Published in final edited form as:
Neurosci Biobehav Rev. 2009 March ; 33(3): 232–252. doi:10.1016/j.neubiorev.2008.08.007.

Adult Hippocampal Neurogenesis: Regulation, Functional Implications, And Contribution to Disease Pathology

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Abstract

It is now well established that the mammalian brain has the capacity to produce new neurons into adulthood. One such region that provides the proper milieu to sustain progenitor cells and is permissive to neuronal fate determination is located in the dentate gyrus of the hippocampus. This review will discuss in detail the complex process of adult hippocampal neurogenesis, including proliferation, differentiation, survival, and incorporation into neuronal networks. The regulation of this phenomenon by a number of factors is described, including neurotransmitter systems, growth factors, paracrine signaling molecules, neuropeptides, transcription factors, endogenous psychotropic systems, sex hormones, stress, and others. This review also addresses the functional significance of adult born hippocampal granule cells with regard to hippocampal circuitry dynamics and behavior. Furthermore, the relevance of perturbations in adult hippocampal neurogenesis to the pathophysiology of various disease states, including depression, schizophrenia, epilepsy, and diabetes are examined. Finally, this review discusses the potential of using hippocampal neurogenesis as a therapeutic target for these disorders.

Keywords

Neurogenesis; hippocampus; depression; schizophrenia; epilepsy; diabetes; cognition; serotonin; stress; antidepressants; antipsychotics; BDNF

1. Adult mammalian neurogenesis: historical perspective

> "In the adult centres, the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated."
>
> - Santiago Ramon y Cajal, 1913

This statement highlights what was one of the central dogmas of neuroscience, that neurogenesis was restricted to prenatal and early postnatal development, and that the adult mammalian brain was unable to facilitate this process. However, in 1912, Ezra Allen provided the first hint of evidence that new neurons could be born in the adult mammalian brain, by showing mitotic figures in the walls of the lateral ventricles of albino rats up to 120 days of age (Allen, 1912). It was not until the 1960's where more evidence of the phenomenon was

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shown in the brain of adult rats. Joseph Altman and colleagues used tritiated thymidine, a nucleoside that is taken up by cells synthesizing DNA in preparation for cell division, to provide autoradiographic evidence for the production of new neurons in the dentate gyrus of the hippocampus in adult rats (Altman, 1963; Altman and Das, 1965b). He was also the first to find the postnatal generation of cells in the subventricular zone (SVZ) (Altman and Das, 1965a) and described in detail their migration path to the olfactory bulb where they became neurons (Altman, 1969). However, at the time, these results were not accepted by the neuroscience community because there was insufficient evidence that the labeled cells were neurons, and it was thought that cells undergoing DNA repair might been partly responsible for the labeling.

Fifteen years later, Michael Kaplan corroborated the results of Altman in the hippocampus and olfactory bulb by using electron microscopic techniques to prove the neuronal nature of the cells labeled with tritiated thymidine (Kaplan and Hinds, 1977; Kaplan and Bell, 1984; Kaplan et al., 1985). Since the cellular phenotype was based on purely morphological criteria, and neuron-specific immunohistochemical markers did not yet exist, the vast majority of the neuroscience community still did not accept Kaplan's results.

Fernando Nottebohm, demonstrating that a substantial number of new neurons are produced in the song system of adult birds (Goldman and Nottebohm, 1983; Burd and Nottebohm, 1985), rekindled the interest of studying adult mammalian neurogenesis in the 1980's. Heather Cameron and Elizabeth Gould made the third rediscovery of adult hippocampal neurogenesis (Gould et al., 1992; Cameron et al., 1993b) in the rat. It was during this time in the early 1990's, that 5-bromo-3'-deoxyuridine (BrdU) was developed. BrdU labeling is conceptually similar to tritiated thymidine, in that it labels mitotically active cells. However, BrdU is detected using immunohistochemistry and can be combined with neuronal and/or glial markers in order to identify cellular phenotype using confocal microscopy.

Adult hippocampal neurogenesis has now been demonstrated in mammals more related to humans. It has been shown to occur in the tree shrew, an animal phylogenetically between insectivores and primates (Gould et al., 1997). This process has also been demonstrated in primates, including the marmoset, a New World monkey (Gould et al., 1998), as well as in the macaque, an Old World primate (Gould et al., 1999c; Kornack and Rakic, 1999). Although the relative rate of hippocampal neurogenesis in the adult macaque is approximately 10-fold lower than in the adult rodent (Kornack and Rakic, 1999), the majority of these newly born cells mature into neurons, similar to the rodent (Gould et al., 2001). Moreover, the rate of neurogenesis in the dentate gyrus was lower in older macaques and decreased linearly with age (Leuner et al., 2007). This decline occurs in midlife before the onset of old age, and was comparable to the decline found in rats and mice (Leuner et al., 2007). Most importantly, adult hippocampal neurogenesis has been measured in human post-mortem tissue using BrdU (Eriksson et al., 1998) and Ki-67 (Reif et al., 2006). Recently, *in vivo* imaging has been used to identify a metabolic biomarker for neural stem and progenitor cells in the brains of living humans (Manganas et al., 2007). This biomarker allowed for the detection and quantification of neural precursor cells, and demonstrated an age-related decline from preadolescence (8-10 years old) to adulthood (30-35 years old) in humans (Manganas et al., 2007). This age-related decline in proliferative activity strikingly parallels the decline observed in rodents and primates. Forty years following the original description by Altman, adult mammalian neurogenesis has been firmly established across distinct species and has finally gained acceptance by the neuroscience community.

2. Neurogenic brain regions

A brain region that supports neurogenesis is classified as neurogenic. Neurogenic implies the presence of immature precursor cells and a microenvironment that is permissive for the production of new neurons. In the adult mammalian brain, there are two neurogenic regions that are generally accepted, the olfactory system and the hippocampus. In the olfactory system, precursor cells reside in the anterior portion of the SVZ in the walls of the lateral ventricles, migrate by 'chain migration' along the rostral migratory stream (RMS) into the olfactory bulb, where they differentiate into granule or periglomerular inhibitory interneurons (Lois and Alvarez-Buylla, 1993; Doetsch et al., 1999). In the hippocampus, the precursor cells are found in the subgranular zone (SGZ) of dentate gyrus. These cells arise in the SGZ and migrate into the granule cell layer (GCL) where they mature into functionally excitatory granule cells. In addition to these two regions, there has been evidence for the production of new neurons in other adult brain areas, including the neocortex (Gould et al., 1999a; Gould et al., 2001; Dayer et al., 2005), striatum (Bedard et al., 2006; Luzzati et al., 2006), amygdala (Fowler et al., 2002), and hypothalamus (Fowler et al., 2002; Kokoeva et al., 2005), though there have been conflicting reports (Benraiss et al., 2001; Kornack and Rakic, 2001; Ehninger and Kempermann, 2003; Chmielnicki et al., 2004). The process of neurogenesis will be described in detail below as it occurs in the adult hippocampus.

3. Neurogenesis: A complex multi-step process

Adult neurogenesis is the production of new neurons in the adult brain. The term comprises a complex process that begins with the proliferation of progenitor cells, followed by commitment to a neuronal phenotype, morphological and physiological maturation with the development of functional neuronal characteristics, and ends with the existence of a new functioning, integrated neuron.

3.1. Proliferation

Adult central nervous system (CNS) stem cells are characterized by their proliferative capacity to continue to undergo mitosis and their multipotency, that is, the ability to generate a multitude of different neuronal and glial lineages (Sohur et al., 2006). Multipotent progenitors of the adult brain are proliferative with only limited self-renewal that can differentiate into at least two different cell lineages (McKay, 1997; Weissman et al., 2001). Lineage-specific precursors, or progenitor cells, are cells with restriction to one distinct lineage (i.e. neuronal, glial, and oligodendroglial). All of these types of cells are broadly classified as 'precursors.' However, the identity of 'true' CNS stem cells is still unknown.

In the adult hippocampus, the precursor cells of the dentate gyrus reside in a narrow band of tissue, the SGZ, a layer about three nuclei wide, including the basal cell band of the granule cell layer and a two nucleus-wide zone into the hilus. The SGZ contains a heterogeneous population of precursor cells. The first type of precursor cell, quiescent neural progenitors, is the putative stem cell residing in the hippocampus. These cells are multipotent, show a characteristic morphology resembling radial glia, a triangular soma with a thick apical process that reaches into the granule cell layer, upon where it branches massively (Seri et al., 2001). This cell type can be distinguished into two classes based on their orientation in the SGZ: radial astrocytes (rA) and horizontal astrocytes (hA) (Seri et al., 2004). They also express the precursor cell marker protein, nestin (class IV intermediate filament), and have astrocytic properties that include the expression of the astrocytic marker protein, glial fibrillary acidic protein (GFAP), but not S100β, another astrocytic protein (Seri et al., 2004). These cells have vascular endfeet in the SGZ and similar electrophysiological properties, such as passive membrane properties and potassium currents (Filippov et al., 2003; Fukuda et al., 2003). They have been reported to divide rarely (Kronenberg et al., 2003), which would be expected, due

to their tree-like morphology and extension between blood vessels. It has been suggested that the quiescent neural progenitors undergo asymmetric division, giving rise to one daughter cell and one neuronal lineage restricted progenitor daughter cell (Kempermann et al., 2004). This hypothesis supports the idea that the astrocytic progenitors are the highest-ranking stem cells in the SGZ.

3.2. Differentiation and migration

The daughter cells of quiescent progenitors express nestin and Sox2, but not GFAP, and have been named amplifying neural progenitors (ANPs) (Encinas et al., 2006). These cells are labeled with BrdU at high frequency, indicating that they are mitotically active. They are often seen in clusters extending along the SGZ, and a fraction of these cells are seen separating from the quiescent progenitors after mitosis (Encinas et al., 2006). This suggests that by undergoing asymmetric division, the quiescent neural progenitors give rise to the ANPs. The next class of cells are D cells (D2, D3), which are the intermediate precursors in the generation of new granule neurons (Seri et al., 2001). These cells have a large, round or ovoid soma with short cytoplasm extensions oriented tangentially and a complex pattern of electrophysiological characteristics clearly different from astrocytes (Filippov et al., 2003). They no longer express nestin or Sox2, but begin to express the polysiliated form of the neural cell adhesion molecule (PSA-NCAM). (Seri et al., 2004). Both subclasses express the microtubule associated protein, doublecortin (DCX) (Encinas and Enikolopov, 2008) that is associated with both the initiation of neuronal differentiation and migration (Francis et al., 1999), and Prox-1, an early-expressed neural lineage-specific homeobox transcription factor selective to dentate granule cells (Kronenberg et al., 2003). The developing granule cells go through a transient stage of DCX and PSA-NCAM expression (Seki and Arai, 1993; Rao and Shetty, 2004). D2 cells have short thick process, while D3 cells have the characteristics of immature granule neurons, including prominent, frequently branched, radial processes that extended through the granule cell layer and thin processes projecting into the hilus (Seri et al., 2004). This evidence suggests that ANPs divide and give rise to postmitotic D2 cells that mature through a D3 stage to form new granule neurons (Seri et al., 2004). At no later time-point has an overlap between glial and neuronal markers or properties been found, which suggests that if the precursor cells of the SGZ are multipotent *in vivo* and can give rise to both neurons and glia, this fate choice should occur on the level of the quiescent neural progenitor or the amplifying progenitor cell. In the rodent SGZ, DCX is strictly associated with neuronal lineage (Rao and Shetty, 2004). However, in humans, it has recently been shown that DCX is present in several cellular compartments of differentiated astrocytes in the neocortex (Verwer et al., 2007).

3.3. Neuronal maturation

According to three dimensional reconstruction, D-cell clusters sit on a nest of rAs, making frequent contact with mature granule neurons (Seri et al., 2004). Postmitotic differentiation is characterized by the transient expression of DCX and the calcium-binding protein calretinin, and expression of the neuronal markers NeuN and calbindin (Kempermann, 2005). The largest part of dendrite and axon formation is during this period (Brandt et al., 2003; Ambrogini et al., 2004), including the transient appearance of basal dendrites (Ribak et al., 2004). Axon elongation occurs rapidly after the cells have become postmitotic (Hastings and Gould, 1999) and appropriate axonal connections to CA3 are established within 4-10 days of their birth (Markakis and Gage, 1999). During the early stages of maturation (within first week after birth), newborn cells display high input resistance and low membrane capacitance (Esposito et al., 2005; Ge et al., 2006), and start to receive functional γ-amino butyric acid (GABA)ergic, but not glutamatergic, inputs (Esposito et al., 2005; Overstreet Wadiche et al., 2005; Ge et al., 2006). These cells are also excited by GABA, which is crucial for the establishment of functional GABAergic and glutamatergic synaptic inputs and for regulating dendritic development (Ge et al., 2006; Overstreet-Wadiche et al., 2006a). During the second and third

weeks of maturation, the newborn cells exhibit more, but not fully, mature electrophysiological features. Functional glutamatergic inputs have been found to appear between 14 and 18 days (Esposito et al., 2005; Ge et al., 2006; Overstreet-Wadiche et al., 2006a), along with the formation of dendritic spines and with continued dendritic growth (Zhao et al., 2006). Seven weeks after division, new granule cells can generate action potentials, show electrophysiological responses very similar to those of surrounding older cells, and are integrated into the hippocampal circuitry (van Praag et al., 2002). Newly born neurons also display a lower threshold for the induction of long-term potentiation (LTP) (Schmidt-Hieber et al., 2004). Recent evidence showed that the survival of newly-born neurons is competitively regulated by their own N-methyl-D-aspartate (NDMA)-type glutamate receptor during a short period soon after birth, suggesting that the survival of new neurons and their incorporation into existing networks are regulated in an input-dependent manner (Tashiro et al., 2006).

3.4. Cell death and cell numbers

The precursor cells in the adult SGZ produce a large surplus of cells destined for neuronal lineage and a surplus of immature neurons. The cells not recruited into function are eliminated by apoptotic cell death (Biebl et al., 2000). Most cell death seems to occur once the cells have exited the cell cycle, become post-mitotic, and express both DCX and calretinin (Kempermann, 2005). It is hypothesized that elimination is the default pathway, counteracted by survival-promoting rescue effects. The elimination of cells is rapid, with the number of new cells remaining stable two to three weeks after exit from the cell cycle (Kempermann et al., 2003). Adult neurogenesis decreases dramatically with age, which correlates with a lack of measurable growth of the dentate gyrus later in life (Kempermann, 2005). This age-related decline in hippocampal neurogenesis has recently been demonstrated in living humans by imaging a biomarker specific to neural progenitor cells (Manganas et al., 2007). Evidence from studies in rats suggests that this reduction in neurogenesis is due to a large decrease in cell proliferation, slowed migration of cells from the SGZ into the GCL, and a reduction in cell differentiation into neuronal phenotypes (Heine et al., 2004a; McDonald and Wojtowicz, 2005).

4. Regulation

Adult hippocampal neurogenesis is bi-directionally regulated by many factors, both intrinsic and extrinsic. They range from neurotrophins, antidepressants, stress, opioids, and seizures, to physical activity, learning, and hormones. Dynamic factors have been shown to affect the different phases of neurogenesis, including expansion (proliferation), differentiation (i.e. neuronal vs. glial), and survival. Therefore, the net effect on neurogenesis often results from different combinations of effects on individual stages of neuronal development. The following sections will provide an overview of many of the factors that regulate hippocampal neurogenesis.

4.1. Progenitor cell microenvironment

The stem cell niche consists of the precursor cells and the cells around them that form the permissive microenvironment. It is in this area that cell-to-cell communication occurs and where the precursor cells receive local regulatory cues. The quiescent progenitors have vascular endfeet that suits them to respond to blood-born factors (Filippov et al., 2003), though the degree of their responsiveness is unknown. In the developing brain, before chemical synapses are established, neural progenitors communicate with each other via connexin-mediated gap junctions. These types of connections persist into adulthood in the adult SGZ. Mice deficient of the connexin32 gap junction protein in a subset of oligodenrocyte progenitors, displayed increased numbers of nestin+ and NG2+ progenitors, an increased turnover of this cell population, and a reduction in terminal differentiation (Melanson-Drapeau et al., 2003). Whether connexin32, or other extracellular matrix molecules such as integrins and laminin,

regulate neurogenesis in the adult hippocampus has yet to be determined. Microglia, the immune-competent cells of the brain and part of the stem cell niche, are activated by many pathological stimuli and are capable of secreting inflammatory factors. Activation of microglia, by irradiation or bacterial lipopolysaccharide, reduced hippocampal neurogenesis (Ekdahl et al., 2003; Monje et al., 2003).

4.2. Ephrins

Two groups of cell-surface molecules that are involved in many aspects of cell migration, axon guidance, and synaptogenesis are the Eph receptor tyrosine kinases and their ephrin ligands. Eph receptors are divided into two subfamilies, EphA and EphB, and contain cytoplasmic tyrosine kinase catalytic domains that are activated after interactions with cell surface-bound ephrin ligands. EphB receptors are specifically expressed in adult hippocampal progenitor cells of the dentate gyrus (Chumley et al., 2007). Mice that lack EphB1, and more profoundly EphB1 and EphB2, had significantly fewer hippocampal neural progenitors (Chumley et al., 2007). Mice that lack the EphB1 receptor or its cognate ephrin-B3 ligand also had disruptions in other aspects of adult hippocampal neurogenesis, including polarity, cell migration, and proliferation (Chumley et al., 2007).

4.3. Synapsins

Synapsins are a family of neural-enriched synaptic vesicle proteins that are comprised of three isoforms I, II, and III. In addition to playing a role in neurotransmission (Feng et al., 2002), synapsins also affect neurodevelopmental processes (Ferreira et al., 1994; Ferreira et al., 1995). Moreover, synapsin III is enriched in the cell bodies of adult neuronal progenitor cells within the hippocampus, the periventricular zone, the rostral migratory stream, and the olfactory bulb (Pieribone et al., 2002). Synapsin III knockout mice had reduced levels of cell proliferation in the adult hippocampus (Kao et al., 2008). However, these knockout mice displayed enhanced levels of cell survival, with a small increase in the proportion of newly born cells that differentiated into neurons (Kao et al., 2008). These findings suggest this synaptic vesicle protein is a regulator of proliferation, differentiation, and survival of neural progenitors in the adult hippocampus.

4.4. Cell cycle regulators

In mammalian cells, cellular proliferation is mainly controlled during the G1 phase of the cell cycle. Cyclins are cell cycle proteins that are, for the most part, positive regulators of the cell cycle. Cyclins D and E are present in the adult SGZ (Heine et al., 2004b), although cyclin D1 does not seem to be necessary for adult hippocampal cell proliferation (Kowalczyk et al., 2004). Cyclin-dependent kinases (Cdks) tightly control the cell cycle by negatively regulating cell cycle progression. Cdk1, also known as p34/cdc2, is expressed at high levels in proliferating neural stem cells (Hayes et al., 1991), and intracerebroventricular (i.c.v.) infusion of a non-selective Cdk inhibitor decreased cell proliferation in the SGZ (Mackowiak et al., 2005). $p21^{cip1}$ is a Cdk inhibitor that delays or blocks progression of the cell cycle into the S phase (Sherr and Roberts, 1999). Chronic activation of p21 can drive the cell into irreversible cell growth arrest and senescence (Sherr and Roberts, 1999), while inhibition increases cell proliferation (Gartel and Radhakrishnan, 2005). It was recently shown that p21 was expressed in the nuclei of cells in the adult SGZ (Pechnick et al., 2008). In addition, p21 knockout mice displayed elevated levels of hippocampal cell proliferation (Pechnick et al., 2008). Little is known about cell cycle regulating proteins in the adult neurogenic hippocampus, and future research in this area will provide valuable information on the effects of stimuli on cell cycle length and regulation (Eisch and Mandyam, 2007).

