts as an inhibitor of GH and TSH secretion. The inhibition of GH by SS appears to be independent of GHRH, although the precise mechanism remains unknown. GH secretion stimulates somatostatinergic neurons in the PeVN to secrete SS from the nerve terminals located at the ME into the hypothalamo-hypophysial portal circulation for delivery to the AP (59). SS neurons that project into the ME are located within the rostral PeVN and the PVN. They first appear at 12.5 dpc in the rat (52). To date, transcription factors that specifically regulate the differentiation of hypothalamic SS neurons have not been identified, although it is possible that similar pathways to those that control SS neuron differentiation in other parts of the brain (e.g. the cerebral cortex) may be employed (60).

2.6. TRH

TRH-synthesizing neurons exert multiple, species-dependent hypophysiotropic activities. However, for the purpose of this review, we will focus on the effects of TRH on TSH. Anatomically, the TRH neuroendocrine cells are situated in the hypothalamic PVN. TRH stimulates the secretion of TSH from the anterior pituitary thereby initiating thyroid hormone synthesis and release from the thyroid gland (61),(62). TRH, identified by mRNA expression of the biosynthetic precursor pre-pro-TRH, was initially localized within the rat lateral hypothalamus at 13.5 dpc, and in the presumptive PVN at 15.5 dpc (63). Immunohistochemical analysis of the TRH peptide revealed the first TRH-immuno-reactive perikarya at 16.5 dpc as

well as 17.5 dpc within the presumptive PVN(64). There are four populations of TRH neurons (appearing at different developmental stages in the rat): (1) lateral hypothalamus (14.5 dpc); (2) VMN (15.5 dpc); (3) PVN (16.5 dpc); and (4) the POA (17.5 dpc). Thus, the differentiation and development of these neuronal populations will differ. Additionally, the identity and origin of the cues that direct TRH neuronal differentiation are poorly understood. However, it has been shown that brain derived neurotropic factor (BDNF) effects TRH neuronal differentiation by tropomyosin-related kinase B receptors during early development (65). BDNF also regulates the expression of pre-pro-TRH throughout development and into postnatal life in the rat (66).

2.7. CRH

CRH-synthesizing neurons are the principal hypothalamic regulators of the glucocorticoid axis and, like the TRH-synthesizing neurons, are closely situated in the hypothalamic PVN. Immuno-histochemical analysis in rat embryos show CRH expression as early as 15.5 dpc, with immune-positive fibers seen at 16.5 dpc in the ME (46). *Crh* mRNA expression studies have also identified CRH expressing cells from 16.5 dpc (67). Given that most CRH neurons areborn at around 13.5 dpc (52), it appears that approximately 3 days is required for CRH neuron differentiation. While this process is poorly understood, one protein that has been shown to be required for generating CRH neurons is the homeodomain transcription factor OTP (68). As discussed above, *Otp* is expressed in the developing PVN, SON, aPeVN and ARC and mutants lack CRH, as well as TRH and SS neurons (68).

3. Role of Hypothalamic Neuropeptides in Neurogenesis

3.1. Adult Hypothalamic Neurogenesis.

The presence of immature mitotic neurons in the hypothalamus has been first reported by Evans et al. (69). Recent evidence for adult hypothalamic neurogenesis has been expanded, which consequently leads to the broad discussion of details on hypothalamic neurogenic cascades, regulatory mechanisms, and potential functions (70),(71). Adult-born neurons were found in the rat, mouse, and sheep hypothalamus (72), however proliferating neural cells in the human hypothalamus has not yet been reliably evidenced. Hypothalamic neurogenic niche has been identified lining the ventral portion of the third ventricle (73). Moreover, surface of the third ventricle has been suggested as a source of neurogenesis in the adult age and one study has shown that voluntary exercise correlates with proliferation of sub-ependymal cells (74),(75). It has been found that median eminence tanycytes (glial cells) generate newborn neurons. Tanycytes represent multi-potential cells retaining the morphological features of embryonic glial cells and neural progenitor cells into adulthood (75). Nevertheless, identity of the hypothalamic neural progenitor cells still remains controversial. It appears that they represent self-renewing cells that give rise to new tanycytes, astrocytes, and neurons (76). Immature migrating neurons are highly present in the vicinity of the hypothalamic neurogenic niche (77). Migrating neurons in the hypothalamus can integrate into functional circuits and modulate brain plasticity. Newly formed neurons in the hypothalamus can synthesize and release various neuropeptides (74). There is evidence suggesting that the newly generated hypothalamic neurons may be involved in metabolism, energy balance, and body weight (78),(79).

