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Review

Hypothalamic neurogenesis in the adult brain

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ABSTRACT

Adult-born new neurons are continuously added to the hippocampus and the olfactory bulb to serve aspects of learning and perceptual functions. Recent evidence establishes a third neurogenic niche in the ventral hypothalamic parenchyma surrounding the third ventricle that ensures the plasticity of specific brain circuits to stabilize physiological functions such as the energy-balance regulatory system. Hypothalamic lesion studies have demonstrated that regions associated with reproduction-related functions are also capable of recruiting newborn neurons to restore physiological functions and courtship behavior. Induced by lesion or other stimulation, elevated neurotrophic factors trigger neurogenic cascades that contribute to remodeling of certain neural circuits to meet specific transient functions. This insight raises the possibility that event-specific changes, such as increased GnRH, may be mediated by courtship-sensitive neurotrophic factors. We will discuss the potentially integral and ubiquitous roles of neurogenesis in physiological and biological phenomena, roles that await future experimental exploration.

1. Introduction

Postnatal neurogenesis is conserved across species, from crustaceans (Harzsch and Dawirs, 1996) to higher vertebrates, including birds (Goldman, 1998; Goldman and Nottebohm, 1983), rodents (Alvarez-Buylla and Lim, 2004; Cameron et al., 1993; Kempermann et al., 1997), primates (Gould et al., 1999b; Kornack and Rakic, 1999), and humans (Arvidsson et al., 2002; Eriksson et al., 1998). In phylogenetically more recent species, however, postnatal neurogenesis appears to be more limited to specific events and specific locations in the brain. For example, it is widely acknowledged that adult neurogenesis in mammals is confined to the hippocampal dentate gyrus and the subependymal layer of the subventricular zone, SVZ (Gage, 2002; Gage et al., 1998). The SVZ neurogenic pool contributes to the olfactory bulb (Lois and Alvarez-Buylla, 1994), the substantial nigra (Zhao et al., 2003), the amygdala and adjoining cortex (Bernier et al., 2002), and striatum (Bedard et al., 2002, 2006; Dayer et al., 2005, but see Luzzati et al., 2006), and to various telencephalic regions of song bird brain, of which most prominent are some of the song control nuclei (Goldman, 1998; Goldman and Nottebohm, 1983). Findings suggesting that adult neurogenesis occurs in the hypothalamus have been met with skepticism. In 2004, a landmark study (Markakis et al., 2004) isolated neural progenitor cells from the hypothalamus. Subsequently, research identifying neurogenically rich areas of the hypothalamus (Kokoeva et al., 2005; Lee et al., 2012) unveiled a critical role for adult neurogenesis in specific physiological mechanisms, endocrine functions and the behavioral control of hypothalamic functions.

This review will cover (1) evidence for a neurogenic niche in the adult hypothalamus, (2) evidence that adult neurogenesis can be induced by lesions in the hypothalamic regions outside of the neurogenic niche, (3) discussion of the ways in which the unique properties of adult neurogenesis and their link to neurotrophic factors may underlie the adaptive nature of multiple functions of the hypothalamus as well as the hippocampus and SVZ, and (4) critical assessment of many published articles linking adult neurogenesis and behavior, with a call for more stringent criteria for identifying new neurons in studies of the endocrine and behavioral implications of neurogenesis.

2. Neurogenic Niche in the hypothalamus

2.1. The 3rd ventricle

The first evidence that the adult hypothalamus is capable of neurogenesis was demonstrated in culture media (Evans et al., 2002). Blocks from adult hypothalamic tissue were labeled with antibodies to several neuronal and astrocyte markers indicating the presence of mitotic cells at this level. Next, Markakis et al. (2004) identified a range of hypothalamic peptides including corticotrophin-releasing hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone, somatostatin, thyrotropin-releasing hormone, oxyotocin and vasopressin from neuronal progenitor hypothalamic culture. These results were obtained in 7-week old adolescent rats and suggested that hypothalamic

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tissues not only retain the ability to generate new neurons but also exhibit various peptide and protein hormone phenotypes normally found in the adult hypothalamus. Are these results also found in fully mature rats? Using adult male rats (8-weeks old), Xu et al. (2005) identified neural progenitor cells in the ependymal layer (cell layer bordering the lumen) of the 3rd ventricle. Tracing by recombinant adenoviral infection (GFP) showed that the neuronal progenitor cells migrated to the hypothalamic parenchyma, the dorso-medial hypothalamus, latero-anterior hypothalamus and ventro-lateral hypothalamus. They found that some of these cells were tanycytes. Tanycytes are glia-like cells that line the 3rd ventricle and contact cerebrospinal fluid. Tanycytes send processes to the arcuate and ventromedial hypothalamic nuclei. They are glucosensitive and respond to several genes and signal systems that have been linked to food and energy balance. It is not clear whether all tanycytes or only a subset of them may be stimulated to generate new neurons (Bolborea and Dale, 2013).

When these GFP-labeled cells were co-labeled with a marker for newborn cells (BrdU, an analogue for thymidine that is incorporated into the DNA of dividing cells) and a neuron-specific marker, NeuN, 3D confocal imaging demonstrated that these labels were co-localized into single cells. This method provides strong evidence that the double- or triple-labeled cells in the parenchyma have migrated from their birthplace in the neurogenic layer of the ventricular zone. Thus, the neural progenitor cells in the adult 3rd ventricle migrate and differentiate into mature neurons in the hypothalamus.