4.5. Growth and neurotrophic factors

Growth factors are extracellular signaling molecules that increase cell growth and maintenance. The effects of growth factor regulation of neurogenesis in the hippocampus are summarized in Table 1. Evidence suggests that epidermal growth factor (EGF) does not play an important role in regulating adult hippocampal neurogenesis. I.c.v. infusion of EGF did not enhance proliferation in the SGZ (Kuhn et al., 1997). In addition, hippocampal progenitor cells isolated from rats do not rely on EGF (Palmer et al., 1995). Fibroblast-growth factor-2 (FGF-2) has been shown to regulate hippocampal neurogenesis. Administration of FGF-2 i.c.v. to rats enhanced hippocampal neurogenesis (Rai et al., 2007), while mice lacking the FGF-1 receptor, a major receptor for FGF-2, displayed deficits in hippocampal neurogenesis (Zhao et al., 2007a). Moreover, deletion of FGF-2 from mice prevented the increase in cell proliferation normally associated with seizure or ischemia, but had no effect on baseline hippocampal neurogenesis (Yoshimura et al., 2001). Insulin-like growth factor-I (IGF-I), a peripherally produced peptide, is a potent regulator of hippocampal neurogenesis. Peripheral or i.c.v. infusion of IGF-I increased proliferation and net neurogenesis in the adult hippocampus (Aberg et al., 2000;Lichtenwalner et al., 2001;Aberg et al., 2003). Genetically modified mice that have low levels of serum IGF-I also have reductions in adult hippocampal neurogenesis (Trejo et al., 2007). Vascular endothelial growth factor (VEGF), in addition to regulating angiogenesis, is also a regulator of hippocampal neurogenesis. Infusion of VEGF i.c.v. elevated hippocampal cell proliferation (Jin et al., 2002), while another study demonstrated its role as a survival promoting factor (Schanzer et al., 2004). However, blockade of the peripheral actions of VEGF had no effect on baseline hippocampal neurogenesis (Fabel et al., 2003).

Neurotrophic factors are extracellular signaling molecules that play important roles in both the developing and adult central nervous system. The several classes of neurotrophic factors are: neurotrophins (nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin –3 (NT-3), NT-4, and NT-5 that signal through tyrosine kinase (trk) and p75 receptors), and the neurotrophic cytokines, such as ciliary neurotrophic factor (CNTF) and interleukin-6 (IL-6). Neurotrophic regulation of hippocampal neurogenesis is shown in Table 2. Chronic administration of BDNF directly into the hippocampus increased neurogenesis of granule cells (Scharfman et al., 2005). Infusion of BDNF into the lateral ventricles also enhanced neurogenesis originating from the SVZ (Zigova et al., 1998;Pencea et al., 2001). Data from genetically altered mice has not yielded totally consistent results. Heterozygous BDNF knockout mice (BDNF +/-) have been shown to display reduced levels of adult hippocampal neurogenesis (Lee et al., 2002). However, others have shown that BDNF +/- and transgenic mice that overexpress a truncated form of the trkB receptor in neurons, had higher levels of baseline cell proliferation in the hippocampus, but reduced levels of cell survival (Sairanen et al., 2005). These discrepancies could be accounted for by differences in derivation of the knockout. BDNF is also involved in the ability of other factors to regulate hippocampal neurogenesis. BDNF is important for the hippocampal neurogenesis promoting effects of an enriched environment (Rossi et al., 2006) and dietary restriction (Lee et al., 2002). It is also implicated in being important for enhancing the survival, but not proliferation, following chronic treatment with a tricyclic antidepressant (Sairanen et al., 2005). Mice that lack NT-3 expression in the brain, demonstrated impairments in differentiation, but not proliferation in the hippocampus (Shimazu et al., 2006). Mice lacking NT-4 did not show baseline changes in hippocampal neurogenesis (Rossi et al., 2006). There is no information on the role of NT-5 in adult neurogenesis. CNTF injection directly into the adult mouse brain increased cell proliferation and net neurogenesis in the hippocampus (Emsley and Hagg, 2003). Continuous infusion of NGF directly into the lateral ventricles had no effect on cell proliferation in the hippocampus, but enhanced survival (Frielingsdorf et al., 2007). The multitude of growth and neurotrophic factors in the brain likely play pivotal roles in finely regulating all the stages of hippocampal neurogenesis.

4.6. Neurotransmitter systems

The dentate gyrus of the hippocampus receives inputs from numerous brain regions. These afferents project axons which release multiple classes of neurotransmitters, including catecholamines, serotonin, glutamate and GABA, as well as acetylcholine. The regulation of adult hippocampal neurogenesis by these neurotransmitters is summarized in Table 3.

The excitatory neurotransmitter glutamate plays a major role in regulating hippocampal neurogenesis. Glutamatergic fibers originating from the entorhinal cortex converge on the dentate gyrus via the perforant path. Lesioning this pathway in the rat increased cell proliferation in the hippocampus (Gould et al., 1994; Cameron et al., 1995). In the mouse, hippocampal cell proliferation was not affected three days after lesioning the entorhinal cortex, but the survival of neurons born after the lesion was increased (Gama Sosa et al., 2004). Glutamate signals through three types of ionotropic receptors: NDMA receptors, kainic acid (KA) receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Antagonism of NMDA receptors with MK-801, increased adult hippocampal neurogenesis (Gould et al., 1994; Cameron et al., 1995; Cameron et al., 1998). Mice that express only 50% of the NR1 subunit of the NMDA receptor, displayed increased levels of adult hippocampal neurogenesis (Bursztajn et al., 2007). NR1 and NR2B subunits are absent from transiently amplifying progenitors (type 2-3 cells), but are found in GFAP-expressing cells in the SGZ, suggesting its presence in type-1 precursor cells (Nacher et al., 2007). In addition, many granule cells express both NMDA receptor subunits two weeks after birth (Nacher et al., 2007). These findings suggest that excitatory input into the hippocampus restricts baseline neurogenesis via NMDA receptors present on precursor cells and in differentiating granule neurons. On the contrary, stimulation of KA receptors, which induces seizures, produced large increases in hippocampal neurogenesis (Parent et al., 1997; Jessberger et al., 2007). In addition, chronic administration of an AMPA receptor potentiator increased hippocampal cell proliferation (Bai et al., 2003). Taken together, glutamatergic transmission plays a critical role in the regulation of hippocampal neurogenesis, but its regulation is complex and dependent on a network of different receptors.

GABA is the main inhibitory neurotransmitter in the brain and GABAergic inhibitory systems are a local network of inhibitory interneurons. The dentate gyrus contains at least seven classes of interneurons (Freund and Buzsaki, 1996) that modulate the activity of granule cells and control the ambient GABA level in the SGZ (Ge et al., 2007). In addition, neural progenitor cells and their progeny express functional GABA-A receptors, with GABA being excitatory during the first 2-3 weeks of neuronal development (Tozuka et al., 2005; Ge et al., 2006). It is unknown whether tonic and/or phasic GABA activation regulates cell proliferation, differentiation, or survival in the hippocampus. Studies have recently emerged to attempt to address the role of GABA in hippocampal neurogenesis. Application of GABA to acute brain slices increased the expression of NeuroD, a transcription factor that facilitates neuronal differentiation, in neural progenitors isolated from the hippocampus (Tozuka et al., 2005). Heterozygous deletion of the γ-2 subunit of the GABA-A receptor, specifically in immature neurons, reduced the survival of newly born hippocampal neurons, without affecting proliferation (Earnheart et al., 2007). Evidence also suggests that GABA-mediated activation is necessary for the synaptic integration of newborn granule cells in the hippocampus (Ge et al., 2006).

There are extensive noradrenergic projections from the locus coeruleus into the dentate gyrus of the hippocampus. Depletion of norepinephrine in rats by the lesioning of noradrenergic cell bodies in the locus by the selective neurotoxin, N-Ethyl-N-(2-chloroethyl)-2-bromobenzylamine (DSP-4), reduced baseline cell proliferation, without effecting cell differentiation or survival (Kulkarni et al., 2002). There is much yet to be known on the role of noradrenergic signaling in regulating hippocampal neurogenesis.

Dopaminergic fibers from the ventral tegmental area innervate the SGZ. Acute administration of 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) to mice, which selectively destroys dopaminergic neurons in an animal model of Parkinson's Disease, decreased the number of cells in the SGZ expressing the cell cycle marker protein, proliferating cell nuclear antigen (PCNA), up to 7 days post-dopamine depletion (Hoglinger et al., 2004). Rats chronically treated for either 8 or 24 days with cocaine (20 mg/kg), which blocks the reuptake of dopamine, had reduced hippocampal cell proliferation, but the differentiation and survival of newly born neurons was unaltered (Dominguez-Escriba et al., 2006). Chronic treatment (14 days) of rats with the antipsychotic haloperidol (2 mg/kg), a dopamine receptor (D2) antagonist, had no effect on hippocampal cell proliferation (Malberg et al., 2000). D3 receptors have been implicated in regulating adult neurogenesis outside of the hippocampus. Chronic administration to rats of the D3 receptor agonist, 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT), increased neurogenesis in the SVZ and neostriatum (Van Kampen et al., 2004), as well as in the substantia nigra (Van Kampen and Robertson, 2005; Van Kampen and Eckman, 2006). In mice, however, 7-OH-DPAT did not stimulate neurogenesis in the SVZ (Baker et al., 2005). Moreover, mice lacking the D3 receptor did not have deficits in SVZ proliferation (Baker et al., 2005). These data suggest potential differences in the role D3 receptors play in regulating neurogenesis across species. The role of dopamine and individual dopamine receptor subtypes in regulating adult neurogenesis in the SGZ still needs to be elucidated.

The hippocampus receives cholinergic input from the septum and the nucleus basalis of Meynert. Toxic lesioning of cholinergic basal forebrain neurons in rats, did not affect the total number of BrdU cells in the hippocampus several weeks after labeling, but reduced the production of new neurons (Cooper-Kuhn et al., 2004). Chronic administration (4 weeks) of the muscarinic receptor antagonist, scopolamine (0.75 mg/day or 3.0 mg/day), to rats, suppressed survival, but did not affect proliferation or differentiation of newly-born hippocampal cells (Kotani et al., 2006). Mice lacking the β–2 subunit of the nicotinic acetylcholine receptor showed reductions in hippocampal cell proliferation (Harrist et al., 2004). Acetylcholinesterase (AchE) inhibitors, which augment cholinergic signaling, are given to patients for the treatment of dementia associated with Alzheimer's disease. In contrast to the effects of cholinergic blockade, chronic administration (4 weeks) of the AchE inhibitor, donepezil (1 mg/kg) to mice or to rats (0.5 or 2 mg/kg), enhanced survival but not proliferation or differentiation in the hippocampus (Kaneko et al., 2006; Kotani et al., 2006). These data suggest a role for acetylcholine in regulating hippocampal neurogenesis, though the exact mechanisms and receptor interactions need to be more extensively characterized.

Serotonergic terminals originating from the dorsal and median raphe nuclei innervate multiple forebrain structures, including the hilus, molecular layers of the dentate gyrus, and the SGZ (Oleskevich et al., 1991). Serotonergic input from the raphe into the hippocampus is important for regulating hippocampal neurogenesis. Depletion of serotonin (5-HT) in adult female rats by either systemic administration of the serotonin synthesis inhibitor parachlorophenylalanine (PCPA) (Banasr et al., 2001) or by the intraraphe injection of the serotonin neurotoxin 5,7-dihyrdoxytryptamine (5,7-DHT) (Brezun and Daszuta, 1999) reduced cell proliferation and the number of immature neurons in the hippocampus. The deficit in proliferation was rescued following intrahippocampal grafts of embryonic 5-HT neurons (Brezun and Daszuta, 2000). Systemic administration of PCPA to female rats also reduced hippocampal cell proliferation and the number of PSA-NCAM cells. Administration of systemic PCPA, but not i.c.v. 5,7-DHT, to male rats reduced cell proliferation and survival in the hippocampus, as well as the number of doublecortin positive hippocampal cells (Jha et al., 2006). The caveats associated with these studies were that either only tissue levels of serotonin in the hippocampus were measured (Banasr et al., 2001) or that hippocampal norepinephrine levels were also decreased following PCPA treatment (Jha et al., 2006). It should be noted that another study in male rats,

found that systemic administration of PCPA did not affect hippocampal cell proliferation (Huang and Herbert, 2005b). The PCPA treatment regimen used in that study depleted serotonin without altering levels of other monoamines (Huang and Herbert, 2005a). Treatment with the antidepressant fluoxetine, which inhibits the reuptake of serotonin, increased hippocampal neurogenesis in rats (Huang and Herbert, 2006) and mice (Wang et al., 2008a). Adult hippocampal neurogenesis was also investigated in mice that lack the serotonin transporter throughout their life. It was found that aged mice, but not young or adult mice, displayed enhanced proliferative capacity in the hippocampus. Differentiation and survival were not affected in these mice at any age (Schmitt et al., 2007).

Although a role for serotonin in the regulation of hippocampal neurogenesis was demonstrated from the regulation of 5-HT levels, there are 15 known serotonin receptors, and it is still unclear which receptors are important for regulating this process. Recent studies have begun to address the issue of receptor specificity. Antagonism of the 5-HT_{1A} receptor reduced cell proliferation in the hippocampus in rats (Radley and Jacobs, 2002), but 5-HT_{1A} receptor knockout mice did not demonstrate reductions in proliferative activity (Santarelli et al., 2003). Activation of 5-HT_{1A} receptors with 8-hydroxy-2-(N-dipropylamino) tetralin (8-OH DPAT) enhanced proliferative capacity in the SGZ (Santarelli et al., 2003; Banasr et al., 2004). Activation of 5-HT_{1A} receptors did not affect the differentiation of the newborn cells, while its ability to regulate cell survival is still unclear (Sahay and Hen, 2007). Interestingly, the 5-HT_{1A} receptor is expressed at low levels in the rat SGZ and is restricted to mature dentate granule cells (Patel and Zhou, 2005). This suggests that the regulatory effects of serotonin on hippocampal cell proliferation via the $5HT_{1A}$ receptor is likely via indirect mechanisms (Sahay et al., 2007). Although neither activation nor antagonism of 5-HT_{1B} receptors in rats affected baseline cell proliferation, activation of 5-HT_{1B} receptors reversed the deficit in proliferation induced by serotonergic depletion (Banasr et al., 2004). In the rat, antagonism of the 5-HT_{2A} receptor decreased hippocampal cell proliferation, while activation had no effect (Banasr et al., 2004). Activation or antagonism of the 5-HT_{2c} receptor had no effect on proliferative activity in the hippocampus (Banasr et al., 2004). Subchronic administration of a 5-HT_4 receptor agonist also increased hippocampal cell proliferation in rats (Lucas et al., 2007). The roles of 5-HT_3, 5-HT_6, 5-HT_7 receptors remain to be studied. In summary, the role of serotonin in regulating adult hippocampal neurogenesis is complex, and is dependent not only on receptor subtype expression, but also the state of the organism. Moreover, serotonin signaling induces neurotrophins and growth factors that can in turn can affect neurogenesis (Duman and Monteggia, 2006).

Nitric oxide (NO) is a free radical that serves as an intercellular messenger, as well as an atypical neurotransmitter/neuromodulator in the central nervous system (Snyder and Ferris, 2000). It is produced by nitric oxide synthase (NOS) during the conversion of L-arginine to citrulline. There are three isoforms of NOS: neuronal NOS (nNOS; NOS-I), inducible NOS (iNOS; NOS-II), and endothelial NOS (eNOS; NOS-III). NOS-I is the predominant isoform in the brain (Liu et al., 2002), although the isoforms are found in other CNS cell types (Dinerman et al., 1994). In the brain, NO is synthesized in specific neurons expressing NOS-I (Bredt et al., 1990). In both humans and rodents, NOS-I and NOS-III have been found in the dentate gyrus of the hippocampus (Reif et al., 2004).

There is substantial evidence demonstrating a regulatory role for NO with respect to hippocampal neurogenesis. The two main strategies used to assess the role of NO have involved inhibition of the various enzyme isoforms that synthesize NO or augmentation of NO signaling. In rats, chronic, nonspecific pharmacologic inhibition of NOS with N^{ω}-nitro-methyl-L[D]-arginine methyl ester (L-NAME) increased cell proliferation (rats sacrificed 7 days after the last BrdU injection) in the hippocampus without affecting differentiation (Packer et al., 2003). The same study demonstrated that cell proliferation was also increased in the dentate

gyrus of genetically modified mice with a non-functional form of NOS-I (Packer et al., 2003). Cell proliferation was enhanced in mice lacking the NOS-I gene (NOS-I KO) or repeatedly administered the NOS-I specific inhibitor, 7-nitroindazole (Zhu et al., 2006). Furthermore, genetic (Zhu et al., 2006; Fritzen et al., 2007) and pharmacologic (Zhu et al., 2006) inhibition of NOS-I enhanced the survival of newly born cells without affecting fate determination. Evidence suggests that the inhibition of neurogenesis by NOS-I does not involve BDNF or VEGF (Fritzen et al., 2007), but might involve NMDA receptor function and CREB (Zhu et al., 2006). In sum, these studies suggest that NOS-I inhibits basal rates of hippocampal neurogenesis. Contrary to the effects of NOS-I inhibition, animals lacking NOS-III (NOS-III KO) showed reductions in hippocampal cell proliferation, without alterations in differentiation or survival (Reif et al., 2004). Interestingly, mice that lacked both NOS-I and NOS-III had reductions in the survival of newly born cells (Fritzen et al., 2007). There are a lack of studies that have examined the effect of augmented NO signaling on neurogenesis. One study found in mice that exogenous administration of NO using the zwitterionic polyamine/NO adduct, (Z)-1-[*N*-(2-aminoethyl)-*N*-(2-ammonioethyl) aminio] diazen-1ium-1,2-diolate (DETA/NONOate), increases cell proliferation and survival (Hua et al., 2008). The regulation of hippocampal neurogenesis by NO is complex and is differentially regulated by the activities of the three NOS isoforms.

4.7. Cannabinoid system

Neural progenitors of the hippocampus produce endocannabinoids and express the cannabinoid-1 (CB1) receptor (Aguado et al., 2005). Mice that lack the CB1 receptor displayed impairments in hippocampal cell proliferation (Jin et al., 2004), while mice that lack FAAH, an enzyme responsible for the hydrolytic elimination of endogenous cannabinoids, had increased levels of hippocampal cell proliferation (Aguado et al., 2005). Treatment of rats for 10 days with the synthetic cannabinoid, HU210, increased hippocampal neurogenesis, without altering the determination of cell fate (Jiang et al., 2005). Another study demonstrated that acute treatment with a CB1 receptor antagonist, AM251, elevated cell proliferation, while the endocannabinoid reuptake inhibitor, AM404, had no effect (Hill et al., 2006). These studies suggest a role for the endocannabinoid system in regulating hippocampal neurogenesis.

4.8. Opioid systems

Mice lacking the μ opioid receptor had normal rates of hippocampal cell proliferation, but had reductions in the number of newborn cells that survived (Harburg et al., 2007). Rats that were chronically administered morphine (Eisch et al., 2000; Kahn et al., 2005) or heroin (Eisch et al., 2000), which bind to the μ opioid receptor, showed decreased levels of cell proliferation and survival in the hippocampus; differentiation was unaffected. Interestingly, mice that lack the endogenous opioid peptide, β-endorphin, which preferentially binds to the μ opioid receptor, demonstrated no deficits in any aspects of hippocampal neurogenesis (Koehl et al., 2008). There is a lack of data examining the role of κ and δ receptor activation in the regulation of hippocampal neurogenesis.