3.2. Hypothalamic Neuropeptides Controlling Neurogenesis

The potential of certain neuropeptides to affect hippocampal neurogenesis has been extensively reviewed elsewhere (80), however the involvement of neuropeptides in hypothalamic neurogenesis is less clear. The generation of new cells in the brain has been proved under influence of certain neuropeptides. Neuropeptide oxytocin has been reported to stimulate neurogenesis; however its effect was predominately described in the adult hippocampus (81),(82). Moreover, oxytocin may affect expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which represent important regulators of neuronal function (83). Infusion of BDNF into the lateral ventricle results in generation of new neurons in the hypothalamus of the adult rat (17). BDNF and many other growth factors and/or neurotrophic factors such as FGF2, ciliary neurotrophic factor (CNTF), vascular endothelial growth factor (VEGF), and transforming growth factor α (TGF-α) have been shown to regulate neural stem cells and neural progenitor proliferation in the adult rodent brain (84),(85). One study has reported that neurogenesis occurs in the adult hypothalamus, including areas containing oxytocin and vasopressin producing neurons (82). Other authors have reported that postnatal neurogenesis occurs in the magnocellular neurons of supraoptic and paraventricular nucleus (13). They have speculated that different time periods of formation exist for neurons that have a specific function. Moreover, it has been reported that production rate of new neurons expressing vasopressinwas positively correlatedwith postnatal growth of the same hypothalamic region (86). In agreement with this finding, important role of vaso-pressin and CRH in the regulation of hippocampal neurogenesis hasbeen suggested (87). Stem-like cells have been isolated from hypothalamus with the ability to generate neurons and glia producing and secreting neuropeptides including oxytocin (88). Few studies suggest an association between eating behavior and hypothalamic neurogenesis (89). This makes a great potential for neuropeptides involved in neurogenesis as neural progenitor cells isolated from fetal rat hypothalamus express NPY, AgRP, and POMC (90). Peptide melanocortin, one of the POMC products, exhibits control of feeding and energy expenditure, neuroprotection, and neurogenesis through melanocortin-4 receptor subtype (MC4R) (91). Moreover, melanocortin-induced neurogenesis triggering the Wnt and Shh signaling pathways has been demonstrated in themodel of cerebral ischemia (92). Control of food intake regulated by orexin may include effects on neurogenesis as well. Few studies have suggested that orexin-A is involved in hippocampal neurogenesis (93),(94). Another neuropeptide, NPY, regulates the biological dynamics of neurogenic niche (95),(7), and plays a role in the modulation of adult neuro-genesis (80),(96),(97),(98). NPY directly targets certain neural stem cell subtypes (nestin- and doublecortin-positive cells), including proliferation, differentiation, migration, and functional integration of newborn neurons. Moreover, microglia and astrocytes also appear to be responsive to the peptide (99). NPY directly interacts with another feeding-regulatory peptide ghrelin (100). Another study has been performed by Chang et al. These authors found that prenatal nicotine exposure stimulates neurogenesis of orexigenic peptide-expressing neurons in the offspring hypothalamus (101). Systemic ghrelin treatment stimulated neuro-genesis in the adult hippocampus in mice (102). In the hypothalamic neuronal cells, ghrelin may act as a survival factor that preserves mitochondrial integrity and inhibits apoptotic pathways during oxygen-glucose deprivation (103). Thus, taken together oxytocin, vasopressin, NPY, and ghrelin belong to neuropeptides likely to participate in the regulation of hypothalamic neuro-genesis