2.2. Paraventricular zone and periventricular zone

A further study (Perez-Martin et al., 2010) of the 3rd ventricle in the adult rat distinguished the following three zones in the 3rd ventricle wall: a dorsal zone, which is populated with non-proliferating multi-ciliated ependyma; a midlevel zone, with an abundance of subependymal labyrinths typical of the SVZ adult neurogenic niche of the lateral ventricle, and a ventral zone, which has a typical tanycyte ependyma. Compared to the ventral zone, which associates with the median eminence, proliferative activity in the midlevel zone, which includes paraventricular and periventricular zones, was low without stimulation by insulin-like neurotrophic factor, IGF-I. These newborn neurons were identified by double labeling them with neuron-specific markers, such as NeuN, and verifying their phenotype by electron microscopic analysis. The proliferative activity in the 3rd ventricle was generally low compared to that in the subgranular zone of the hippocampal dentate gyrus and subventricular zone of the lateral ventricle (SVZ).

In this review, we take the position that the SVZ refers to the lateral ventricle where an abundant neurogenic activity has been reported. The third ventricle is part of the ventricular system in the central nervous system; however, its proliferative activity is less abundant than in the lateral ventricle, and it does not appear to give rise to neurogenesis outside of the hypothalamic niche. It seems appropriate therefore to reserve the term SVZ for the subventricular zone of the lateral ventricle and to consider the tanycyte cells in the median eminence as a third separate neurogenic niche.

3. Functions of newborn neurons in the adult hypothalamus

3.1. 3rd ventricle newborn cells and fat-responsive mechanisms

The link of adult-born neurons to the 3rd ventricle became known rather serendipitously during efforts to account for the intriguing finding that the neurocytokine ciliary neurotrophic factor (CNTF) causes anorexia and weight loss (Gloaguen et al., 1997). CNTF and its analogue Axokine were developed as drugs to lower body weight. The drug's appeal rests on the fact that its weight losseffect continues for weeks, in some cases up to 12 months, after cessation of treatment (Ettinger et al., 2003). However, this energy-control effect does not seem to come from leptin-mediated signal transduction mechanisms, which are normally activated to reduce food intake (Lambert et al., 2001). Because leptin-treated animals do not maintain their body weight after cessation of treatment, Kokoeva et al. (2005) focused on another known effect of CNTF, namely, its mitogenic potency. To address whether CNTF triggers hypothalamic neurogenesis in the treated obese animals, adult mice were fed a high-fat diet for 2 months followed by 7 days of continuous infusion of CNTF or saline into the lateral ventricle of the brain. The brains (hypothalamus) were examined for the presence of newborn cells (BrdU positive) at 7 days post surgery, co-labeling with markers for immature neurons (TuJ1) and mature neurons (Hu), and the results were further confirmed with 3D confocal imaging analysis at 42 days post surgery. CNTF-treated mice showed dramatic increases of BrdU-positive cells as well as immature and mature new neurons. These findings suggest that the continued reduction of body weight in CNTF-treated mice is mediated by the mitogenic effect of CNTF. Newborn cells were also present in saline-treated animals but at a lower level than in CNTF-treated animals, suggesting that newborn cells are normally generated in the hypothalamic parenchyma, arcuate nuclei, and ventromedial and dorsomedial nuclei, which are all well-known hypothalamic sites for energy-balance regulation. Specifically, these nuclei contain neuropeptide Y (NPY) and pro-opiomelanocortin (POMC) neurons; the former trigger food intake and the latter reduce food intake. Some of the newborn cells express POMC and STAT3 signal transduction after leptin treatment, suggesting that these newborn neurons acquired responsiveness to leptin.

These findings suggest that the CNTF-induced increase in newborn neurons might be the mechanism by which long-term weight loss is sustained after cessation of CNTF. This was experimentally verified by the finding that, when an anti-mitotic drug, Ara-C (cytosine-darabinofuranoside), blocked neurogenesis, mice fed a high-fat diet lost weight during CNTF treatment but regained weight after cessation of Ara-C treatment. Importantly, Ara-C at the dose used was shown not to affect STAT3 phosphorylation. The fact that animals given a high-fat diet could not regulate energy balance by reducing intake (they remained fat) is consistent with the fact that obesity has been shown to be leptin resistant (Heymsfield et al., 1999). A murine study (McNay et al., 2012) suggests that, whereas existing neurons might be insensitive to leptin, newborn neurons can activate signal transduction in lieu of their responsiveness to leptin. An intriguing question is whether animals fed a normal diet would maintain their weight after being given Ara-C treatment. Such a study could determine when neurogenesis is normally activated to achieve energy homeostasis. A further question is whether there is a special neurogenic niche in the hypothalamus that regularly provides new neurons.

The aforementioned studies suggest that the adult hypothalamus retains the capacity for neurogenesis, with the median eminence being the most proliferative area. Interestingly, there is prominent ventricular neurogenesis in the intact adult frog hypothalamus (Polenov and Chetverukhin, 1993). Hypothalamic neurogenesis may be phylogenetically conserved.

3.2. The median eminence: a neurogenic niche in the hypothalamus?

Recently, Lee et al. (2012) identified the median eminence as the most neurogenic area in the hypothalamus. Transgenic mice were used to selectively map the fate of tanycytes and their progeny. Tanycytes were shown to give rise directly to neurons in vivo (Fig. 1). By tracking quantitative changes in the region of the