4.9. Neuropeptides

In addition to the classical neurotransmitters, neuropeptides play an important role in CNS regulating neurogenesis. Mice lacking the neuropeptide Y-1 receptor displayed lower levels of cell proliferation (Howell et al., 2005; Howell et al., 2007) and fewer immature neurons in the adult hippocampus, but no differences in survival (Howell et al., 2005). However, another group failed to show a difference in hippocampal cell proliferation between wild type and NPY-1 receptor knockout mice (Karlsson et al., 2008). Deletion of the neurokinin-1 receptor, the preferred receptor for the neuropeptide substance P, increased hippocampal cell proliferation, but not survival (Morcuende et al., 2003). Chronic infusion of the neuropeptide

VGF (nonacronymic), which is expressed in the dentate gyrus (Snyder and Salton, 1998), increased hippocampal cell proliferation and survival (Thakker-Varia et al., 2007).

4.10. Sex hormones

Sex hormones, in both males and females, modulate adult hippocampal neurogenesis. In intact female rats, the level of cell proliferation is highest during proestrus, when estrogen levels are high, and is lower in the phases of the estrous cycle when estrogen levels are reduced (Tanapat et al., 1999). In ovariectomized females, exogenous administration of estradiol increased cell proliferation (Tanapat et al., 1999), but this stimulatory effect was dependent on the duration of treatment (Ormerod et al., 2003). However, estradiol did not affect survival (Tanapat et al., 1999). Exogenous estradiol can also reverse reductions in hippocampal cell proliferation caused by the induction of experimental Type-1 diabetes in intact male mice (Saravia et al., 2006) and aging in ovariectomized female rats (Perez-Martin et al., 2005; De Nicola et al., 2006). In addition, short-term (6 days), but not long-term (21 days) removal of estrogen in rats by ovariectomy, reduced proliferative activity and the number of PSA-NCAM cells in the hippocampus (Banasr et al., 2001).

Several studies have provided insight into the mechanisms underlying the influence of estrogen on neurogenesis. Activation of both estrogen receptor (ER) α or ERβ subtypes significantly enhanced cell proliferation in the dentate gyrus of female rats (Mazzucco et al., 2006). The central serotonergic system has also been linked to the positive neurogenic effects of estradiol in the hippocampus (Banasr et al., 2001). In addition, several studies have shown that estrogen influences 5-HT_{1A} receptors in the hippocampus and this could be the mechanism for regulating hippocampal neurogenesis (Birzniece et al., 2001).

There is a paucity of published work that addresses the neurogenic effect of androgen (Hajszan et al., 2007). In adult male rats, castration decreased new cell survival in the dentate gyrus but had no effect on cell proliferation when compared to intact male rats (Spritzer and Galea, 2007). Thirty days of exposure to testosterone increased hippocampal neurogenesis, via prolonged cell survival, of castrated adult male rats by an androgen receptor dependent mechanism (Spritzer and Galea, 2007). However, another study showed that nandrolone, a testosterone analog, reduced cell proliferation in the dentate gyrus, in both female and male rats (Brannvall et al., 2005). More work still is needed to better understand the role of male sex hormones in regulating adult hippocampal neurogenesis.

4.11. Paracrine signaling molecules

Wnt (wingless) plays an important role in maintaining self-renewal in hematopoetic stem cells (Reya et al., 2003) and in the induction of neural specification (Muroyama et al., 2002). Interaction of Wnts with their receptors can trigger several signaling pathways, including the β-catenin dependent pathway. Wnt proteins and their receptors are expressed in adult hippocampal progenitors (Lie et al., 2005). Overexpression of Wnt3 increased, while blockade of Wnt signaling reduced adult hippocampal neurogenesis (Lie et al., 2005). Evidence also suggests that β-catenin, which is present in neural progenitors and newborn granule neurons, plays an important role in the dendritic development of adult born hippocampal neurons (Gao et al., 2007).

Notch (1-4 in mammals) is a transmembrane protein, which after ligand binding is cleaved, releasing an intracellular portion that translocates to the nucleus (Schroeter et al., 1998). In postnatal and adult mice, overexpression of activated Notch1 increased hippocampal cell proliferation and led to the maintenance of GFAP-expressing neural stem cells, while abrogation of Notch signaling led to an decrease in cell proliferation and a shift in the differentiation of newly born cells towards a neuronal lineage (Breunig et al., 2007). In addition,

genetic Notch1 manipulation modulated the dendritic morphology of newborn granule cells, whereby the deletion of Notch1 decreased dendritic arborization while Notch1 overexpression increased dendritic complexity (Breunig et al., 2007). This evidence suggests that Notch1 signaling is involved in the cell proliferation, fate determination, and maturation steps of adult hippocampal neurogenesis.

Bone morphogenic proteins (BMPs) are extracellular signaling molecules that generally antagonize neurogenesis. Noggin, which inhibits BMPs, enhances neurogenesis. The inhibition of noggin in vivo by antisense methods, decreased hippocampal cell proliferation (Fan et al., 2004).

Sonic hedgehog (Shh) is a soluble signaling protein that is crucial in regulating processes during nervous system development (Ruiz i Altaba et al., 2002). Moreover, Shh signaling plays a critical role in the expansion and establishment of postnatal hippocampal progenitors (Han et al., 2008). Its role in regulating adult hippocampal neurogenesis has only recently begun to be addressed. The Shh receptors Patched (Ptc) and Smoothened (Smo) are expressed in the adult hippocampus and in progenitors isolated from this region (Traiffort et al., 1998; Lai et al., 2003). In rats, chronic administration of a recombinant adenovirus vector (rAAV) containing the active fragment of Shh into the dentate gyrus increased cell proliferation and survival, but did not affect differentiation (Lai et al., 2003). On the other hand, intrahippocampal (Lai et al., 2003) and i.c.v. (Banerjee et al., 2005) injections of cyclopamine to rats, an inhibitor of Shh signaling, reduced cell proliferation. Using *in vivo* genetic fate mapping, it was shown that both quiescent neural stem cells and transit-amplifying progenitors in the SGZ are responsive to Shh signaling (Ahn and Joyner, 2005). These studies emphasize the importance of the Shh signaling pathway in adult neurogenesis.

4.12. Transcriptional regulation

cAMP response element-binding protein (CREB) is a transcription factor that is at the distal end of the cAMP signaling cascade. It is activated by phosphorylation (pCREB) via several mechanisms, including neurotrophic factor cascades. Immature neurons of the hippocampus express pCREB and chronic administration (14 days) of the phosphodiesterase-4 inhibitor rolipram to mice, which stimulates of the cAMP pathway, increased the number of dividing cells (Nakagawa et al., 2002b) and the survival of newly born neurons (Nakagawa et al., 2002a). Transgenic mice that expressed a dominant-negative form of CREB in the hippocampus had reduced levels of cell proliferation (Nakagawa et al., 2002b). Interestingly, mice that lack the α/Δ isoform of CREB throughout life, display elevated levels of hippocampal neurogenesis (Gur et al., 2007). These data suggest that the cAMP signaling cascade, and CREB in particular, play an important role in regulating hippocampal neurogenesis.

Neuronal PAS domain protein 3 (NPAS3) is a basic helix-loop-helix (bHLH) Per-Arnt-Sim (PAS) domain transcription factor that is expressed principally within the central nervous system. It possesses three regions vital for its activity as a transcription factor and changes in its activity or function could impact many target genes with varied neuronal functions (Pickard et al., 2006). Mice that lacked NPAS3, but not NPAS1, were deficient in FGF-1 receptor mRNA and had 85% less adult hippocampal cell proliferation than wild type mice (Pieper et al., 2005). Moreover, central infusion of FGF-2 was unable to elevate hippocampal cell proliferation in NPAS3, but not NPAS1, knockout mice (Pieper et al., 2005). These data suggest NPAS3 regulates the proliferative activity of progenitor cells in the adult hippocampus. The ability of NPAS3 and NPAS1 to affect the survival of adult born neurons in the hippocampus, as well as ability of NPAS2 to regulate hippocampal neurogenesis, have not been examined.

4.13 Protein kinase B (Akt)

Akt (protein kinase B) is an important serine/threonine kinase that is involved in numerous signaling cascades and is downstream of neurotrophic and growth factor receptors, as well as monoamine receptors (Datta et al., 1999). In mammals, the serine/threonine kinase Akt (protein kinase B), has three different isoforms, Akt1, -2, -3, each encoded by independent genes (Coffer et al., 1998). These enzymes have their own distinct anatomic distributions and physiologic functions. Akt1 deficient (Akt1KO) mice display deficits in both fetal and postnatal growth that continues into adulthood, with a proportional reduction in the size of all organs (Cho et al., 2001a). Akt2 KO mice grow normally, but are insulin intolerant due to deficits in the action of this hormone at liver and skeletal muscle (Cho et al., 2001b). Akt3 KO mice have normal carbohydrate metabolism, but display a selective decrease in brain size due to smaller and fewer cells (Easton et al., 2005). By using flow cytometry, it was shown that Akt1KO and Akt2KO mice, but not Akt3 KO mice, had lower levels of hippocampal cell proliferation compared to wild type animals (Balu et al., 2008). However, only Akt2KO mice had impairment in the survival of adult born hippocampal progenitors (Balu et al., 2008). This demonstrates the nonredundant roles the several Akt isoforms play in the regulation of hippocampal neurogenesis.

4.14. Stress

Stress is one of the most potent inhibitors of adult hippocampal neurogenesis, and has been demonstrated in multiple mammalian species, including the mouse, rat, tree shrew, and marmoset (Mirescu and Gould, 2006). The deleterious effect of stress on cell proliferation have been shown using a variety of different stress paradigms, such as subordination stress (Gould et al., 1997), resident intruder stress (Gould et al., 1998), footshock (Malberg and Duman, 2003), predator odor (Tanapat et al., 2001), and others. The duration of stress does not seem to be critical as both acute and chronic stress paradigms decrease cell proliferation (Mirescu and Gould, 2006). Stress has also been demonstrated to reduce the survival of newly born hippocampal cells (Czeh et al., 2002; Westenbroek et al., 2004).

Although the antineurogenic effects of stress in the hippocampus are well known, the underlying mechanisms remain ill defined. There is substantial evidence that adrenal stress hormones play an important role in this process. In addition to the hippocampus having a high expression of adrenal steroid receptors, glucocorticoids are themselves regulators of hippocampal neurogenesis, capable of influencing proliferation (Wong and Herbert, 2005), differentiation (Wong and Herbert, 2006), and survival (Wong and Herbert, 2004). Inhibition of the hypothalamic-pituitary axis (HPA) by adrenalectomy (Cameron and Gould, 1994), which removes circulating adrenal steroids, or by other methods (Alonso et al., 2004) enhanced neurogenesis. On the other hand, neurogenesis was reduced by exogenous corticosterone administration (Gould et al., 1992; Murray et al., 2008). Moreover, corticosterone replacement in adrenalectomized animals, which prevents the stress-induced increase in corticosterone while maintaining diurnal rhythm, eliminated the antineurogenic effect of fox odor stress (Tanapat et al., 2001). These data suggest that glucocorticoids are involved in mediating the effects of stress on neurogenesis.

Some studies however, have demonstrated persistent inhibition of neurogenesis despite restoration of normal glucocorticoid levels (Mirescu and Gould, 2006). The decrease in cell proliferation following the maternal separation of rat pups, persisted into adulthood when basal levels of corticosterone were normal (Mirescu et al., 2004). A similar prolonged effect on cell proliferation, without maintenance of elevated corticosterone, was observed following the administration of inescapable shock to rats (Czeh et al., 2001; Malberg and Duman, 2003). It is not fully understood exactly how glucocorticoids affect hippocampal neurogenesis. Although only 10-20% of hippocampal progenitors express glucocorticoid receptors (Cameron

et al., 1993a), some evidence points to their involvement in effects of stress (Wong and Herbert, 2005).

Stress also increases glutamate release in the hippocampus (Abraham et al., 1998), and evidence suggests that enhanced excitatory transmission reduces cell proliferation. Activation of NMDA receptors inhibited cell proliferation, while blockade had the opposite effect (Cameron et al., 1995; Nacher et al., 2003). NDMA receptor antagonism also prevented the exogenous corticosterone-induced decrease in cell proliferation (Cameron et al., 1998).

Pro-inflammatory cytokines might also contribute to the actions of stress on neurogenesis. Hippocampal neural progenitors express the interlukin-1β (IL-1β) receptor (Koo and Duman, 2008) and chronic isolation stress elevates levels of IL-1β in the hippocampus (Ben Menachem-Zidon et al., 2008). Administration of IL-1β reduced hippocampal cell proliferation, while blockade of the IL-1β receptor with an antagonist prevented the reductions in neurogenesis caused by chronic unpredictable stress (Koo and Duman, 2008). Mice with a null mutation of the IL-1β receptor (Goshen et al., 2008; Koo and Duman, 2008) or transgenic overexpression a IL-1β receptor antagonist in brain (Ben Menachem-Zidon et al., 2008) were protected against the reductions in hippocampal neurogenesis associated with stress.

Stress also reduces trophic support in the brain, which might contribute to its deleterious effects on hippocampal neurogenesis. The interaction between stress and the neurotrophin, BDNF, is the most well studied relationship. Many different types of stress paradigms, both acute and chronic, decrease the expression of BDNF in the hippocampus (Duman and Monteggia, 2006). The reduction of BDNF due to stress might in part, be due to elevated levels of corticosterone because adrenalectomy increased BDNF expression (Chao et al., 1998) and chronic administration of corticosterone decreased BDNF expression and protein levels (Jacobsen and Mork, 2006). However, removal of adrenal hormones did not completely block the effects of immobilization stress on BDNF (Smith et al., 1995). In addition, stress reduces the expression of other growth and neurotrophic factors that could also influence neurogenesis. Long-term immobilization stress reduced hippocampal NGF and NT-3 expression (Ueyama et al., 1997). Chronic unpredictable stress decreased the expression of VEGF and the type 2 VEGF receptor in the hippocampus (Heine et al., 2005).

It is well established that stress reduces adult hippocampal neurogenesis, but the functional consequences of this phenomenon remain unanswered. At the circuitry level, one recent study has provided evidence that chronic mild stress in rats adversely affected hippocampal network dynamics, as measured by voltage sensitive dye imaging (Airan et al., 2007). At the behavioral level, stress has been shown to influence learning and memory, as well as to precipitate affective disorders, items linked to adult hippocampal neurogenesis. Because stress influences numerous cellular processes, including neurotransmission, maintenance of dendritic architecture, and growth factor levels (McEwen, 1999), it is likely that if inhibition of neurogenesis contributes to the effects of stress, it does so in concert with multiple other mechanisms (Mirescu and Gould, 2006).

5. Functional role of hippocampal neurogenesis

It has been well established using a variety of different techniques that the newly born cells in the adult hippocampus are electrophysiologically functional and become integrated granule cells (Stanfield and Trice, 1988; Hastings and Gould, 1999; Markakis and Gage, 1999; Carlen et al., 2002; van Praag et al., 2002). However, the role these neurons play in hippocampal function is still unclear and this topic has been the subject of intense research during recent years.

Ablation of adult neurogenesis is the most straightforward way to study its contribution to hippocampal function. One of the methods used to test the effects of eliminating adult neurogenesis was the administration of the DNA methylating agent methylazoxymethanol (MAM), which prevents dividing cells from completing the cell cycle (Shors et al., 2001). MAM treatment (14 days) in rats down-regulated hippocampal neurogenesis and consequently impaired the learning of trace eye-blink conditioning, a hippocampal-dependent task. Moreover, depletion of neurogenesis did not alter the ability of rats to learn delay conditioning, a task that does not require the hippocampus. When rats recovered normal rates of neurogenesis, three weeks after MAM treatment, they were then able to acquire trace conditioning (Shors et al., 2001). These data implicate newly born neurons at 1-2 weeks old are functionally important in this hippocampal-dependent task (Bruel-Jungerman et al., 2007). A separate study which used the same MAM protocol, indicated that there were no performance deficits in two other hippocampal-dependent tasks, contextual fear conditioning and spatial learning in the Morris water maze (Shors et al., 2002), suggesting that hippocampal neurogenesis may relates best to specific aspects of learning such as timing or task difficulty.

A second experimental approach used to abolish neurogenesis is x-irradiation. This procedure, when directed to the hippocampus, has been shown to impair the performance of rats in a hippocampal-dependent working memory task, delayed non-matching-to-sample, but only when relatively long delays were used (Winocur et al., 2006). Irradiation focused at the hippocampus in mice (Saxe et al., 2006) and at the head (Winocur et al., 2006; Warner-Schmidt et al., 2008) or hippocampus (Madsen et al., 2003) in rats impaired contextual fear conditioning. The discrepancy in fear conditioning performance following irradiation and the MAM treatment could be due to the different methodologies employed to reduce neurogenesis, the time at which animals were tested following depletion of neurogenesis, as well as the complexity of the conditioning environments (Bruel-Jungerman et al., 2007). Spatial memory in the Morris water maze has also been shown to be unaffected by irradiation (Madsen et al., 2003; Snyder et al., 2005; Saxe et al., 2006). However, long-term retention (2-4 weeks) in the Morris water maze was impaired in cranially-irradiated rats, suggesting that adult hippocampal neurogenesis may be necessary for long-term storage of spatial information (Snyder et al., 2005). In contrast to the water maze results, irradiation directed to the hippocampus/cortex, impaired the spatial memory of mice in the Barnes maze (Raber et al., 2004), and impaired spatial working memory of rats using the T-maze (Madsen et al., 2003). These differences in spatial memory could be due to the level of stress associated with the different tasks, the reinforcers used in each task, and the time after irradiation at which the animals were tested (Bruel-Jungerman et al., 2007). Short-term recognition memory is not affected by irradiation (Madsen et al., 2003; Raber et al., 2004).

Both irradiation and MAM treatment are not selective for interfering with the production of neurons and cause other detrimental effects on brain physiology and function (Bruel-Jungerman et al., 2007). Therefore, several non-invasive genetic approaches have recently been developed to selectively destroy neural progenitors. One such approach used transgenic mice that express herpes virus thymidine kinase in GFAP-positive cells in the brain; the progenitor cells from which adult born neurons are derived. Upon delivery of the antiviral prodrug gancyclovir, proliferating thymidine kinase cells were destroyed thereby ablating adult neurogenesis in all neurogenic brain regions (Garcia et al., 2004). Animals with reduced neurogenesis showed impairments in contextual fear conditioning and perturbations in a certain type of dentate gyral LTP, without deficits in spatial memory (Saxe et al., 2006). A second group ablated nestin positive neural precursors in adult mice (Dupret et al., 2008). This model was based on the inducible and cell type-restricted over-expression of the pro-apoptotic protein Bax using the reverse tetracycline-controlled transactivator-regulated system (Tet-ON system). By using this model system, Dupret et al. demonstrated that mice with drastically lower levels of neurogenesis had deficits in acquisition and spatial memory in the Morris water

maze, but normal fear-conditioned learning. A third group reduced hippocampal neurogenesis in adult mice by inducible removal of the orphan nuclear receptor TLX from neural stem cells (Zhang et al., 2008a). Reductions of adult-born hippocampal neurons in this manner produced a phenotype similar to what was reported by Dupret et al. Neurogenic depleted mice had deficits in spatial memory, but no impairments in contextual fear conditioning. The divergence in results obtained from these studies underscores the complexities in trying to understand the role of hippocampal neurogenesis using genetically modified animals and in comparing results between laboratories.