and differentiation. Recently, it has been demonstrated that Substance P increased proliferation of neural stem/progenitor cells in the spinal cord (104). Although no direct effect of TRH on neurogenesis is so far known, a lot of knowledge has been gained on neurogenic effects of thyroid hormones (105). Recent study has evidenced that CRH regulates neurogenesis. The same authors have demonstrated that CRH induced proliferation and protection from apoptosis in the human neuroblastoma cells (106).

4. Role of Hypothalamic Neuropeptides in Neuritogenesis

4.1. Hypothalamic Neuritogenesis

Reviews dealing with methodological approaches related to the analysis of hypothalamic circuitry and extensive data on the development of the major axonal tracts coursing through the hypothalamus have been recently published (107),(108),(109). Neurite outgrowth has been studied in cultures of dissociated hypothalamic cells as well (110),(111). Sex differences in neuritogenesis in neuronal hypothalamic cultures have been also suggested (112). The formation of projection pathways in and out of the hypothalamus is critical for a variety of neuroendocrine functions and its postnatal regulation is under control of neuropeptides

4.2. Hypothalamic Neuropeptides Controlling Food Related Circuits

Development of certain hypothalamic circuits depends on daily energy and food requirements. Moreover, age dependent formation of intra hypothalamic axonal connection related to regulation of food intake has been extensively described (113). Recent studies suggest that neuropeptide oxytocin is involved in energy balance control. It has been shown that hypothalamic oxytocin pathways to the brain stem contribute to the reduction of food intake (114),(115). Oxytocin-producing cells appear early in the development of the hypothalamus (116), and their maturation, and, in particular, their ability to produce oxytocin may influence the formation of hypothalamic circuits and growth of neurites. Several studies suggest that hypothalamic neurons expressing orexigenic and anorexigenic peptides play a role in regulation of neurite growth in early developmental stage (117). Neurons that express α-MSH are particularly important for regulation of hypothalamic development. It has been shown that α- MSH promotes neurite elongation throughMC4R G-protein coupled receptor (118). Moreover POMC neurons together with α-MSH producing neurons send axonal projections to the brain stem suggesting a functional role in the control of food intake (119). Melanocortin α-MSH has been found to influence the differentiation of neural processes in brain neurons via increase in the levels of neurofilament proteins (120). Reduction of food intake and body weight regulated by α-MSH represents a control mechanism for maintenance of energy balance. As neuro-peptides represent large group of signaling molecules, they may act on the large number of receptors and share the mechanism of action on neurite extension with other neuropeptides. It has been shown that NPY promotes axonal growth and affects growth cone turning (121). Another orexigenic peptide orexin-A has been shown to inhibit neurite retraction (122). The same authors also observed the effect of orexin on neuronal cytoskeleton morphologic changes of actin and vimentin (123). It has been found that neuropeptide galanin stimulates neurite outgrowth (121),(124). Within the hypothalamus, neurons of the suprachiasmatic nucleus contain galanin and galanin mRNA distribution has been described in the arcuate and

dorsomedial hypothalamic nuclei aswell (125). Axon tip accumulation of Substance P, NPY, and galanin has been observed in the model of nerve injury suggesting their role in neurite sprouting (126). Moreover it has been found that ghrelin acts directly on hypothalamic neurons to block axon growth and reduce the overall length of axon extensions (127). Although not directly related to the topic of the present review, it should be mentioned that recent study demonstrated that gastric peptide ghrelin mediates neural fiber growth in the arcuate nucleus of the hypothalamus during the neonatal Period (127). Development of appetite-related hypothalamic neural projections thus remains complex involving various neuropeptides originating in the central nervous system and periphery as well.

