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Review

Functional implications of hypothalamic neurogenesis in the adult mammalian brain

Daniel A. Lee[a,b,*], Seth Blackshaw[c,d,e,f,g,**]

[a] Division of Biology, Pasadena, CA 91125, USA
[b] California Institute of Technology, Pasadena, CA 91125, USA
[c] Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore 21287, MD, USA
[d] Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore 21287, MD, USA
[e] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore 21287, MD, USA
[f] Center for High-Throughput Biology, Johns Hopkins University School of Medicine, Baltimore 21287, MD, USA
[g] Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore 21287, MD, USA

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ABSTRACT

Adult neurogenesis represents a striking example of structural plasticity in the mature brain. Research on adult mammalian neurogenesis today focuses almost exclusively on two areas: the subgranular zone (SGZ) in the dentate gyrus of the hippocampus, and the subventricular zone (SVZ) 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. It remains to be seen what other functional roles adult hypothalamic neurogenesis may play. 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.

Contents

Abbreviations: Ara-C, cytosine-b-d-arabinofuranoside; BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CNTF, ciliary neurotrophic factor; CNS, central nervous system; HFD, high-fat diet; HPZ, hypothalamic proliferative zone; HVZ, hypothalamic ventricular zone; ME, median eminence; SGZ, subgranular zone; SVZ, subventricular zone.

* Corresponding author at: California Institute of Technology, Pasadena, CA 91125, USA. Tel.: +1 4439558535.
** Corresponding author at: Johns Hopkins School of Medicine, Baltimore, MD 21287, USA. Tel.: +1 4432875609.
E-mail addresses: leed@caltech.edu (D.A. Lee), sblack@jhmi.edu (S. Blackshaw).

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1. Introduction

> "Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated.
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> -Santiago Ramón y Cajal, 1928

For more than a century, medical science clung to a fundamental dogma: the adult brain is a static structure, and human beings are born with all the brain cells they will ever have. Over the last 15 years, however, studies have shown that neurogenesis, the generation of newborn neurons, occurs in the postnatal and adult human brain (Eriksson et al., 1998; Curtis et al., 2007; Quinones-Hinojosa and Chaichana, 2007). 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 Altman and Das (1965). However, the functional relevance of these findings was not clear at the time, and several decades passed before this finding aroused wide interest. It was not until the work of Nottebohm and colleagues in the mid-1980s, which demonstrated that newborn neurons in the adult songbird CNS were auditory-responsive, that the capacity of newborn neurons to functionally integrate into local neural circuitry was broadly accepted (Paton and Nottebohm, 1984; Alvarez-Buylla et al., 1988). Methodological advancements in electron microscopy techniques revealed that adult-generated mammalian hippocampal neurons could survive for an extended period and receive synaptic inputs (Kaplan and Hinds, 1977; Kaplan and Bell, 1984), further suggesting that neurogenesis could modify neural circuits. Advances in immunohistochemistry combined with ^{3}H-thymidine-labeling demonstrated that adult neurogenesis was a robust phenomenon (Cameron et al., 1993). Immunohistochemical detection of neuronal markers and the introduction of bromodeoxyuridine (BrdU), a synthetic thymidine analog lineage tracer of DNA replication (Kuhn et al., 1996), further propelled the understanding of adult neurogenesis in the mammalian CNS by allowing for broader visualization and stereological quantification of newborn neurons (Ming and Song, 2005).

Research on adult mammalian neurogenesis today focuses almost exclusively on two areas: the subgranular zone (SGZ) in the dentate gyrus of the hippocampus, where new dentate granule cells are generated, and the subventricular zone (SVZ) of the lateral ventricles, where new neurons are generated and migrate through the rostral migratory stream to the olfactory bulb (Ming and Song, 2005, 2011; Lie et al., 2004; Gould, 2007). However, neurogenesis has been reported in multiple brain regions outside the SGZ and SVZ (Gould, 2007), such as the basal forebrain (Palmer et al., 1995), striatum (Pencea et al., 2001; Reynolds and Weiss, 1992), amygdala (Rivers et al., 2008), substantia nigra (Lie et al., 2002), subcortical white matter (Nunes et al., 2003), and more recently the hypothalamus (Kokoeva et al., 2005; Migaud et al., 2010; Lee et al., 2012).

These findings, however, have been met with relatively subdued interest from the field, as the absolute levels of neurogenesis reported *in vivo* are substantially lower than that observed in the SVZ and SGZ. An important qualification to this assumption is that the ability to detect ongoing neurogenesis outside the highly vascularized SVZ and SGZ may be limited by the inadequacy of traditional methods used to reveal new-born neurons. Recent methods, such as intracerebroventricular (icv) delivery of BrdU, demonstrate that new cells are born continuously and in substantial numbers in the adult murine hypothalamus and that many of these cells appear to differentiate into neurons (Kokoeva et al., 2007). Additionally, very small numbers of neurons in classically neurogenic regions such as the hippocampus have been found to be critical to the regulation of memory formation (Han et al., 2009). Thus, even if levels of neurogenesis are low, this does not mean this process is not physiologically important.

While these studies on neurogenesis outside the SVZ and SGZ represent only a small fraction of the published studies on adult neurogenesis, the prospect of hypothalamic neurogenesis has aroused substantial interest due to this region's role as a master regulator of neuroendocrine function. Furthermore, this region also 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 behaviors. It is also well established that various hypothalamic neuronal subtypes display high levels of morphological plasticity, suggesting that newly generated neurons may integrate quite readily into existing hypothalamic neural circuitry (Theodosis et al., 2004, 2006; Prevot et al., 2010).

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.

2. Postnatal and adult hypothalamic neurogenesis

Among the first studies describing observations of hypothalamic neurogenesis, were a series of experiments in which co-intraventricular infusion of brain derived neurotrophic factor (BDNF) and the proliferative lineage tracer BrdU led to increased levels of BrdU labeling, not only in the SGZ and SVZ, but also in the hypothalamus, striatum, and other forebrain regions (Pencea et al., 2001). Within the hypothalamic parenchyma, these BrdU labeled cells were found in a widely scattered pattern with the density of labeled cells declining as a function of distance from the ventricular wall (Pencea et al., 2001). Notably, the fraction of BrdU^{+} cells co-labeled with βIII-tubulin, a neuron-specific marker, was substantially higher in the hypothalamus (~42%) than near the SVZ (~27%). Subsequent studies used BrdU incorporation to provide evidence for FGF and CNTF-induced neurogenesis in the adult hypothalamus (Xu et al., 2005; Kokoeva et al., 2005; Perez-Martin et al., 2010). While these studies suggested that adult neurogenesis, as measured by BrdU incorporation, can occur in the mammalian hypothalamus, the non-physiological levels of growth factors used in these experiments made it unclear to what degree adult neurogenesis occurs in basal conditions.

Studies into physiological levels of hypothalamic neurogenesis have been hampered by the lackluster observation of newborn neurons with a single peripheral pulse of BrdU, as generally carried out in studies of neurogenesis in the SVZ and SGZ. This may be due to a number of reasons including, but not limited to, permeability of blood–brain barrier, the existence of relatively slow dividing progenitors in the hypothalamus, and a more limited temporal neurogenic window in the hypothalamus *versus* other neurogenic niches in the brain. Firstly, parenchymal exposure to circulating levels of BrdU following a single peripheral pulse is most likely to be exceeding low compared to ventricular-associated