Another strategy employed to gain insight into the function of adult generated hippocampal neurons, has been to examine the effects of learning on neurogenesis. It was shown that learning tasks that are hippocampal-dependent (trace eye-blink conditioning and spatial learning in the Morris water maze) enhanced the survival of one-week old neurons, while learning non-hippocampal dependent tasks did not affect cell survival (Gould et al., 1999b). Interestingly, learning a hippocampal-dependent task did not affect cell proliferation (Gould et al., 1999b). The enhancement in neuronal survival following trace eye-blink conditioning was correlated with the ability to learn the paradigm and persisted for 2 months after training (Leuner et al., 2004). Moreover, a recent study demonstrated that animals that learned the MWM well retained more cells in the hippocampus than animals that did not learn or learned poorly. This suggests that learning, and not simply exposure to the task, enhances the survival of cells born one week prior to training (Sisti et al., 2007). Others have reported that spatial learning enhances the proliferation and survival of newly born hippocampal cells when they were labeled at the end of training, when the animals were near asymptotic performance (Lemaire et al., 2000; Dobrossy et al., 2003).

There is other correlative data suggesting a link between hippocampal neurogenesis and learning. There was a small but significant correlation between the acquisition phase of the Morris water maze and genetically determined baseline levels of hippocampal neurogenesis (Kempermann and Gage, 2002). Similarly, the performance of aged rats in the water maze predicted their level of hippocampal neurogenesis (Drapeau et al., 2003). Moreover, environmental enrichment and voluntary physical exercise, which improve performance in hippocampal-dependent tasks, also increase hippocampal neurogenesis (van Praag et al., 1999; Brown et al., 2003; Bruel-Jungerman et al., 2005). On the other hand, negative modulators of hippocampal neurogenesis impair performance in learning tasks (Lledo et al., 2006).

One possible function of these newly born cells may be related to their physiological properties, such that their plasticity makes them particularly suited to respond to and integrate stimuli during memory formation (Bruel-Jungerman et al., 2007). This idea is supported by evidence that demonstrates newly born neurons have lower thresholds for LTP induction and express immediate early genes known to play a role in plasticity and memory formation. Interestingly, LTP, which is thought to play a critical role in memory formation and learning, was found to regulate hippocampal neurogenesis. Induction of LTP at medial perforant path-granule cell synapses increased cell proliferation in the dentate gyrus and promoted the survival of 1-2 week old dentate granule neurons (Bruel-Jungerman et al., 2006). This finding raises the possibility that activity-dependent plasticity in the dentate gyrus during learning may provide signals involved in learning-induced neurogenesis (Bruel-Jungerman et al., 2007).

6. Adult hippocampal neurogenesis and disease states

6.1. Depression

The neurogenic hypothesis postulates that a reduced production of new neurons in the hippocampus relates to the pathogenesis of depression and that successful antidepressant

treatment requires an enhancement in hippocampal neurogenesis (Duman et al., 2001). This hypothesis was initially predicated on several lines of evidence. First, there is abundant preclinical evidence that stress suppresses hippocampal neurogenesis (see previous section). Clinically, stressful life events are known to precipitate depression in vulnerable individuals (Gold and Chrousos, 2002) and about half of the patients suffering from depression (Carroll et al., 1968) have dysregulation of the HPA system. Second, most antidepressant treatments elevate hippocampal neurogenesis only following chronic administration, which parallels the time-course of the emergence of clinical therapeutic effects.

There is significant clinical data that demonstrates impaired declarative learning and memory and diminished cognitive flexibility in patients suffering from depression (Austin et al., 2001; Fossati et al., 2002). In addition, by using magnetic resonance imaging, depressed individuals have been shown to have reduced hippocampal volume (Sheline et al., 1996; Sheline et al., 1999; Bremner et al., 2000), with the magnitude of the atrophy related to the frequency of the depressive episodes and the duration for which the depression went untreated (Sheline et al., 2003). Volumetric changes can be due to several mechanisms including, increased apoptosis of neurons or glia, a loss of neuropil, and decreased neurogenesis and/or gliogenesis in the dentate gyrus (Sahay et al., 2007). Recent clinical (Czeh and Lucassen, 2007) and preclinical (Santarelli et al., 2003; McEwen, 2005) evidence suggests that the volumetric reductions are likely due to changes in neuropil, glial number, and/or dendritic complexity, not necessarily in cell proliferation (Reif et al., 2006) or apoptosis (Lucassen et al., 2001; Muller et al., 2001).

Although hippocampal neurogenesis might not be involved in the pathogenesis of depression, it might be important for some of the therapeutic effects of antidepressant treatments (Sahay and Hen, 2007). The several week delay in the therapeutic onset of antidepressant treatment coincides with the maturation time of newly born hippocampal neurons and that one reason for believing that adult hippocampal neurogenesis is a possible substrate for the actions of antidepressants (Sahay and Hen, 2007). Numerous antidepressants from distinct classes, including monamine reuptake inhibitors, tricyclics, electroconvulsive shock (ECS), and phosphodiesterase inhibitors all specifically increase hippocampal neurogenesis in rodents (Madsen et al., 2000; Malberg et al., 2000; Manev et al., 2001; Nakagawa et al., 2002b). Other treatments that have antidepressant effect, such as exercise (van Praag et al., 1999) and environmental enrichment (Meshi et al., 2006), also increase hippocampal neurogenesis. The majority of newly-born cells adopt a neuronal phenotype (Malberg et al., 2000). Although antidepressants do not affect fate determination of these cells, chronic (3 or 4 weeks) treatment of mice with fluoxetine accelerated the maturation of immature neurons (Wang et al., 2008b). The ability of chronic antidepressant treatments to enhance the survival of newly born neurons is less well defined. One initial study showed that two weeks of fluoxetine treatment to rats did not alter cell survival (Malberg et al., 2000), but a later study demonstrated that four weeks was effective in prolonging cell survival (Nakagawa et al., 2002a). Another recent study demonstrated that chronic (28 days), but not acute (5 days), fluoxetine enhanced survival of postnatally-born hippocampal neurons in mice (Wang et al., 2008b). Moreover, antidepressant treatments blocked the reductions in hippocampal neurogenesis caused by stress (Czeh et al., 2001; Malberg and Duman, 2003; Dranovsky and Hen, 2006). Finally, ablation of adult neurogenesis in mice either by x-irradiation delivered specifically to the hippocampus (Santarelli et al., 2003; Saxe et al., 2006) or by transgenic approaches (Saxe et al., 2006), failed to produce animals with a ‘depressive’ or ‘anxious’ behavioral phenotype, but blocked the ability of antidepressants to produce a behavioral response in the novelty suppression of feeding (NSF) paradigm, which is sensitive to chronic antidepressant treatments (Santarelli et al., 2003). In rats, ablation of neurogenesis by x-irradiation, either specifically in the hippocampus (Jiang et al., 2005) or by whole-head radiation (Airan et al., 2007), blocked the ability of a synthetic cannabinoid to modulate behavior in the forced swim test (FST) and NSF paradigm

(Jiang et al., 2005), and fluoxetine to affect immobility in the FST (Airan et al., 2007). These data suggest that hippocampal neurogenesis alone, might not be a major contributor to development of depression, but is important for the beneficial effects of antidepressant treatments.

Although the neurogenic effects of antidepressant treatments have been well established in rodents, there are very few studies to date demonstrating the same effect in species more closely related to humans. In tree shrews, tianeptine reversed stress-induced reductions in hippocampal cell proliferation (Czeh et al., 2001), while ECS increased hippocampal neurogenesis in bonnet monkeys, which are nonhuman primates (Perera et al., 2007).

Even though almost all antidepressant treatments from many different classes all commonly increase hippocampal neurogenesis, the pharmacological substrates underlying the regulation of this process is lacking. Most of the information comes from studies manipulating the serotonergic system. The $5HT_{1A}$ receptor is essential for the fluoxetine-induced, but not imipramine-induced, increase in hippocampal neurogenesis (Santarelli et al., 2003). The role of other serotonin receptors in modulating the serotonin antidepressant-induced increase in neurogenesis is unknown. There is also a lack of information regarding the mechanisms involved in enhancing neurogenesis with other types of antidepressant treatments.

The molecular mechanisms responsible for the positive neurogenic effects of antidepressant treatments are also not yet well understood. Chronic antidepressant treatments up-regulate the expression of growth and neurotrophic factors in the brain, including BDNF, FGF-2, VEGF, and IGF-I (Duman and Monteggia, 2006). The increased survival of newly born neurons, but not increased proliferation, following treatment with a tricyclic antidepressant was blocked in BDNF +/- mice or TrkB dominant negative transgenic mice (Sairanen et al., 2005). Administration of a Flk-1 receptor antagonist, which inhibits VEGF signaling, blocked the induction of cell proliferation following treatment with desipramine, fluoxetine, or ECS (Warner-Schmidt and Duman, 2007). Antidepressant treatments also up-regulate the expression of the transcription factor, CREB (Nibuya et al., 1996). In addition, the ability of desipramine, a tricyclic antidepressant, to elevate BDNF expression was blocked in CREB deficient mice, suggesting that BDNF is downstream of CREB signaling (Conti et al., 2002). Interestingly, it was recently shown that mice lacking CREB α/Δ had enhanced basal levels of hippocampal cell proliferation and neurogenesis that were not further augmented by chronic desipramine treatment (Gur et al., 2007).

Although it is well established that chronic antidepressant treatments increase hippocampal neurogenesis, it is unclear exactly which population of precursor cells these drugs are affecting. Recent studies have begun to shed light on this issue. The first study used a reporter mouse line to determine that fluoxetine did not affect the division of the stem-like cells in the SGZ, but increased the proliferation of ANPs without affecting the number of neuroblasts or immature neurons, suggesting that the increased number of neurons following fluoxetine administration is due to the expansion of these cells (Encinas et al., 2006). A recent study demonstrated that chronic, but not subchronic, fluoxetine caused a decrease in the number of immature neurons and an increase in mature neurons, suggesting that chronic fluoxetine accelerated the maturation of newly born immature neurons (Wang et al., 2008a). It is unclear whether antidepressants from different pharmacologic classes work through similar mechanisms.

A fundamental question that still needs to be answered is, what are the functional consequences for the neural circuitry of the dentate gyrus once these new neurons are incorporated following antidepressant treatment. Chronic, but not subchronic, fluoxetine treatment to mice enhanced a form of long-term potentiation (LTP) in the dentate gyrus that was blocked when mice were

administered x-irradiation focally to the hippocampus (Wang et al., 2008a). Chronic (14 days) fluoxetine and imipramine treatment given to rats enhanced circuit level activity in the dentate gyrus, and whole head irradiation blocked the effects of fluoxetine on hippocampal neurophysiology, whereas chronic treatment with the typical antipsychotic, haloperidol, did not affect network dynamics (Airan et al., 2007). Future investigations will inform us how enhancement of dentate gyrus function following antidepressant treatment affects the contribution of other subfields of the hippocampus to circuit level output as well as other brain structures associated with depression downstream of the hippocampal formation (Sahay and Hen, 2007). The key question is how changes in neurogenesis may be translated into changes in affective behavior that could be beneficial in treating depression.

6.2. Schizophrenia

It has recently been shown that neural stem cell proliferation in the hippocampus, as measured by Ki-67 immunohistochemistry, was decreased in patients with schizophrenia, and that this deficiency might contribute to the pathogenesis of the disease (Reif et al., 2006). Genetic studies during the past decade have identified genes associated with schizophrenia risk. One such gene is Disrupted-In-Schizophrenia 1 (DISC1), which was originally identified in a study that revealed a chromosomal translocation with strong linkage to schizophrenia (Millar et al., 2000). DISC1 is broadly expressed in the embryonic brain (Austin et al., 2004) and plays a role during neuronal development (Millar et al., 2003). A recent study investigated the role of DISC1 in adult hippocampal neurogenesis (Duan et al., 2007). DISC1 knockdown, via an RNA interference approach, in newborn dentate granule cells of the adult hippocampus lead to soma hypertrophy, accelerated dendritic outgrowth with appearance of ectopic dendrites, mispositioning from overextended migration, enhanced intrinsic excitability, and accelerated synapse formation of new neurons (Duan et al., 2007). Their results suggest that DISC1 orchestrates the tempo of functional neuronal integration in the adult brain and demonstrates essential roles of a susceptibility gene for major mental illness in neuronal development, including adult neurogenesis (Duan et al., 2007).

Another gene that has been linked to schizophrenia is NPAS3. A disruption in the human NPAS3 gene was recently reported in a family suffering from schizophrenia (Kamnasaran et al., 2003). There was a translocation between chromosomes 9 and 14 that resulted in truncation of the NPAS3 gene between exons 2 and 3. It is predicted that the protein product would contain an intact bHLH DNA-binding domain missing both PAS domains and all amino acids C-terminal to the PAS domains. As described previously, NPAS3 knockout mice have reduced levels of hippocampal cell proliferation associated with deficits in FGF-1 receptor mRNA (Pieper et al., 2005). Moreover, mice that lacked this transcription factor exhibited a reduction in reelin (Erbel-Sieler et al., 2004), a large, secreted protein whose expression was attenuated in the postmortem brains of patients with schizophrenia (Impagnatiello et al., 1998). Interestingly, reelin knockout mice displayed marked reductions in adult hippocampal neurogenesis, but elevated levels of gliagenesis (Zhao et al., 2007b).

Studies have also investigated the effects of antipsychotic treatments on hippocampal neurogenesis. Antipsychotic drugs have been divided into two broad classes, typical and atypical, based on their propensity for producing extrapyramidal side effects (De Oliveira and Juruena, 2006). Chronic treatment with the typical antipsychotic haloperidol had no effect on hippocampal neurogenesis in rats (Madsen et al., 2000; Malberg et al., 2000; Manev et al., 2001; Nakagawa et al., 2002b), but acute treatment increased cell proliferation in gerbils (Dawirs et al., 1998). However, atypical antipsychotics have been shown to regulate hippocampal neurogenesis. Chronic treatment with olanzapine (Kodama et al., 2004) elevated neurogenesis, while clozapine increased cell proliferation without affecting survival (Halim et al., 2004). Chronic treatment with clozapine, but not haloperidol, prevented phencyclidine-

induced decreases in hippocampal cell proliferation; neither drug affected cell proliferation when administered alone (Maeda et al., 2007). However, the stimulatory effects of atypical antipsychotics on hippocampal neurogenesis have not been consistently reported, as some have found no effects following administration of olanzapine (Wakade et al., 2002; Wang et al., 2004) or clozapine (Schmitt et al., 2004).

In summary, these data suggest that alterations in adult hippocampal neurogenesis might be involved in the pathogenesis of schizophrenia. Impairments in the proliferative capacity of the hippocampus might contribute to the cognitive deficits observed in schizophrenia. It is possible that antipsychotics may produce their therapeutic effects, in part, by reversing the deficits in hippocampal neurogenesis (Reif et al., 2006). Drugs that are more effective at increasing neurogenesis might be more efficacious at counteracting the cognitive deficits associated with schizophrenia.

6.3. Epilepsy

Seizure activity influences dentate granule cell neurogenesis. Epileptic seizures initially trigger cell death of selective neuronal populations (Gorter et al., 2003). Animal studies of limbic epileptogenesis or acute seizures indicate that prolonged seizures potently stimulate hippocampal neurogenesis (Bengzon et al., 1997; Parent et al., 1997; Scott et al., 1998), as well as angiogenesis (Hellsten et al., 2005). In the adult rodent, kainate and pilocarpine models of temporal lobe epilepsy (TLE), and chemoconvulsant-induced status epilepticus (SE) robustly increase dentate gyrus cell proliferation after a latent period of at least several days (Parent et al., 1997; Gray and Sundstrom, 1998). Approximately 80–90% of the newly generated cells differentiate into granule cells. However, some of these new cells may be recruited from SVZ-derived gliogenesis, and seizures may attract newly generated glia to regions of hippocampal damage (Parent et al., 2006a).

Although more severe seizures enhance neurogenesis to a greater extent, the survival of newborn neurons may decrease with increased seizure severity (Mohapel et al., 2004). Moreover, while shortly after the induction (16 days) of TLE, the injured hippocampus exhibited increased dentate neurogenesis, the chronically epileptic hippocampus (5 months after the first seizure), showed severely declined neurogenesis, which was associated with considerable spontaneous recurrent motor seizures (Hattiangady et al., 2004). Chronic TLE in humans is associated with decreased neurogenesis in the hippocampus (Mathern et al., 2002; Fahrner et al., 2007).

Seizures not only affect the production of new neurons, but also induce dispersion of at least some of the neurogenic cells to ectopic locations. The granule cell layer in patients with TLE is often abnormal due to dispersion and the presence of ectopic granule-like neurons in the hilus and inner molecular layer (Houser, 1990; Parent et al., 2006b). Hilar ectopic granule cells are also observed in several animal models of TLE and may persist for many months (Dashtipour et al., 2001; Parent et al., 2006b). Hilar-ectopic granule-like cells display an accelerated functional maturation resulting in persistent hyperexcitability, fire in abnormal bursts synchronously with CA3 pyramidal cells, and exhibit a much higher percentage of persistent basal dendrites than is normally found (Scharfman et al., 2000; Dashtipour et al., 2001; Overstreet-Wadiche et al., 2006b). The antimitotic agent AraC was shown to inhibit hippocampal neurogenesis after pilocarpine treatment, and resulted in fewer and shorter spontaneous recurrent seizures (Jung et al., 2004). As a fraction of the newly born neurons become GABAergic interneurons, a decline in neurogenesis may contribute to the increased seizure susceptibility of the DG during chronic epilepsy (Shetty and Hattiangady, 2007). Taken together, these data suggest that hilar-ectopic granule cells integrate abnormally and might contribute to seizure generation or propagation.

The mechanisms by which seizure activity stimulates neurogenesis or gliogenesis are unknown. Epileptic activity directly stimulates dentate gyrus and caudal SVZ precursors (Parent et al., 1999; Parent et al., 2006a), but may act to increase neurogenesis indirectly through activation of astrocytes, which stimulate hippocampal neurogenesis via wnt signaling and perhaps other mechanisms (Song et al., 2002; Lie et al., 2005). Seizures also increase the expression of growth factors (Humpel et al., 1993) and neurotrophins (Isackson et al., 1991), which promote neurogenesis. Alternatively, SE-induced death of some mature granule cells may increase cell turnover in the dentate gyrus via other mechanisms (Parent, 2007). Seizure activity might also alter neurotransmitter or neuromodulatory systems that normally influence neurogenesis (Parent, 2007).

In terms of potential mechanisms underlying hilar- or molecular-layer ectopic cells, it is possible that a loss of GABA caused by SE-induced depletion of dentate interneurons could be responsible, as GABA influences differentiation of newly born hippocampal neurons and decreases neuroblast migration in the SVZ-olfactory bulb pathway (Liu et al., 2005). Neurotrophins might also play a role in aberrant migration, as chronic infusion of BDNF into the hippocampus of adult rats led to the appearance of ectopic dentate granule cells (Scharfman et al., 2005).

Production of adult-born neurons increases in rodent models of temporal lobe epilepsy, and both newborn and pre-existing granule neurons contribute to aberrant axonal reorganization in the epileptic hippocampus (Parent, 2007). Prolonged seizures also disrupt the migration of dentate granule cell progenitors and lead to hilar-ectopic granule cells. The ectopic granule neurons appear to integrate abnormally and contribute to network hyperexcitability. Seizure-generated new neurons may thus be involved in the recurrent continuation of seizure activity in rodent models. Similar findings of granule cell layer dispersion and ectopic granule neurons in human TLE suggest that aberrant neurogenesis contributes to epileptogenesis and learning and memory disturbances. Manipulation of adult neurogenesis for therapeutic purposes therefore is likely to involve suppression of aberrant integration in certain instances rather than simply stimulation of neurogenesis for neuronal replacement (Parent, 2007).