4.3. Hypothalamic Neuropeptides Controlling Social Behavior Related Circuits

On the basis of functional and anatomical data, comparative studies have described "social behavior network" in mammals that represents the complex neural machinery for the regulation of social behavior (128). As components, medial amygdala, bed nucleus of the stria terminalis, lateral septum, and ventromedial and anterior hypothalamus have been included to the circuit. These areas are all reciprocally connected and express various neuropeptides and sex steroid hormone receptors as well. Many studies have examined the role of hypothalamic neuropeptides in social behavior. Recent studies have shown that olfactory receptor neurons participate in polysynaptic circuits with hypothalamic sub-regions, involving neuropeptides urocortins in the processing of social cues (129),(130). It is known for a long time that vasopressin and oxytocin enhance social recognition (131). Neural mechanisms regulating social cognition and affiliative behavior always include oxytocin action (132). Traditionally, it is believed that oxytocin and vasopressin are released within the hypothalamic and limbic areas from axons, dendrites, and cell bodies resulting in regulation of mating, reproductive, and affiliative behavior (133). Particularly detailed review on central oxytocin pathways in the development has been recently published (134). Embryonic hypothalamus produces immature oxytocin and cells start to generate mature (amidated) oxytocin after birth. Authors suggest that oxytocin axons grow from hypothalamus to forebrain regions and to brain stem/spinal cord after weaning (134). Individual oxytocin neuronal projections can be found in the bed nucleus of the stria terminalis and the lateral hypothalamic area (135). Although the bodies of oxytocin neurons are mainly restricted to the hypothalamus, oxytocin fibers are spread throughout the entire brain (132). Oxytocin increases the firing of inhibitory hippocampal neurons (136). Recent study has reported that oxytocin is involved in the regulation of social behavior through special cortical circuit (137). A number of studies suggest that oxytocin modulates social perception, social cognition, and social behavior in humans. Recent reviews have been published dealing with the role of oxytocin and vasopressin in social behavior (138),(139). Neural circuitry for social cognition depends on oxytocin and vasopressin receptor density in specific brain regions (140),(141). Link between the individual variation in social behavior and neuropeptidergic systems including oxytocin system has been repeatedly suggested (142). Oxytocin has sex-specific effects and it can contribute to gregariousness in both sexes in different species (143). It can be suggested that contribution of specific peptide cell groups in the hypothalamus is important for pair bonds.

5. Conclusion

Multiple studies have observed that neurospheres can be grown from adult hypothalamus and that BrdU incorporation is observed in hypothalamic neurons, consistent with the possibility that ongoing neurogenesis can occur in this brain region (17),(88),(16),(144),(145),(146). However, definitive evidence for ongoing postnatal hypothalamic neurogenesis requires the identification of the stem/progenitor cell population that give rise to newborn neurons, which until recently has been lacking. The identification of β2 tanycytes as neural progenitors capable of generating hypothalamic neurons in vivo, should both facilitate studies into the functional role of adult hypothalamic neurogenesis, as well as spur studies aimed at identifying other neural progenitor population in the hypothalamus (73). Neural progenitor cells were reported in many areas of the brain (147), and consistent neurogenesis was reported in several new areas other than SVZ and hippocampus, such as the Amygdala (148), and hypothalamus. The ability of these new neurons to contribute to adult brain function is yet to be studied with more specific ablation experiments. The local infusion of anti-mitotic drugs into the third ventricle or directly into the hypothalamus may provide valid approaches to eliminate proliferating cells along the ventricle 12, but site-specificity remains to be addressed in further experiments utilizing, for example, genetically modified animals. It is necessary to understand neuronal cell apoptosis in a normal hypothalamus, as in the avian song nucleus neuron death is necessary for recruiting of new neurons (149). Apoptosis of existing neurons may instruct the integration of new neurons, with this type of plastic change contributing to weight control. Hormones also have important roles in regulating hypothalamus neurogenesis (150). More research needs to be done to test how widespread hypothalamic neurogenesis is during adulthood, or among different species.

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