6.4. Diabetes mellitus

Diabetes mellitus, regardless of its type, is associated with cerebral alterations in both humans and animal models of the disease (Gispen and Biessels, 2000; Selvarajah and Tesfaye, 2006). These alterations include decreased hippocampal synaptic plasticity (Gispen and Biessels, 2000), neurotoxicity, and changes in glutamate neurotransmission (Gardoni et al., 2002; Valastro et al., 2002). A streptozotocin model of type 1 diabetes reduced proliferation and survival in the adult hippocampus of both mice (Saravia et al., 2004; Beauquis et al., 2006; Saravia et al., 2006) and rats (Jackson-Guilford et al., 2000; Zhang et al., 2008b). Interestingly the reductions in cell proliferation caused by streptozotocin, were prevented by estrogen (Saravia et al., 2004) and chronic fluoxetine (Beauquis et al., 2006) administration. It has been recently shown that hippocampal cell proliferation and survival, but not cell fate determination were impaired in female nonobese diabetic (NOD) mice, a spontaneous type-1 diabetes model (Beauquis et al., 2008). Diabetes mellitus, or type-2 diabetes, is associated with cognitive deficits and an increased risk of dementia, particularly in the elderly (Gispen and Biessels, 2000). *db/db* mice, which have a mutation that inactivates the leptin receptor, are a model of type-2 diabetes. These insulin-resistant mice had impairments of LTP in the dentate gyrus and impaired learning in the Morris water maze (MWM), a hippocampal-dependent task (Stranahan et al., 2008). The deficits in hippocampal plasticity and cognition were associated with increased circulating levels of corticosterone along with impairments in hippocampal cell proliferation and survival, but not differentiation. Changes in hippocampal plasticity and function in both models were reversed when normal physiological levels of corticosterone were

maintained, which suggests that the cognitive impairment in diabetes may result from glucocorticoid-mediated deficits in neurogenesis and synaptic plasticity (Stranahan et al., 2008). The deficits in hippocampal neurogenesis caused by hyperglycemia may shed light on causes of diabetic neuropathology and provide an explanation for the memory deficiencies seen in some diabetic patients (Zhang et al., 2008b). Drugs that could enhance neurogenesis, either through direct or indirect mechanisms, such as glucocorticoid regulation, might be viable therapeutic options for treating patients suffering from cognitive deficits caused by diabetes.

7. Concluding remarks

The addition of new neurons to the adult hippocampus can influence its structure and function by multiple possible mechanisms and provides a new mechanism of plasticity that can be used to change the properties of certain neural circuits. Neurogenesis could serve to increase the number of dentate granule cells, provide a reservoir of highly plastic immature neurons, generate multiple cell types, and/or drive the turnover and replacement of mature granule cells (Sahay et al., 2007). There are several models regarding the role of neurogenesis in hippocampal function. These new neurons might be involved in refining the hippocampal circuitry, optimizing it for future memory storage (Kempermann, 2002). Another idea is that adult-born neurons are involved in hippocampal trace memories and play a role in establishing temporal contiguity between events (Ehninger and Kempermann, 2008). Young granule neurons have enhanced plasticity, which allows for the preferential association of representations that are closely related in time (Aimone et al., 2006). Computational modeling has highlighted the merits of the net addition and replacement of neurons. The addition of new neurons to the network would increase its storage capacity and prevent the collapse of network function due to increased connectivity following increased memory storage (Wiskott et al., 2006). Advantages include a better ability to adapt to new information by avoiding catastrophic interference, increasing the stability of newly acquired information (Chambers et al., 2004), or improving recall by minimizing interference between highly similar items (Becker, 2005). The role adult neurogenesis plays in hippocampal function and disease etiology will begin to be more understood as more selective, inducible, and reversible manipulations of *in vivo* neurogenesis are developed. The discovery of novel therapeutic compounds for various diseases may involve mechanisms that induce a superior regulation of adult hippocampal neurogenesis.

Acknowledgements

The authors would like to thank Dr. Georgia Hodes for the critical reading of this manuscript and her expert opinions. This work was supported by NIH grant MH72832 for a National Center for Drug Discovery Group in Mood Disorders established between the University of Pennsylvania and Wyeth Research.

References

Aberg MA, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J Neurosci 2000;20:2896–2903. [PubMed: 10751442]

Aberg MA, Aberg ND, Palmer TD, Alborn AM, Carlsson-Skwirut C, Bang P, Rosengren LE, Olsson T, Gage FH, Eriksson PS. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. Mol Cell Neurosci 2003;24:23–40. [PubMed: 14550766]

Abraham I, Juhasz G, Kekesi KA, Kovacs KJ. Corticosterone peak is responsible for stress-induced elevation of glutamate in the hippocampus. Stress 1998;2:171–181. [PubMed: 9787265]

Aguado T, Monory K, Palazuelos J, Stella N, Cravatt B, Lutz B, Marsicano G, Kokaia Z, Guzman M, Galve-Roperh I. The endocannabinoid system drives neural progenitor proliferation. Faseb J 2005;19:1704–1706. [PubMed: 16037095]

Ahn S, Joyner AL. In vivo analysis of quiescent adult neural stem cells responding to Sonic hedgehog. Nature 2005;437:894–897. [PubMed: 16208373]

Aimone JB, Wiles J, Gage FH. Potential role for adult neurogenesis in the encoding of time in new memories. Nat Neurosci 2006;9:723–727. [PubMed: 16732202]

Airan RD, Meltzer LA, Roy M, Gong Y, Chen H, Deisseroth K. High-speed imaging reveals neurophysiological links to behavior in an animal model of depression. Science 2007;317:819–823. [PubMed: 17615305]

Allen E. The cessation of the mitosis in the central nervous system of the albino rat. J Comp Neurol 1912;22:547–568.

Alonso R, Griebel G, Pavone G, Stemmelin J, Le Fur G, Soubrie P. Blockade of CRF(1) or V(1b) receptors reverses stress-induced suppression of neurogenesis in a mouse model of depression. Mol Psychiatry 2004;9:278–286. 224. [PubMed: 14699428]

Altman J. Autoradiographic investigation of cell proliferation in the brains of rats and cats. Anat Rec 1963;145:573–591. [PubMed: 14012334]

Altman J. Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 1969;137:433–457. [PubMed: 5361244]

Altman J, Das GD. Post-natal origin of microneurones in the rat brain. Nature 1965a;207:953–956. [PubMed: 5886931]

Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 1965b;124:319–335. [PubMed: 5861717]

Ambrogini P, Lattanzi D, Ciuffoli S, Agostini D, Bertini L, Stocchi V, Santi S, Cuppini R. Morpho-functional characterization of neuronal cells at different stages of maturation in granule cell layer of adult rat dentate gyrus. Brain Res 2004;1017:21–31. [PubMed: 15261095]

Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ. Expression of Disrupted-In-Schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. Neuroscience 2004;124:3–10. [PubMed: 14960334]

Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry 2001;178:200–206. [PubMed: 11230029]

Bai F, Bergeron M, Nelson DL. Chronic AMPA receptor potentiator (LY451646) treatment increases cell proliferation in adult rat hippocampus. Neuropharmacology 2003;44:1013–1021. [PubMed: 12763094]

Baker SA, Baker KA, Hagg T. D3 dopamine receptors do not regulate neurogenesis in the subventricular zone of adult mice. Neurobiol Dis 2005;18:523–527. [PubMed: 15755679]

Balu, DT.; Easton, RM.; Birnbaum, MJ.; Lucki, I. Society for Neuroscience. Vol. 157.11. Washington, DC: 2008. Deletion of Akt isoforms reduce hippocampal neurogenesis, fear conditioning, and antidepressant behavioral responses.

Banasr M, Hery M, Brezun JM, Daszuta A. Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus. Eur J Neurosci 2001;14:1417–1424. [PubMed: 11722603]

Banasr M, Hery M, Printemps R, Daszuta A. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 2004;29:450–460. [PubMed: 14872203]

Banerjee SB, Rajendran R, Dias BG, Ladiwala U, Tole S, Vaidya VA. Recruitment of the Sonic hedgehog signalling cascade in electroconvulsive seizure-mediated regulation of adult rat hippocampal neurogenesis. Eur J Neurosci 2005;22:1570–1580. [PubMed: 16197497]

Beauquis J, Roig P, Homo-Delarche F, De Nicola A, Saravia F. Reduced hippocampal neurogenesis and number of hilar neurones in streptozotocin-induced diabetic mice: reversion by antidepressant treatment. Eur J Neurosci 2006;23:1539–1546. [PubMed: 16553617]

Beauquis J, Saravia F, Coulaud J, Roig P, Dardenne M, Homo-Delarche F, De Nicola A. Prominently decreased hippocampal neurogenesis in a spontaneous model of type 1 diabetes, the nonobese diabetic mouse. Exp Neurol 2008;210:359–367. [PubMed: 18190910]

Becker S. A computational principle for hippocampal learning and neurogenesis. Hippocampus 2005;15:722–738. [PubMed: 15986407]

Bedard A, Gravel C, Parent A. Chemical characterization of newly generated neurons in the striatum of adult primates. Exp Brain Res 2006;170:501–512. [PubMed: 16328260]

Ben Menachem-Zidon O, Goshen I, Kreisel T, Ben Menahem Y, Reinhartz E, Ben Hur T, Yirmiya R. Intrahippocampal transplantation of transgenic neural precursor cells overexpressing interleukin-1 receptor antagonist blocks chronic isolation-induced impairment in memory and neurogenesis. Neuropsychopharmacology 2008;33:2251–2262. [PubMed: 17987063]

Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. Proc Natl Acad Sci U S A 1997;94:10432–10437. [PubMed: 9294228]

Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. J Neurosci 2001;21:6718–6731. [PubMed: 11517261]

Biebl M, Cooper CM, Winkler J, Kuhn HG. Analysis of neurogenesis and programmed cell death reveals a self-renewing capacity in the adult rat brain. Neurosci Lett 2000;291:17–20. [PubMed: 10962143]

Birzniece V, Johansson IM, Wang MD, Seckl JR, Backstrom T, Olsson T. Serotonin 5-HT(1A) receptor mRNA expression in dorsal hippocampus and raphe nuclei after gonadal hormone manipulation in female rats. Neuroendocrinology 2001;74:135–142. [PubMed: 11474221]

Brandt MD, Jessberger S, Steiner B, Kronenberg G, Reuter K, Bick-Sander A, von der Behrens W, Kempermann G. Transient calretinin expression defines early postmitotic step of neuronal differentiation in adult hippocampal neurogenesis of mice. Mol Cell Neurosci 2003;24:603–613. [PubMed: 14664811]

Brannvall K, Bogdanovic N, Korhonen L, Lindholm D. 19-Nortestosterone influences neural stem cell proliferation and neurogenesis in the rat brain. Eur J Neurosci 2005;21:871–878. [PubMed: 15787693]

Bredt DS, Hwang PM, Snyder SH. Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 1990;347:768–770. [PubMed: 1700301]

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry 2000;157:115–118. [PubMed: 10618023]

Breunig JJ, Silbereis J, Vaccarino FM, Sestan N, Rakic P. Notch regulates cell fate and dendrite morphology of newborn neurons in the postnatal dentate gyrus. Proc Natl Acad Sci U S A 2007;104:20558–20563. [PubMed: 18077357]

Brezun JM, Daszuta A. Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience 1999;89:999–1002. [PubMed: 10362289]

Brezun JM, Daszuta A. Serotonin may stimulate granule cell proliferation in the adult hippocampus, as observed in rats grafted with foetal raphe neurons. Eur J Neurosci 2000;12:391–396. [PubMed: 10651896]

Brown J, Cooper-Kuhn CM, Kempermann G, Van Praag H, Winkler J, Gage FH, Kuhn HG. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. Eur J Neurosci 2003;17:2042–2046. [PubMed: 12786970]

Bruel-Jungerman E, Laroche S, Rampon C. New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. Eur J Neurosci 2005;21:513–521. [PubMed: 15673450]

Bruel-Jungerman E, Rampon C, Laroche S. Adult hippocampal neurogenesis, synaptic plasticity and memory: facts and hypotheses. Rev Neurosci 2007;18:93–114. [PubMed: 17593874]

Bruel-Jungerman E, Davis S, Rampon C, Laroche S. Long-term potentiation enhances neurogenesis in the adult dentate gyrus. J Neurosci 2006;26:5888–5893. [PubMed: 16738230]

Burd GD, Nottebohm F. Ultrastructural characterization of synaptic terminals formed on newly generated neurons in a song control nucleus of the adult canary forebrain. J Comp Neurol 1985;240:143–152. [PubMed: 4056107]

Bursztajn S, Falls WA, Berman SA, Friedman MJ. Cell proliferation in the brains of NMDAR NR1 transgenic mice. Brain Res 2007;1172:10–20. [PubMed: 17803978]

Cameron HA, Gould E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. Neuroscience 1994;61:203–209. [PubMed: 7969902]

Cameron HA, Woolley CS, Gould E. Adrenal steroid receptor immunoreactivity in cells born in the adult rat dentate gyrus. Brain Res 1993a;611:342–346. [PubMed: 8392896]

Cameron HA, McEwen BS, Gould E. Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. J Neurosci 1995;15:4687–4692. [PubMed: 7790933]

Cameron HA, Tanapat P, Gould E. Adrenal steroids and N-methyl-D-aspartate receptor activation regulate neurogenesis in the dentate gyrus of adult rats through a common pathway. Neuroscience 1998;82:349–354. [PubMed: 9466447]

Cameron HA, Woolley CS, McEwen BS, Gould E. Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. Neuroscience 1993b;56:337–344. [PubMed: 8247264]

Carlen M, Cassidy RM, Brismar H, Smith GA, Enquist LW, Frisen J. Functional integration of adult-born neurons. Curr Biol 2002;12:606–608. [PubMed: 11937032]

Carroll BJ, Martin FI, Davies B. Resistance to suppression by dexamethasone of plasma 11-O.H.C.S levels in severe depressive illness. Br Med J 1968;3:285–287. [PubMed: 4385601]

Chambers RA, Potenza MN, Hoffman RE, Miranker W. Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. Neuropsychopharmacology 2004;29:747–758. [PubMed: 14702022]

Chao HM, Sakai RR, Ma LY, McEwen BS. Adrenal steroid regulation of neurotrophic factor expression in the rat hippocampus. Endocrinology 1998;139:3112–3118. [PubMed: 9645683]

Chmielnicki E, Benraiss A, Economides AN, Goldman SA. Adenovirally expressed noggin and brain-derived neurotrophic factor cooperate to induce new medium spiny neurons from resident progenitor cells in the adult striatal ventricular zone. J Neurosci 2004;24:2133–2142. [PubMed: 14999064]

Cho H, Thorvaldsen JL, Chu Q, Feng F, Birnbaum MJ. Akt1/PKBalpha is required for normal growth but dispensable for maintenance of glucose homeostasis in mice. J Biol Chem 2001a;276:38349–38352. [PubMed: 11533044]

Cho H, Mu J, Kim JK, Thorvaldsen JL, Chu Q, Crenshaw EB 3rd, Kaestner KH, Bartolomei MS, Shulman GI, Birnbaum MJ. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta). Science 2001b;292:1728–1731. [PubMed: 11387480]

Chumley MJ, Catchpole T, Silvany RE, Kernie SG, Henkemeyer M. EphB receptors regulate stem/progenitor cell proliferation, migration, and polarity during hippocampal neurogenesis. J Neurosci 2007;27:13481–13490. [PubMed: 18057206]

Coffer PJ, Jin J, Woodgett JR. Protein kinase B (c-Akt): a multifunctional mediator of phosphatidylinositol 3-kinase activation. Biochem J 1998;335(Pt 1):1–13. [PubMed: 9742206]

Conti AC, Cryan JF, Dalvi A, Lucki I, Blendy JA. cAMP response element-binding protein is essential for the upregulation of brain-derived neurotrophic factor transcription, but not the behavioral or endocrine responses to antidepressant drugs. J Neurosci 2002;22:3262–3268. [PubMed: 11943827]

Cooper-Kuhn CM, Winkler J, Kuhn HG. Decreased neurogenesis after cholinergic forebrain lesion in the adult rat. J Neurosci Res 2004;77:155–165. [PubMed: 15211583]

Czeh B, Lucassen PJ. What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? Eur Arch Psychiatry Clin Neurosci 2007;257:250–260. [PubMed: 17401728]

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A 2001;98:12796–12801. [PubMed: 11675510]

Czeh B, Welt T, Fischer AK, Erhardt A, Schmitt W, Muller MB, Toschi N, Fuchs E, Keck ME. Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: effects on stress hormone levels and adult hippocampal neurogenesis. Biol Psychiatry 2002;52:1057–1065. [PubMed: 12460689]

Dashtipour K, Tran PH, Okazaki MM, Nadler JV, Ribak CE. Ultrastructural features and synaptic connections of hilar ectopic granule cells in the rat dentate gyrus are different from those of granule cells in the granule cell layer. Brain Res 2001;890:261–271. [PubMed: 11164792]

Datta SR, Brunet A, Greenberg ME. Cellular survival: a play in three Akts. Genes Dev 1999;13:2905–2927. [PubMed: 10579998]

Dawirs RR, Hildebrandt K, Teuchert-Noodt G. Adult treatment with haloperidol increases dentate granule cell proliferation in the gerbil hippocampus. J Neural Transm 1998;105:317–327. [PubMed: 9660110]

Dayer AG, Cleaver KM, Abouantoun T, Cameron HA. New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. J Cell Biol 2005;168:415–427. [PubMed: 15684031]

De Nicola AF, Saravia FE, Beauquis J, Pietranera L, Ferrini MG. Estrogens and neuroendocrine hypothalamic-pituitary-adrenal axis function. Front Horm Res 2006;35:157–168. [PubMed: 16809931]

De Oliveira IR, Juruena MF. Treatment of psychosis: 30 years of progress. J Clin Pharm Ther 2006;31:523–534. [PubMed: 17176358]

Dinerman JL, Dawson TM, Schell MJ, Snowman A, Snyder SH. Endothelial nitric oxide synthase localized to hippocampal pyramidal cells: implications for synaptic plasticity. Proc Natl Acad Sci U S A 1994;91:4214–4218. [PubMed: 7514300]

Dobrossy MD, Drapeau E, Aurousseau C, Le Moal M, Piazza PV, Abrous DN. Differential effects of learning on neurogenesis: learning increases or decreases the number of newly born cells depending on their birth date. Mol Psychiatry 2003;8:974–982. [PubMed: 14647395]

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 1999;97:703–716. [PubMed: 10380923]

Dominguez-Escriba L, Hernandez-Rabaza V, Soriano-Navarro M, Barcia JA, Romero FJ, Garcia-Verdugo JM, Canales JJ. Chronic cocaine exposure impairs progenitor proliferation but spares survival and maturation of neural precursors in adult rat dentate gyrus. Eur J Neurosci 2006;24:586–594. [PubMed: 16903860]

Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. Biol Psychiatry 2006;59:1136–1143. [PubMed: 16797263]

Drapeau E, Mayo W, Aurousseau C, Le Moal M, Piazza PV, Abrous DN. Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. Proc Natl Acad Sci U S A 2003;100:14385–14390. [PubMed: 14614143]

Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, Liu XB, Yang CH, Jordan JD, Ma DK, Liu CY, Ganesan S, Cheng HJ, Ming GL, Lu B, Song H. Disrupted-In-Schizophrenia 1 regulates integration of newly generated neurons in the adult brain. Cell 2007;130:1146–1158. [PubMed: 17825401]

Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006;59:1116–1127. [PubMed: 16631126]

Duman RS, Malberg J, Nakagawa S. Regulation of adult neurogenesis by psychotropic drugs and stress. J Pharmacol Exp Ther 2001;299:401–407. [PubMed: 11602648]

Dupret D, Revest JM, Koehl M, Ichas F, De Giorgi F, Costet P, Abrous DN, Piazza PV. Spatial relational memory requires hippocampal adult neurogenesis. PLoS ONE 2008;3:e1959. [PubMed: 18509506]

Earnheart JC, Schweizer C, Crestani F, Iwasato T, Itohara S, Mohler H, Luscher B. GABAergic control of adult hippocampal neurogenesis in relation to behavior indicative of trait anxiety and depression states. J Neurosci 2007;27:3845–3854. [PubMed: 17409249]

Easton RM, Cho H, Roovers K, Shineman DW, Mizrahi M, Forman MS, Lee VM, Szabolcs M, de Jong R, Oltersdorf T, Ludwig T, Efstratiadis A, Birnbaum MJ. Role for Akt3/protein kinase Bgamma in attainment of normal brain size. Mol Cell Biol 2005;25:1869–1878. [PubMed: 15713641]

Ehninger D, Kempermann G. Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. Cereb Cortex 2003;13:845–851. [PubMed: 12853371]

Ehninger D, Kempermann G. Neurogenesis in the adult hippocampus. Cell Tissue Res 2008;331:243–250. [PubMed: 17938969]

Eisch AJ, Mandyam CD. Adult neurogenesis: can analysis of cell cycle proteins move us “Beyond BrdU”? Curr Pharm Biotechnol 2007;8:147–165. [PubMed: 17584088]

Eisch AJ, Barrot M, Schad CA, Self DW, Nestler EJ. Opiates inhibit neurogenesis in the adult rat hippocampus. Proc Natl Acad Sci U S A 2000;97:7579–7584. [PubMed: 10840056]

Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A 2003;100:13632–13637. [PubMed: 14581618]

Emsley JG, Hagg T. Endogenous and exogenous ciliary neurotrophic factor enhances forebrain neurogenesis in adult mice. Exp Neurol 2003;183:298–310. [PubMed: 14552871]

Encinas JM, Enikolopov G. Identifying and quantitating neural stem and progenitor cells in the adult brain. Methods Cell Biol 2008;85:243–272. [PubMed: 18155466]

Encinas JM, Vaahtokari A, Enikolopov G. Fluoxetine targets early progenitor cells in the adult brain. Proc Natl Acad Sci U S A 2006;103:8233–8238. [PubMed: 16702546]

Erbel-Sieler C, Dudley C, Zhou Y, Wu X, Estill SJ, Han T, Diaz-Arrastia R, Brunskill EW, Potter SS, McKnight SL. Behavioral and regulatory abnormalities in mice deficient in the NPAS1 and NPAS3 transcription factors. Proc Natl Acad Sci U S A 2004;101:13648–13653. [PubMed: 15347806]

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. Nat Med 1998;4:1313–1317. [PubMed: 9809557]

Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, Schinder AF. Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci 2005;25:10074–10086. [PubMed: 16267214]

Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci 2003;18:2803–2812. [PubMed: 14656329]

Fahrner A, Kann G, Flubacher A, Heinrich C, Freiman TM, Zentner J, Frotscher M, Haas CA. Granule cell dispersion is not accompanied by enhanced neurogenesis in temporal lobe epilepsy patients. Exp Neurol 2007;203:320–332. [PubMed: 17049346]

Fan XT, Xu HW, Cai WQ, Yang H, Liu S. Antisense Noggin oligodeoxynucleotide administration decreases cell proliferation in the dentate gyrus of adult rats. Neurosci Lett 2004;366:107–111. [PubMed: 15265600]

Feng J, Chi P, Blanpied TA, Xu Y, Magarinos AM, Ferreira A, Takahashi RH, Kao HT, McEwen BS, Ryan TA, Augustine GJ, Greengard P. Regulation of neurotransmitter release by synapsin III. J Neurosci 2002;22:4372–4380. [PubMed: 12040043]

Ferreira A, Kosik KS, Greengard P, Han HQ. Aberrant neurites and synaptic vesicle protein deficiency in synapsin II-depleted neurons. Science 1994;264:977–979. [PubMed: 8178158]

Ferreira A, Han HQ, Greengard P, Kosik KS. Suppression of synapsin II inhibits the formation and maintenance of synapses in hippocampal culture. Proc Natl Acad Sci U S A 1995;92:9225–9229. [PubMed: 7568106]

Filippov V, Kronenberg G, Pivneva T, Reuter K, Steiner B, Wang LP, Yamaguchi M, Kettenmann H, Kempermann G. Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. Mol Cell Neurosci 2003;23:373–382. [PubMed: 12837622]

Fossati P, Coyette F, Ergis AM, Allilaire JF. Influence of age and executive functioning on verbal memory of inpatients with depression. J Affect Disord 2002;68:261–271. [PubMed: 12063154]

Fowler CD, Liu Y, Ouimet C, Wang Z. The effects of social environment on adult neurogenesis in the female prairie vole. J Neurobiol 2002;51:115–128. [PubMed: 11932953]

Francis F, Koulakoff A, Boucher D, Chafey P, Schaar B, Vinet MC, Friocourt G, McDonnell N, Reiner O, Kahn A, McConnell SK, Berwald-Netter Y, Denoulet P, Chelly J. Doublecortin is a developmentally regulated, microtubule-associated protein expressed in migrating and differentiating neurons. Neuron 1999;23:247–256. [PubMed: 10399932]

Freund TF, Buzsaki G. Interneurons of the hippocampus. Hippocampus 1996;6:347–470. [PubMed: 8915675]

Frielingsdorf H, Simpson DR, Thal LJ, Pizzo DP. Nerve growth factor promotes survival of new neurons in the adult hippocampus. Neurobiol Dis 2007;26:47–55. [PubMed: 17270453]

Fritzen S, Schmitt A, Koth K, Sommer C, Lesch KP, Reif A. Neuronal nitric oxide synthase (NOS-I) knockout increases the survival rate of neural cells in the hippocampus independently of BDNF. Mol Cell Neurosci 2007;35:261–271. [PubMed: 17459722]

Fukuda S, Kato F, Tozuka Y, Yamaguchi M, Miyamoto Y, Hisatsune T. Two distinct subpopulations of nestin-positive cells in adult mouse dentate gyrus. J Neurosci 2003;23:9357–9366. [PubMed: 14561863]

Gama Sosa MA, Wen PH, De Gasperi R, Perez GM, Senturk E, Friedrich VL Jr, Elder GA. Entorhinal cortex lesioning promotes neurogenesis in the hippocampus of adult mice. Neuroscience 2004;127:881–891. [PubMed: 15312900]

Gao X, Arlotta P, Macklis JD, Chen J. Conditional knock-out of beta-catenin in postnatal-born dentate gyrus granule neurons results in dendritic malformation. J Neurosci 2007;27:14317–14325. [PubMed: 18160639]

Garcia AD, Doan NB, Imura T, Bush TG, Sofroniew MV. GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. Nat Neurosci 2004;7:1233–1241. [PubMed: 15494728]

Gardoni F, Kamal A, Bellone C, Biessels GJ, Ramakers GM, Cattabeni F, Gispent WH, Di Luca M. Effects of streptozotocin-diabetes on the hippocampal NMDA receptor complex in rats. J Neurochem 2002;80:438–447. [PubMed: 11908465]

Gartel AL, Radhakrishnan SK. Lost in transcription: p21 repression, mechanisms, and consequences. Cancer Res 2005;65:3980–3985. [PubMed: 15899785]

Ge S, Pradhan DA, Ming GL, Song H. GABA sets the tempo for activity-dependent adult neurogenesis. Trends Neurosci 2007;30:1–8. [PubMed: 17116335]

Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 2006;439:589–593. [PubMed: 16341203]

Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. Trends Neurosci 2000;23:542–549. [PubMed: 11074263]

Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 2002;7:254–275. [PubMed: 11920153]

Goldman SA, Nottebohm F. Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain. Proc Natl Acad Sci U S A 1983;80:2390–2394. [PubMed: 6572982]

Gorter JA, Goncalves Pereira PM, van Vliet EA, Aronica E, Lopes da Silva FH, Lucassen PJ. Neuronal cell death in a rat model for mesial temporal lobe epilepsy is induced by the initial status epilepticus and not by later repeated spontaneous seizures. Epilepsia 2003;44:647–658. [PubMed: 12752463]

Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, Yirmiya R. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Mol Psychiatry 2008;13:717–728. [PubMed: 17700577]

Gould E, Cameron HA, McEwen BS. Blockade of NMDA receptors increases cell death and birth in the developing rat dentate gyrus. J Comp Neurol 1994;340:551–565. [PubMed: 7911808]

Gould E, Reeves AJ, Graziano MS, Gross CG. Neurogenesis in the neocortex of adult primates. Science 1999a;286:548–552. [PubMed: 10521353]

Gould E, Vail N, Wagers M, Gross CG. Adult-generated hippocampal and neocortical neurons in macaques have a transient existence. Proc Natl Acad Sci U S A 2001;98:10910–10917. [PubMed: 11526209]

Gould E, Cameron HA, Daniels DC, Woolley CS, McEwen BS. Adrenal hormones suppress cell division in the adult rat dentate gyrus. J Neurosci 1992;12:3642–3650. [PubMed: 1527603]

Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997;17:2492–2498. [PubMed: 9065509]

Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A 1998;95:3168–3171. [PubMed: 9501234]

Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ. Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 1999b;2:260–265. [PubMed: 10195219]

Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci U S A 1999c;96:5263–5267. [PubMed: 10220454]

Gray WP, Sundstrom LE. Kainic acid increases the proliferation of granule cell progenitors in the dentate gyrus of the adult rat. Brain Res 1998;790:52–59. [PubMed: 9593820]

Gur TL, Conti AC, Holden J, Bechtholt AJ, Hill TE, Lucki I, Malberg JE, Blendy JA. cAMP response element-binding protein deficiency allows for increased neurogenesis and a rapid onset of antidepressant response. J Neurosci 2007;27:7860–7868. [PubMed: 17634380]

Hajszan T, Milner TA, Leranth C. Sex steroids and the dentate gyrus. Prog Brain Res 2007;163:399–415. [PubMed: 17765731]

Halim ND, Weickert CS, McClintock BW, Weinberger DR, Lipska BK. Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. Neuropsychopharmacology 2004;29:1063–1069. [PubMed: 15010699]

Han YG, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, Alvarez-Buylla A. Hedgehog signaling and primary cilia are required for the formation of adult neural stem cells. Nat Neurosci 2008;11:277–284. [PubMed: 18297065]

Harburg GC, Hall FS, Harrist AV, Sora I, Uhl GR, Eisch AJ. Knockout of the mu opioid receptor enhances the survival of adult-generated hippocampal granule cell neurons. Neuroscience 2007;144:77–87. [PubMed: 17055658]

Harrist A, Beech RD, King SL, Zanardi A, Cleary MA, Caldarone BJ, Eisch A, Zoli M, Picciotto MR. Alteration of hippocampal cell proliferation in mice lacking the beta 2 subunit of the neuronal nicotinic acetylcholine receptor. Synapse 2004;54:200–206. [PubMed: 15472930]

Hastings NB, Gould E. Rapid extension of axons into the CA3 region by adult-generated granule cells. J Comp Neurol 1999;413:146–154. [PubMed: 10464376]

Hattiangady B, Rao MS, Shetty AK. Chronic temporal lobe epilepsy is associated with severely declined dentate neurogenesis in the adult hippocampus. Neurobiol Dis 2004;17:473–490. [PubMed: 15571983]

Hayes TE, Valtz NL, McKay RD. Downregulation of CDC2 upon terminal differentiation of neurons. New Biol 1991;3:259–269. [PubMed: 1715184]

Heine VM, Maslam S, Joels M, Lucassen PJ. Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus-pituitary-adrenal axis activation. Neurobiol Aging 2004a;25:361–375. [PubMed: 15123342]

Heine VM, Maslam S, Joels M, Lucassen PJ. Increased P27KIP1 protein expression in the dentate gyrus of chronically stressed rats indicates G1 arrest involvement. Neuroscience 2004b;129:593–601. [PubMed: 15541881]

Heine VM, Zareno J, Maslam S, Joels M, Lucassen PJ. Chronic stress in the adult dentate gyrus reduces cell proliferation near the vasculature and VEGF and Flk-1 protein expression. Eur J Neurosci 2005;21:1304–1314. [PubMed: 15813940]

Hellsten J, West MJ, Arvidsson A, Ekstrand J, Jansson L, Wennstrom M, Tingstrom A. Electroconvulsive seizures induce angiogenesis in adult rat hippocampus. Biol Psychiatry 2005;58:871–878. [PubMed: 16043138]

Hill MN, Kambo JS, Sun JC, Gorzalka BB, Galea LA. Endocannabinoids modulate stress-induced suppression of hippocampal cell proliferation and activation of defensive behaviours. Eur J Neurosci 2006;24:1845–1849. [PubMed: 17067290]

Hoglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 2004;7:726–735. [PubMed: 15195095]

Houser CR. Granule cell dispersion in the dentate gyrus of humans with temporal lobe epilepsy. Brain Res 1990;535:195–204. [PubMed: 1705855]

Howell OW, Doyle K, Goodman JH, Scharfman HE, Herzog H, Pringle A, Beck-Sickinger AG, Gray WP. Neuropeptide Y stimulates neuronal precursor proliferation in the post-natal and adult dentate gyrus. J Neurochem 2005;93:560–570. [PubMed: 15836615]

Howell OW, Silva S, Scharfman HE, Sosunov AA, Zaben M, Shatya A, McKhann G 2nd, Herzog H, Laskowski A, Gray WP. Neuropeptide Y is important for basal and seizure-induced precursor cell proliferation in the hippocampus. Neurobiol Dis 2007;26:174–188. [PubMed: 17317195]

Hua Y, Huang XY, Zhou L, Zhou QG, Hu Y, Luo CX, Li F, Zhu DY. DETA/NONOate, a nitric oxide donor, produces antidepressant effects by promoting hippocampal neurogenesis. Psychopharmacology (Berl). 2008

Huang GJ, Herbert J. Serotonin modulates the suppressive effects of corticosterone on proliferating progenitor cells in the dentate gyrus of the hippocampus in the adult rat. Neuropsychopharmacology 2005a;30:231–241. [PubMed: 15536491]

Huang GJ, Herbert J. The role of 5-HT1A receptors in the proliferation and survival of progenitor cells in the dentate gyrus of the adult hippocampus and their regulation by corticoids. Neuroscience 2005b;135:803–813. [PubMed: 16129565]

Huang GJ, Herbert J. Stimulation of neurogenesis in the hippocampus of the adult rat by fluoxetine requires rhythmic change in corticosterone. Biol Psychiatry 2006;59:619–624. [PubMed: 16325782]

Humpel C, Lippoldt A, Chadi G, Ganten D, Olson L, Fuxe K. Fast and widespread increase of basic fibroblast growth factor messenger RNA and protein in the forebrain after kainate-induced seizures. Neuroscience 1993;57:913–922. [PubMed: 8309552]

Impagnatiello F, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG, Uzunov DP, Smalheiser NR, Davis JM, Pandey GN, Pappas GD, Tueting P, Sharma RP, Costa E. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. Proc Natl Acad Sci U S A 1998;95:15718–15723. [PubMed: 9861036]

Isackson PJ, Huntsman MM, Murray KD, Gall CM. BDNF mRNA expression is increased in adult rat forebrain after limbic seizures: temporal patterns of induction distinct from NGF. Neuron 1991;6:937–948. [PubMed: 2054188]

Jackson-Guilford J, Leander JD, Nisenbaum LK. The effect of streptozotocin-induced diabetes on cell proliferation in the rat dentate gyrus. Neurosci Lett 2000;293:91–94. [PubMed: 11027841]

Jacobsen JP, Mork A. Chronic corticosterone decreases brain-derived neurotrophic factor (BDNF) mRNA and protein in the hippocampus, but not in the frontal cortex, of the rat. Brain Res 2006;1110:221–225. [PubMed: 16876769]

Jessberger S, Zhao C, Toni N, Clemenson GD Jr, Li Y, Gage FH. Seizure-associated, aberrant neurogenesis in adult rats characterized with retrovirus-mediated cell labeling. J Neurosci 2007;27:9400–9407. [PubMed: 17728453]

Jha S, Rajendran R, Davda J, Vaidya VA. Selective serotonin depletion does not regulate hippocampal neurogenesis in the adult rat brain: differential effects of p-chlorophenylalanine and 5,7-dihydroxytryptamine. Brain Res 2006;1075:48–59. [PubMed: 16460708]

Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji SP, Bai G, Zhang X. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J Clin Invest 2005;115:3104–3116. [PubMed: 16224541]

Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc Natl Acad Sci U S A 2002;99:11946–11950. [PubMed: 12181492]

Jin K, Xie L, Kim SH, Parmentier-Batteur S, Sun Y, Mao XO, Childs J, Greenberg DA. Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice. Mol Pharmacol 2004;66:204–208. [PubMed: 15266010]

Jung KH, Chu K, Kim M, Jeong SW, Song YM, Lee ST, Kim JY, Lee SK, Roh JK. Continuous cytosine-b-D-arabinofuranoside infusion reduces ectopic granule cells in adult rat hippocampus with attenuation of spontaneous recurrent seizures following pilocarpine-induced status epilepticus. Eur J Neurosci 2004;19:3219–3226. [PubMed: 15217378]

Kahn L, Alonso G, Normand E, Manzoni OJ. Repeated morphine treatment alters polysialylated neural cell adhesion molecule, glutamate decarboxylase-67 expression and cell proliferation in the adult rat hippocampus. Eur J Neurosci 2005;21:493–500. [PubMed: 15673448]

Kamnasaran D, Muir WJ, Ferguson-Smith MA, Cox DW. Disruption of the neuronal PAS3 gene in a family affected with schizophrenia. J Med Genet 2003;40:325–332. [PubMed: 12746393]

Kaneko N, Okano H, Sawamoto K. Role of the cholinergic system in regulating survival of newborn neurons in the adult mouse dentate gyrus and olfactory bulb. Genes Cells 2006;11:1145–1159. [PubMed: 16999735]

Kao HT, Li P, Chao HM, Janoschka S, Pham K, Feng J, McEwen BS, Greengard P, Pieribone VA, Porton B. Early involvement of synapsin III in neural progenitor cell development in the adult hippocampus. J Comp Neurol 2008;507:1860–1870. [PubMed: 18271024]

Kaplan MS, Hinds JW. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. Science 1977;197:1092–1094. [PubMed: 887941]

Kaplan MS, Bell DH. Mitotic neuroblasts in the 9-day-old and 11-month-old rodent hippocampus. J Neurosci 1984;4:1429–1441. [PubMed: 6726341]

Kaplan MS, McNelly NA, Hinds JW. Population dynamics of adult-formed granule neurons of the rat olfactory bulb. J Comp Neurol 1985;239:117–125. [PubMed: 4044929]

Karlsson RM, Choe JS, Cameron HA, Thorsell A, Crawley JN, Holmes A, Heilig M. The neuropeptide Y Y1 receptor subtype is necessary for the anxiolytic-like effects of neuropeptide Y, but not the antidepressant-like effects of fluoxetine, in mice. Psychopharmacology (Berl) 2008;195:547–557. [PubMed: 17891380]

Kempermann G. Why new neurons? Possible functions for adult hippocampal neurogenesis. J Neurosci 2002;22:635–638. [PubMed: 11826092]

Kempermann, G. Adult Neurogenesis: Stem Cells and Neuronal Development in the Adult Brain. USA: Oxford University Press; 2005.

Kempermann G, Gage FH. Genetic determinants of adult hippocampal neurogenesis correlate with acquisition, but not probe trial performance, in the water maze task. Eur J Neurosci 2002;16:129–136. [PubMed: 12153537]

Kempermann G, Jessberger S, Steiner B, Kronenberg G. Milestones of neuronal development in the adult hippocampus. Trends Neurosci 2004;27:447–452. [PubMed: 15271491]

Kempermann G, Gast D, Kronenberg G, Yamaguchi M, Gage FH. Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. Development 2003;130:391–399. [PubMed: 12466205]

Kodama M, Fujioka T, Duman RS. Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. Biol Psychiatry 2004;56:570–580. [PubMed: 15476686]

Koehl M, Meerlo P, Gonzales D, Rontal A, Turek FW, Abrous DN. Exercise-induced promotion of hippocampal cell proliferation requires {beta}-endorphin. Faseb J. 2008

Kokoeva MV, Yin H, Flier JS. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. Science 2005;310:679–683. [PubMed: 16254185]

Koo JW, Duman RS. IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci U S A 2008;105:751–756. [PubMed: 18178625]

Kornack DR, Rakic P. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc Natl Acad Sci U S A 1999;96:5768–5773. [PubMed: 10318959]

Kornack DR, Rakic P. Cell proliferation without neurogenesis in adult primate neocortex. Science 2001;294:2127–2130. [PubMed: 11739948]

Kotani S, Yamauchi T, Teramoto T, Ogura H. Pharmacological evidence of cholinergic involvement in adult hippocampal neurogenesis in rats. Neuroscience 2006;142:505–514. [PubMed: 16889901]

Kowalczyk A, Filipkowski RK, Rylski M, Wilczynski GM, Konopacki FA, Jaworski J, Ciemerych MA, Sicinski P, Kaczmarek L. The critical role of cyclin D2 in adult neurogenesis. J Cell Biol 2004;167:209–213. [PubMed: 15504908]

Kronenberg G, Reuter K, Steiner B, Brandt MD, Jessberger S, Yamaguchi M, Kempermann G. Subpopulations of proliferating cells of the adult hippocampus respond differently to physiologic neurogenic stimuli. J Comp Neurol 2003;467:455–463. [PubMed: 14624480]

Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci 1997;17:5820–5829. [PubMed: 9221780]

Kulkarni VA, Jha S, Vaidya VA. Depletion of norepinephrine decreases the proliferation, but does not influence the survival and differentiation, of granule cell progenitors in the adult rat hippocampus. Eur J Neurosci 2002;16:2008–2012. [PubMed: 12453065]

Lai K, Kaspar BK, Gage FH, Schaffer DV. Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. Nat Neurosci 2003;6:21–27. [PubMed: 12469128]

Lee J, Duan W, Mattson MP. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 2002;82:1367–1375. [PubMed: 12354284]

Lemaire V, Koehl M, Le Moal M, Abrous DN. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc Natl Acad Sci U S A 2000;97:11032–11037. [PubMed: 11005874]

Leuner B, Kozorovitskiy Y, Gross CG, Gould E. Diminished adult neurogenesis in the marmoset brain precedes old age. Proc Natl Acad Sci U S A 2007;104:17169–17173. [PubMed: 17940008]

Leuner B, Mendolia-Loffredo S, Kozorovitskiy Y, Samburg D, Gould E, Shors TJ. Learning enhances the survival of new neurons beyond the time when the hippocampus is required for memory. J Neurosci 2004;24:7477–7481. [PubMed: 15329394]

Lichtenwalner RJ, Forbes ME, Bennett SA, Lynch CD, Sonntag WE, Riddle DR. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience 2001;107:603–613. [PubMed: 11720784]

Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A, Lein ES, Jessberger S, Lansford H, Dearie AR, Gage FH. Wnt signalling regulates adult hippocampal neurogenesis. Nature 2005;437:1370–1375. [PubMed: 16251967]

Liu PK, Robertson CS, Valadka A. The association between neuronal nitric oxide synthase and neuronal sensitivity in the brain after brain injury. Ann N Y Acad Sci 2002;962:226–241. [PubMed: 12076978]

Liu X, Wang Q, Haydar TF, Bordey A. Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors. Nat Neurosci 2005;8:1179–1187. [PubMed: 16116450]

Lledo PM, Alonso M, Grubb MS. Adult neurogenesis and functional plasticity in neuronal circuits. Nat Rev Neurosci 2006;7:179–193. [PubMed: 16495940]

Lois C, Alvarez-Buylla A. Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. Proc Natl Acad Sci U S A 1993;90:2074–2077. [PubMed: 8446631]

Lucas G, Rymar VV, Du J, Mnie-Filali O, Bisgaard C, Manta S, Lambas-Senas L, Wiborg O, Haddjeri N, Pineyro G, Sadikot AF, Debonnel G. Serotonin(4) (5-HT(4)) receptor agonists are putative antidepressants with a rapid onset of action. Neuron 2007;55:712–725. [PubMed: 17785179]

Lucassen PJ, Muller MB, Holsboer F, Bauer J, Holtrop A, Wouda J, Hoogendijk WJ, De Kloet ER, Swaab DF. Hippocampal apoptosis in major depression is a minor event and absent from subareas at risk for glucocorticoid overexposure. Am J Pathol 2001;158:453–468. [PubMed: 11159183]

Luzzati F, De Marchis S, Fasolo A, Peretto P. Neurogenesis in the caudate nucleus of the adult rabbit. J Neurosci 2006;26:609–621. [PubMed: 16407559]

Mackowiak M, Kolasiewicz W, Markowicz-Kula K, Wedzony K. Purvalanol A, inhibitor of cyclin-dependent kinases attenuates proliferation of cells in the dentate gyrus of the adult rat hippocampus. Pharmacol Rep 2005;57:845–849. [PubMed: 16382206]

Madsen TM, Kristjansen PE, Bolwig TG, Wortwein G. Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. Neuroscience 2003;119:635–642. [PubMed: 12809684]

Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingstrom A. Increased neurogenesis in a model of electroconvulsive therapy. Biol Psychiatry 2000;47:1043–1049. [PubMed: 10862803]

Maeda K, Sugino H, Hirose T, Kitagawa H, Nagai T, Mizoguchi H, Takuma K, Yamada K. Clozapine prevents a decrease in neurogenesis in mice repeatedly treated with phencyclidine. J Pharmacol Sci 2007;103:299–308. [PubMed: 17341843]

Malberg JE, Duman RS. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. Neuropsychopharmacology 2003;28:1562–1571. [PubMed: 12838272]

Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20:9104–9110. [PubMed: 11124987]

Manev H, Uz T, Smalheiser NR, Manev R. Antidepressants alter cell proliferation in the adult brain in vivo and in neural cultures in vitro. Eur J Pharmacol 2001;411:67–70. [PubMed: 11137860]

Manganas LN, Zhang X, Li Y, Hazel RD, Smith SD, Wagshul ME, Henn F, Benveniste H, Djuric PM, Enikolopov G, Maletic-Savatic M. Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science 2007;318:980–985. [PubMed: 17991865]

Markakis EA, Gage FH. Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. J Comp Neurol 1999;406:449–460. [PubMed: 10205022]

Mathern GW, Leiphart JL, De Vera A, Adelson PD, Seki T, Neder L, Leite JP. Seizures decrease postnatal neurogenesis and granule cell development in the human fascia dentata. Epilepsia 2002;43(Suppl 5):68–73. [PubMed: 12121298]

Mazzucco CA, Lieblich SE, Bingham BI, Williamson MA, Viau V, Galea LA. Both estrogen receptor alpha and estrogen receptor beta agonists enhance cell proliferation in the dentate gyrus of adult female rats. Neuroscience 2006;141:1793–1800. [PubMed: 16797852]

McDonald HY, Wojtowicz JM. Dynamics of neurogenesis in the dentate gyrus of adult rats. Neurosci Lett 2005;385:70–75. [PubMed: 15967575]

McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci 1999;22:105–122. [PubMed: 10202533]

McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 2005;54:20–23. [PubMed: 15877308]

McKay R. Stem cells in the central nervous system. Science 1997;276:66–71. [PubMed: 9082987]

Melanson-Drapeau L, Beyko S, Dave S, Hebb AL, Franks DJ, Sellitto C, Paul DL, Bennett SA. Oligodendrocyte progenitor enrichment in the connexin32 null-mutant mouse. J Neurosci 2003;23:1759–1768. [PubMed: 12629180]

Meshi D, Drew MR, Saxe M, Ansorge MS, David D, Santarelli L, Malapani C, Moore H, Hen R. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. Nat Neurosci 2006;9:729–731. [PubMed: 16648847]

Millar JK, Christie S, Porteous DJ. Yeast two-hybrid screens implicate DISC1 in brain development and function. Biochem Biophys Res Commun 2003;311:1019–1025. [PubMed: 14623284]

Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, Clair DM, Muir WJ, Blackwood DH, Porteous DJ. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet 2000;9:1415–1423. [PubMed: 10814723]

Mirescu C, Gould E. Stress and adult neurogenesis. Hippocampus 2006;16:233–238. [PubMed: 16411244]

Mirescu C, Peters JD, Gould E. Early life experience alters response of adult neurogenesis to stress. Nat Neurosci 2004;7:841–846. [PubMed: 15273691]

Mohapel P, Ekdahl CT, Lindvall O. Status epilepticus severity influences the long-term outcome of neurogenesis in the adult dentate gyrus. Neurobiol Dis 2004;15:196–205. [PubMed: 15006689]

Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. Science 2003;302:1760–1765. [PubMed: 14615545]

Morcuende S, Gadd CA, Peters M, Moss A, Harris EA, Sheasby A, Fisher AS, De Felipe C, Mantyh PW, Rupniak NM, Giese KP, Hunt SP. Increased neurogenesis and brain-derived neurotrophic factor in neurokinin-1 receptor gene knockout mice. Eur J Neurosci 2003;18:1828–1836. [PubMed: 14622216]

Muller MB, Lucassen PJ, Yassouridis A, Hoogendijk WJ, Holsboer F, Swaab DF. Neither major depression nor glucocorticoid treatment affects the cellular integrity of the human hippocampus. Eur J Neurosci 2001;14:1603–1612. [PubMed: 11860455]

Muroyama Y, Fujihara M, Ikeya M, Kondoh H, Takada S. Wnt signaling plays an essential role in neuronal specification of the dorsal spinal cord. Genes Dev 2002;16:548–553. [PubMed: 11877374]

Murray F, Smith DW, Hutson PH. Chronic low dose corticosterone exposure decreased hippocampal cell proliferation, volume and induced anxiety and depression like behaviours in mice. Eur J Pharmacol 2008;583:115–127. [PubMed: 18289522]

Nacher J, Alonso-Llosa G, Rosell DR, McEwen BS. NMDA receptor antagonist treatment increases the production of new neurons in the aged rat hippocampus. Neurobiol Aging 2003;24:273–284. [PubMed: 12498961]

Nacher J, Varea E, Miguel Blasco-Ibanez J, Gomez-Climent MA, Castillo-Gomez E, Crespo C, Martinez-Guijarro FJ, McEwen BS. N-methyl-d-aspartate receptor expression during adult neurogenesis in the rat dentate gyrus. Neuroscience 2007;144:855–864. [PubMed: 17157994]

Nakagawa S, Kim JE, Lee R, Chen J, Fujioka T, Malberg J, Tsuji S, Duman RS. Localization of phosphorylated cAMP response element-binding protein in immature neurons of adult hippocampus. J Neurosci 2002a;22:9868–9876. [PubMed: 12427843]

Nakagawa S, Kim JE, Lee R, Malberg JE, Chen J, Steffen C, Zhang YJ, Nestler EJ, Duman RS. Regulation of neurogenesis in adult mouse hippocampus by cAMP and the cAMP response element-binding protein. J Neurosci 2002b;22:3673–3682. [PubMed: 11978843]

Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J Neurosci 1996;16:2365–2372. [PubMed: 8601816]

Oleskevich S, Descarries L, Watkins KC, Seguela P, Daszuta A. Ultrastructural features of the serotonin innervation in adult rat hippocampus: an immunocytochemical description in single and serial thin sections. Neuroscience 1991;42:777–791. [PubMed: 1956515]

Ormerod BK, Lee TT, Galea LA. Estradiol initially enhances but subsequently suppresses (via adrenal steroids) granule cell proliferation in the dentate gyrus of adult female rats. J Neurobiol 2003;55:247–260. [PubMed: 12672021]

Overstreet Wadiche L, Bromberg DA, Bensen AL, Westbrook GL. GABAergic signaling to newborn neurons in dentate gyrus. J Neurophysiol 2005;94:4528–4532. [PubMed: 16033936]

Overstreet-Wadiche LS, Bensen AL, Westbrook GL. Delayed development of adult-generated granule cells in dentate gyrus. J Neurosci 2006a;26:2326–2334. [PubMed: 16495460]

Overstreet-Wadiche LS, Bromberg DA, Bensen AL, Westbrook GL. Seizures accelerate functional integration of adult-generated granule cells. J Neurosci 2006b;26:4095–4103. [PubMed: 16611826]

Packer MA, Stasiv Y, Benraiss A, Chmielnicki E, Grinberg A, Westphal H, Goldman SA, Enikolopov G. Nitric oxide negatively regulates mammalian adult neurogenesis. Proc Natl Acad Sci U S A 2003;100:9566–9571. [PubMed: 12886012]

Palmer TD, Ray J, Gage FH. FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. Mol Cell Neurosci 1995;6:474–486. [PubMed: 8581317]

Parent JM. Adult neurogenesis in the intact and epileptic dentate gyrus. Prog Brain Res 2007;163:529–540. [PubMed: 17765736]

Parent JM, von dem Bussche N, Lowenstein DH. Prolonged seizures recruit caudal subventricular zone glial progenitors into the injured hippocampus. Hippocampus 2006a;16:321–328. [PubMed: 16435310]

Parent JM, Tada E, Fike JR, Lowenstein DH. Inhibition of dentate granule cell neurogenesis with brain irradiation does not prevent seizure-induced mossy fiber synaptic reorganization in the rat. J Neurosci 1999;19:4508–4519. [PubMed: 10341251]

Parent JM, Elliott RC, Pleasure SJ, Barbaro NM, Lowenstein DH. Aberrant seizure-induced neurogenesis in experimental temporal lobe epilepsy. Ann Neurol 2006b;59:81–91. [PubMed: 16261566]

Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. J Neurosci 1997;17:3727–3738. [PubMed: 9133393]

Patel TD, Zhou FC. Ontogeny of 5-HT1A receptor expression in the developing hippocampus. Brain Res Dev Brain Res 2005;157:42–57.

Pechnick RN, Zonis S, Wawrowsky K, Pourmorady J, Chesnokova V. p21Cip1 restricts neuronal proliferation in the subgranular zone of the dentate gyrus of the hippocampus. Proc Natl Acad Sci U S A 2008;105:1358–1363. [PubMed: 18172194]

Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. J Neurosci 2001;21:6706–6717. [PubMed: 11517260]

Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C, Spitzer G, Santarelli L, Scharf B, Hen R, Rosoklija G, Sackeim HA, Dwork AJ. Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. J Neurosci 2007;27:4894–4901. [PubMed: 17475797]

Perez-Martin M, Salazar V, Castillo C, Ariznavarreta C, Azcoitia I, Garcia-Segura LM, Tresguerres JA. Estradiol and soy extract increase the production of new cells in the dentate gyrus of old rats. Exp Gerontol 2005;40:450–453. [PubMed: 15885957]

Pickard BS, Pieper AA, Porteous DJ, Blackwood DH, Muir WJ. The NPAS3 gene--emerging evidence for a role in psychiatric illness. Ann Med 2006;38:439–448. [PubMed: 17008307]

Pieper AA, Wu X, Han TW, Estill SJ, Dang Q, Wu LC, Reece-Fincanon S, Dudley CA, Richardson JA, Brat DJ, McKnight SL. The neuronal PAS domain protein 3 transcription factor controls FGF-mediated adult hippocampal neurogenesis in mice. Proc Natl Acad Sci U S A 2005;102:14052–14057. [PubMed: 16172381]

Pieribone VA, Porton B, Rendon B, Feng J, Greengard P, Kao HT. Expression of synapsin III in nerve terminals and neurogenic regions of the adult brain. J Comp Neurol 2002;454:105–114. [PubMed: 12412137]

Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mizumatsu S, VandenBerg SR, Fike JR. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat Res 2004;162:39–47. [PubMed: 15222778]

Radley JJ, Jacobs BL. 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res 2002;955:264–267. [PubMed: 12419546]

Rai KS, Hattiangady B, Shetty AK. Enhanced production and dendritic growth of new dentate granule cells in the middle-aged hippocampus following intracerebroventricular FGF-2 infusions. Eur J Neurosci 2007;26:1765–1779. [PubMed: 17883411]

Rao MS, Shetty AK. Efficacy of doublecortin as a marker to analyse the absolute number and dendritic growth of newly generated neurons in the adult dentate gyrus. Eur J Neurosci 2004;19:234–246. [PubMed: 14725617]

Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch KP. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 2006;11:514–522. [PubMed: 16415915]

Reif A, Schmitt A, Fritzen S, Chourbaji S, Bartsch C, Urani A, Wycislo M, Mossner R, Sommer C, Gass P, Lesch KP. Differential effect of endothelial nitric oxide synthase (NOS-III) on the regulation of adult neurogenesis and behaviour. Eur J Neurosci 2004;20:885–895. [PubMed: 15305857]

Reya T, Duncan AW, Ailles L, Domen J, Scherer DC, Willert K, Hintz L, Nusse R, Weissman IL. A role for Wnt signalling in self-renewal of haematopoietic stem cells. Nature 2003;423:409–414. [PubMed: 12717450]

Ribak CE, Korn MJ, Shan Z, Obenaus A. Dendritic growth cones and recurrent basal dendrites are typical features of newly generated dentate granule cells in the adult hippocampus. Brain Res 2004;1000:195–199. [PubMed: 15053968]

Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, Fabbri ME, Tessarollo L, Maffei L, Berardi N, Caleo M. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. Eur J Neurosci 2006;24:1850–1856. [PubMed: 17040481]

Ruiz i Altaba A, Palma V, Dahmane N. Hedgehog-Gli signalling and the growth of the brain. Nat Rev Neurosci 2002;3:24–33. [PubMed: 11823802]

Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci 2007;10:1110–1115. [PubMed: 17726477]

Sahay A, Drew MR, Hen R. Dentate gyrus neurogenesis and depression. Prog Brain Res 2007;163:697–822. [PubMed: 17765746]

Sairanen M, Lucas G, Ernfors P, Castren M, Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. J Neurosci 2005;25:1089–1094. [PubMed: 15689544]

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301:805–809. [PubMed: 12907793]

Saravia F, Revsin Y, Lux-Lantos V, Beauquis J, Homo-Delarche F, De Nicola AF. Oestradiol restores cell proliferation in dentate gyrus and subventricular zone of streptozotocin-diabetic mice. J Neuroendocrinol 2004;16:704–710. [PubMed: 15271063]

Saravia FE, Beauquis J, Revsin Y, Homo-Delarche F, de Kloet ER, De Nicola AF. Hippocampal neuropathology of diabetes mellitus is relieved by estrogen treatment. Cell Mol Neurobiol 2006;26:943–957. [PubMed: 16807785]

Saxe MD, Battaglia F, Wang JW, Malleret G, David DJ, Monckton JE, Garcia AD, Sofroniew MV, Kandel ER, Santarelli L, Hen R, Drew MR. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc Natl Acad Sci U S A 2006;103:17501–17506. [PubMed: 17088541]

Schanzer A, Wachs FP, Wilhelm D, Acker T, Cooper-Kuhn C, Beck H, Winkler J, Aigner L, Plate KH, Kuhn HG. Direct stimulation of adult neural stem cells in vitro and neurogenesis in vivo by vascular endothelial growth factor. Brain Pathol 2004;14:237–248. [PubMed: 15446578]

Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 2005;192:348–356. [PubMed: 15755552]

Scharfman HE, Goodman JH, Sollas AL. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. J Neurosci 2000;20:6144–6158. [PubMed: 10934264]

Schmidt-Hieber C, Jonas P, Bischofberger J. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 2004;429:184–187. [PubMed: 15107864]

Schmitt A, Weber S, Jatzko A, Braus DF, Henn FA. Hippocampal volume and cell proliferation after acute and chronic clozapine or haloperidol treatment. J Neural Transm 2004;111:91–100. [PubMed: 14714218]

Schmitt A, Benninghoff J, Moessner R, Rizzi M, Paizanis E, Doenitz C, Gross S, Hermann M, Gritti A, Lanfumey L, Fritzen S, Reif A, Hamon M, Murphy DL, Vescovi A, Lesch KP. Adult neurogenesis in serotonin transporter deficient mice. J Neural Transm 2007;114:1107–1119. [PubMed: 17510734]

Schroeter EH, Kisslinger JA, Kopan R. Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain. Nature 1998;393:382–386. [PubMed: 9620803]

Scott BW, Wang S, Burnham WM, De Boni U, Wojtowicz JM. Kindling-induced neurogenesis in the dentate gyrus of the rat. Neurosci Lett 1998;248:73–76. [PubMed: 9654345]

Seki T, Arai Y. Highly polysialylated neural cell adhesion molecule (NCAM-H) is expressed by newly generated granule cells in the dentate gyrus of the adult rat. J Neurosci 1993;13:2351–2358. [PubMed: 7684771]

Selvarajah D, Tesfaye S. Central nervous system involvement in diabetes mellitus. Curr Diab Rep 2006;6:431–438. [PubMed: 17118225]

Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A. Astrocytes give rise to new neurons in the adult mammalian hippocampus. J Neurosci 2001;21:7153–7160. [PubMed: 11549726]

Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. J Comp Neurol 2004;478:359–378. [PubMed: 15384070]

Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003;160:1516–1518. [PubMed: 12900317]

Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034–5043. [PubMed: 10366636]

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 1996;93:3908–3913. [PubMed: 8632988]

Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev 1999;13:1501–1512. [PubMed: 10385618]

Shetty AK, Hattiangady B. Concise review: prospects of stem cell therapy for temporal lobe epilepsy. Stem Cells 2007;25:2396–2407. [PubMed: 17600108]

Shimazu K, Zhao M, Sakata K, Akbarian S, Bates B, Jaenisch R, Lu B. NT-3 facilitates hippocampal plasticity and learning and memory by regulating neurogenesis. Learn Mem 2006;13:307–315. [PubMed: 16705139]

Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 2002;12:578–584. [PubMed: 12440573]

Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. Neurogenesis in the adult is involved in the formation of trace memories. Nature 2001;410:372–376. [PubMed: 11268214]

Sisti HM, Glass AL, Shors TJ. Neurogenesis and the spacing effect: learning over time enhances memory and the survival of new neurons. Learn Mem 2007;14:368–375. [PubMed: 17522028]

Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 1995;15:1768–1777. [PubMed: 7891134]

Snyder JS, Hong NS, McDonald RJ, Wojtowicz JM. A role for adult neurogenesis in spatial long-term memory. Neuroscience 2005;130:843–852. [PubMed: 15652983]

Snyder SE, Salton SR. Expression of VGF mRNA in the adult rat central nervous system. J Comp Neurol 1998;394:91–105. [PubMed: 9550144]

Snyder SH, Ferris CD. Novel neurotransmitters and their neuropsychiatric relevance. Am J Psychiatry 2000;157:1738–1751. [PubMed: 11058466]

Sohur US, Emsley JG, Mitchell BD, Macklis JD. Adult neurogenesis and cellular brain repair with neural progenitors, precursors and stem cells. Philos Trans R Soc Lond B Biol Sci 2006;361:1477–1497. [PubMed: 16939970]

Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. Nature 2002;417:39–44. [PubMed: 11986659]

Spritzer MD, Galea LA. Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. Dev Neurobiol 2007;67:1321–1333. [PubMed: 17638384]

Stanfield BB, Trice JE. Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp Brain Res 1988;72:399–406. [PubMed: 2465172]

Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nat Neurosci 2008;11:309–317. [PubMed: 18278039]

Tanapat P, Hastings NB, Reeves AJ, Gould E. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. J Neurosci 1999;19:5792–5801. [PubMed: 10407020]

Tanapat P, Hastings NB, Rydel TA, Galea LA, Gould E. Exposure to fox odor inhibits cell proliferation in the hippocampus of adult rats via an adrenal hormone-dependent mechanism. J Comp Neurol 2001;437:496–504. [PubMed: 11503148]

Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH. NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. Nature 2006;442:929–933. [PubMed: 16906136]

Thakker-Varia S, Krol JJ, Nettleton J, Bilimoria PM, Bangasser DA, Shors TJ, Black IB, Alder J. The neuropeptide VGF produces antidepressant-like behavioral effects and enhances proliferation in the hippocampus. J Neurosci 2007;27:12156–12167. [PubMed: 17989282]

Tozuka Y, Fukuda S, Namba T, Seki T, Hisatsune T. GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells. Neuron 2005;47:803–815. [PubMed: 16157276]

Traiffort E, Charytoniuk DA, Faure H, Ruat M. Regional distribution of sonic hedgehog, patched, and smoothened mRNA in the adult rat brain. J Neurochem 1998;70:1327–1330. [PubMed: 9489757]

Trejo JL, Llorens-Martin MV, Torres-Aleman I. The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. Mol Cell Neurosci. 2007

Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S, Senba E. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. Neurosci Res 1997;28:103–110. [PubMed: 9220467]

Valastro B, Cossette J, Lavoie N, Gagnon S, Trudeau F, Massicotte G. Up-regulation of glutamate receptors is associated with LTP defects in the early stages of diabetes mellitus. Diabetologia 2002;45:642–650. [PubMed: 12107744]

Van Kampen JM, Robertson HA. A possible role for dopamine D3 receptor stimulation in the induction of neurogenesis in the adult rat substantia nigra. Neuroscience 2005;136:381–386. [PubMed: 16216425]

Van Kampen JM, Eckman CB. Dopamine D3 receptor agonist delivery to a model of Parkinson's disease restores the nigrostriatal pathway and improves locomotor behavior. J Neurosci 2006;26:7272–7280. [PubMed: 16822985]

Van Kampen JM, Hagg T, Robertson HA. Induction of neurogenesis in the adult rat subventricular zone and neostriatum following dopamine D3 receptor stimulation. Eur J Neurosci 2004;19:2377–2387. [PubMed: 15128392]

van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999;2:266–270. [PubMed: 10195220]

van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. Functional neurogenesis in the adult hippocampus. Nature 2002;415:1030–1034. [PubMed: 11875571]

Verwer RW, Sluiter AA, Balesar RA, Baayen JC, Noske DP, Dirven CM, Wouda J, van Dam AM, Lucassen PJ, Swaab DF. Mature astrocytes in the adult human neocortex express the early neuronal marker doublecortin. Brain 2007;130:3321–3335. [PubMed: 18055496]

Wakade CG, Mahadik SP, Waller JL, Chiu FC. Atypical neuroleptics stimulate neurogenesis in adult rat brain. J Neurosci Res 2002;69:72–79. [PubMed: 12111817]

Wang HD, Dunnavant FD, Jarman T, Deutch AY. Effects of antipsychotic drugs on neurogenesis in the forebrain of the adult rat. Neuropsychopharmacology 2004;29:1230–1238. [PubMed: 15085089]

Wang JW, David DJ, Monckton JE, Battaglia F, Hen Rt. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. J Neurosci 2008a;28:1374–1384. [PubMed: 18256257]

Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. J Neurosci 2008b;28:1374–1384. [PubMed: 18256257]

Warner-Schmidt JL, Duman RS. VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proc Natl Acad Sci U S A 2007;104:4647–4652. [PubMed: 17360578]

Warner-Schmidt JL, Madsen TM, Duman RS. Electroconvulsive seizure restores neurogenesis and hippocampus-dependent fear memory after disruption by irradiation. Eur J Neurosci 2008;27:1485–1493. [PubMed: 18336568]

Weissman IL, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and transdifferentiations. Annu Rev Cell Dev Biol 2001;17:387–403. [PubMed: 11687494]

Westenbroek C, Den Boer JA, Veenhuis M, Ter Horst J. Chronic stress and social housing differentially affect neurogenesis in male and female rats. Brain Res Bull 2004;64:303–308. [PubMed: 15561464]

Winocur G, Wojtowicz JM, Sekeres M, Snyder JS, Wang S. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 2006;16:296–304. [PubMed: 16411241]

Wiskott L, Rasch MJ, Kempermann G. A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. Hippocampus 2006;16:329–343. [PubMed: 16435309]

Wong EY, Herbert J. The corticoid environment: a determining factor for neural progenitors' survival in the adult hippocampus. Eur J Neurosci 2004;20:2491–2498. [PubMed: 15548194]

Wong EY, Herbert J. Roles of mineralocorticoid and glucocorticoid receptors in the regulation of progenitor proliferation in the adult hippocampus. Eur J Neurosci 2005;22:785–792. [PubMed: 16115202]

Wong EY, Herbert J. Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. Neuroscience 2006;137:83–92. [PubMed: 16289354]

Yoshimura S, Takagi Y, Harada J, Teramoto T, Thomas SS, Waeber C, Bakowska JC, Breakefield XO, Moskowitz MA. FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. Proc Natl Acad Sci U S A 2001;98:5874–5879. [PubMed: 11320217]

Zhang CL, Zou Y, He W, Gage FH, Evans RM. A role for adult TLX-positive neural stem cells in learning and behaviour. Nature 2008a;451:1004–1007. [PubMed: 18235445]

Zhang WJ, Tan YF, Yue JT, Vranic M, Wojtowicz JM. Impairment of hippocampal neurogenesis in streptozotocin-treated diabetic rats. Acta Neurol Scand 2008b;117:205–210. [PubMed: 17854417]

Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 2006;26:3–11. [PubMed: 16399667]

Zhao M, Li D, Shimazu K, Zhou YX, Lu B, Deng CX. Fibroblast growth factor receptor-1 is required for long-term potentiation, memory consolidation, and neurogenesis. Biol Psychiatry 2007a; 62:381–390. [PubMed: 17239352]

Zhao S, Chai X, Frotscher M. Balance between neurogenesis and gliogenesis in the adult hippocampus: role for reelin. Dev Neurosci 2007b;29:84–90. [PubMed: 17148951]

Zhu XJ, Hua Y, Jiang J, Zhou QG, Luo CX, Han X, Lu YM, Zhu DY. Neuronal nitric oxide synthase-derived nitric oxide inhibits neurogenesis in the adult dentate gyrus by down-regulating cyclic AMP response element binding protein phosphorylation. Neuroscience 2006;141:827–836. [PubMed: 16735094]

Zigova T, Pencea V, Wiegand SJ, Luskin MB. Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb. Mol Cell Neurosci 1998;11:234–245. [PubMed: 9675054]

Table 1

Effects of various growth factors on adult hippocampal neurogenesis. Abbreviations: FGF-1R (fibroblast growth factor-1 receptor), FGF-2 (fibroblast growth factor-2), i.c.v. (intracerebraventricular), IGF-I (insulin-like growth factor one), LID (liver insulin deficient), VEGF (vascular endothelial growth factor).

Growth Factor	Species	Manipulation	Proliferation	Differentiation	Survival	Reference
EGF	Rat	i.c.v. (14 days)	↔	—	—	Kuhn et al., 1997
FGF-2	Rat	i.c.v. (14 days)	—	—	↑ [a]	Rai et al., 2007
	Mouse	FGF-1R (-/-)	↓	↓ Neurons, glia	↓	Zhao et al., 2007a
	Mouse	FGF-2 (-/-)	↔	↔	↔	Yoshimura et al., 2001
IGF-I	Rat (aged)	i.c.v. (Chronic)	↑	↔	↑	Lichtenwalner et al., 2001
	Rat	Peripheral (Chronic)	↑	↑ Neurons	↑	Aberg et al., 2000; Aberg et al., 2003
	Mouse	LID	↔	↔	↓	Trejo et al., 2007
VEGF	Rat	i.c.v. (3 days)	↑ [b]	—	—	Jin et al., 2002
	Rat	i.c.v. (8 days)	↔	↔	↑	Schanzer et al., 2004

[a] Sacrificed 10d after last BrdU injection

[b] Sacrificed 7d after last BrdU injection

Table 2

Regulation of adult hippocampal neurogenesis by neurotrophic factors. Abbreviations: BDNF (brain derived neurotrophic factor), CNTF (ciliary neurotrophic factor), NT-3,-4 (neurotrophin-3,-4), NGF (nerve growth factor)

Neurotrophin	Species	Manipulation	Proliferation	Differentiation	Survival	Reference
BDNF	Rat	Intrahippocampal (14 days)	—	—	↑	Scharfman et al., 2005
		BDNF (+/-)	↓	—	↓	Lee et al., 2002
		BDNF (+/-)	↑	—	↓	Sairanen et al., 2005
		Truncated TrkB transgenic	↑	—	↓	Sairanen et al., 2005
NT-3	Mouse	NT-3 (-/-)	↔	↓ Neurons	↔	Shimazu et al., 2006
NT-4	Mouse	NT-4 (-/-)	—	↔	↔	Rossi et al., 2006
CNTF	Mouse	Intrafrontalcortical (single injection)	↑ [a]	↑ Neurons	↔	Emsley and Hagg, 2003
NGF	Rat	i.c.v.	↔	↔	↑	Frielingsdorf et al., 2007

[a] Sacrificed 10d after last BrdU injection

Table 3

Regulation of hippocampal neurogenesis by neurotransmitter systems. Abbreviations: AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor); DETA/NONOate ((Z)-1-[*N*-(2-aminoethyl)-*N*-(2-ammonioethyl) aminio] diazen-1ium-1,2-diolate); 5,7-DHT (5,7-dihyrdoxytryptamine); DSP-4 (N-Ethyl-N-(2-chloroethyl)-2-bromobenzylamine); GABA-A (γ amino butyric acid); L-NAME (N^{ω}-nitro-methyl-L[D]-arginine methyl ester); MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine); nAChR (nicotinic acetylcholine receptor); NMDAR (N-methyl-D-aspartate receptor); NOS (nitric oxide synthase); NR1 (NMDAR subunit1); 8-OH DPAT (8-hydroxy-2-(N-dipropylamino) tetralin); PCPA (parachlorophenylalanine); SERT(serotonin transporter)

Neurotransmitter	Species	Manipulation	Mechanism	Proliferation	Differentiation	Survival	Reference
Glutamate	Rat	Lesion of perfornt path	N/A	↑	—	—	Cameron et al., 1995; Gould et al., 1994
	Mouse	Lesion of entorhinal cortex	N/A	↔	↔	↑	Gama Sosa et al., 2004
	Rat	MK-801	NMDAR antagonist	↑	—	↑	Cameron et al., 1995
	Mouse	NR1 subunit (+/-)	N/A	—	↔	↑	Bursztajn et al., 2007
	Rat	LY451646	AMPA receptor potentiator	↑	—	—	Bai et al., 2003
GABA	Mouse	γ-2 subunit of GABA-A receptor (+/-)	N/A	↔	↓	↓	Earnheart et al., 2007
Norepinephrine	Rat	DSP-4	Noradrenergic toxin	↓	↔	↔	Kulkarni et al., 2002
Dopamine	Mouse	MPTP	Dopamine depletion	↓	—	↔	Hoglinger et al., 2004
	Rat	Cocaine	Dopamine transporter inhibitor	↓	↔	↔	Dominguez-Escriba et al., 2006
	Rat	Haloperidol	D2 receptor antagonist	↔	—	—	Malberg et al., 2000
Acetylcholine	Rat	Lesion of cholinergic forebrain neurons	N/A	—	↓ Neurons	↔	Cooper-Kuhn et al., 2004
	Mice	Donepezil	Acetylcholinesteras e inhibitor	↔	↔	↑	Kaneko et al., 2006
	Rat	Donepezil	Acetylcholinesteras e inhibitor	↔	↔	↑	Kotani et al., 2006
	Rat	Scopolamine	Muscarinic receptor antagonist	↔	↔	↓	Kotani et al., 2006
	Mouse	β-2 subunit of nAChR (-/-)	N/A	↓	—	—	Harrist et al., 2004
Serotonin	Rat	5,7-DT (intraraphe)	Serotonergic lesion	↓	—	—	Brezun and Daszuta, 1999

Neurotransmitter	Species	Manipulation	Mechanism	Proliferation	Differentiation	Survival	Reference
		5,7-DT (i.c.v.)	Serotonergic lesion	↔	↔	↔	Jha et al., 2006
	Rat	PCPA	Serotonin depletion	↓	↔	↔	Banasr et al., 2001; Jha et al., 2006
	Mouse	SERT (-/-) aged	N/A	↑	↔	↔	Schmitt et al., 2007
	Rat	NAN-190, p-MPPI and WAY-100635	5-HT1AR antagonists	↓	—	—	Radley and Jacobs, 2002
	Rat	8-OH DPAT	5-HT1AR agonist	↑	—	—	Banasr et al., 2004
	Mouse	8-OH DPAT	5-HT1AR agonist	↑	—	—	Santarelli et al., 2003
	Rat	Sumatriptan / GR 127935	5-HT1BR agonist / antagonist	↔/↔	—	—	Banasr et al., 2004
	Rat	DOI / Ketanserin	5-HT 2A/2C antagonists	↔/↓	—	—	Banasr et al., 2004
	Rat	RO 600175 / SB 206553	5-HT2CR agonist / antagonist	↔/↔	—	—	Banasr et al., 2004
	Rat	RS 67333	5-HT4R agonist	↑	—	—	Lucas et al., 2007
Nitric oxide	Rat	L-NAME	nonspecific NOS inhibitor	↑ [a]	↔	—	Packer er al., 2003
	Mouse	NOS-I null mutant	N/A	↑	—	—	Packer er al., 2003
	Mouse	NOS-I -/-	N/A	↑	↔	↑	Zhu et al., 2006, Fritzen et al., 2006
	Mouse	7-nitroindazole	NOS-I inhibitor	↑	↔	↑	Zhu et al., 2006
	Mouse	NOS-III -/-	N/A	↓ [b]	↔	↔	Reif et al., 2004
	Mouse	NOS-I/III -/-	N/A	—	—	↓	Fritzen et al., 2007
	Mouse	DETA/NONOate	polyamine / NO adduct	↑	—	↑	Hua et al., 2008

[a] Sacrificed 7d after last BrdU injection

[b] Sacrificed 6d after the last BrdU injection

Neurosci Biobehav Rev. Author manuscript; available in PMC 2010 March 1.