NeuroMolecular Medicine

Volume 5 • No. 1 • 2004 • ISSN 1535–1084

HUMANA PRESS

Special Issue:

Psychiatric Disorder

Guest Editor: Eric J. Nestler

NeuroMolecular Medicine

ISSN 1535-1084/04/05:1–9/$25.00

Neurogenesis and Neuroadaptation

David V. Schaffer*[*,1] and Fred H. Gage[2]

[1]Department of Chemical Engineering and the Helen Wills Neuroscience Institute, University of California, Berkeley, CA 94720-1462, and [2]Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA 92037

Received October 24, 2003; Accepted October 27, 2003

Abstract

Adult neurogenesis has been established as a further mechanism of neural plasticity in the adult nervous system, and numerous studies are beginning to provide insights into the functional purposes and consequences for this new mode of neuroadaptation. These studies have approached the problem from a molecular scale, attempting to identify signaling factors that regulate stem cell function, as well as a systems or behavioral level, attempting to establish correlative and potentially causal links between neurogenesis and behavior. These two approaches have begun to reveal several potential functions for adult hippocampal neurogenesis, including adaptive roles in learning and memory, adaptation to novel environments, potential links to depression and moods, and possible responses to injury. The further implementation and convergence of these two approaches and the development of new methods to study the problem will yield further insights into both what are the many neuroadaptive roles of neurogenesis and potential means to harness it for neuroregeneration.

Index Entries: Neural progenitors; neural stem cells; adult neurogenesis; hippocampus; fibroblast growth factor; depression.

It has only recently been established and widely accepted that the central nervous system continually generates new neurons throughout adulthood, and the field has now evolved into addressing two fundamental sets of questions. First, what are the mechanisms that regulate and control adult neurogenesis at the cellular and molecular levels? Second, what are the biological purposes and consequences of this additional mechanism for neural plasticity? This article discusses how these questions can be viewed as representing two closely related and complementary approaches to understanding how neurogenesis underlies the process of neuroadaptation in the adult.

*Author to whom all correspondence and reprint requests should be addressed. E-mail: schaffer@cchem.berkeley.edu.

A Brief History of Adult Neurogenesis in Mammals

Altman originally presented evidence for adult neurogenesis in the early 1960s (Altman, 1965); however, this work, which was based on autoradiography and light microscopy of general cytological stains, was not generally accepted. A decade later, Kaplan combined autoradiography with much higher resolution electron microscopy imaging to demonstrate tritiated thymidine uptake into cells that later exhibited definite neuronal morphology, but again the results were not widely accepted. The advent of more advanced cellular and molecular techniques in the 1990s finally established the phenomenon. First, Weiss and colleagues isolated and cultured rodent neural stem or progenitor cells from the subventricular zone (SVZ) of the adult forebrain and dentate gyrus of the hippocampal formation. Multipotent cell differentiation into neurons, astrocytes, and oligodendrocytes in vitro was subsequently demonstrated (Lois and Alvarez-Buylla, 1993; Ray et al., 1993; Reynolds and Weiss, 1992). In parallel, the development of immunostaining techniques enabled the simultaneous imaging of stem cell proliferation and neuronal differentiation to firmly establish the differentiation of new cells into neurons in vivo. These techniques demonstrated that higher primates and humans also exhibit adult neurogenesis in the SVZ of the forebrain and in the dentate gyrus (Eriksson et al., 1998; Gould, 1999c). Finally, it has been established that newly generated neurons in the dentate gyrus are functional. That is, they migrate into the granule cell layer, differentiate into granule neurons, extend the appropriate projections to the CA3 target area (Markakis and Gage, 1999), and acquire electrophysiological properties similar to those of neighboring, older neurons (van Praag et al., 2002). In addition, there is recent evidence that hippocampal stem cells of the subgranular zone (SGZ) can also give rise to functional inhibitory interneurons (Liu et al., 2003).

There are two approaches to elucidating the functional and neuroadaptive roles of adult neurogenesis. First, in light of the known functions of these molecules in other contexts, a molecular approach that identifies and analyzes the molecules and signaling mechanisms that regulate neurogenesis can lead to insights into the potential functions of adult neurogenesis. Second, a systems-level approach can endeavor to develop correlative or causal relationships between the rates of functional neurogenesis and behavioral changes. These molecular and systems approaches analyze the problem from seemingly opposite perspectives; however, they provide complementary and often converging data that are beginning to yield hypotheses on the functional and adaptive purposes of adult neurogenesis.

A Molecular Understanding of Neurogenesis

Recent reviews have presented a solid, comprehensive list of molecules and factors that regulate adult neurogenesis (Kempermann, 2002; Zhao et al., 2003); this article instead focuses only on several molecules whose role can lend insights into neurogenesis' potential functions. Furthermore, the authors focus primarily on the hippocampus, because this is the region where neurogenesis is presumed to have the most impact on the neuroadaptive processes of learning and memory.

Creating a new neuron is a complex process composed of many steps, including stem cell proliferation, differentiation, and survival, and numerous molecules and factors have been identified in vitro and in vivo to regulate these steps (Fig. 1). The existence of numerous opportunities for molecular control over neurogenesis makes it a highly regulated process, indicating that its tight control is important for hippocampal and central nervous system (CNS) function.

Basic fibroblast growth factor (FGF-2) was the first molecule identified to promote the proliferation of adult neural progenitor cells, because it was necessary for their expansion in culture (Palmer et al., 1995; Palmer et al., 1999; Ray et al., 1993). These in vitro mitogenic effects of FGF-2 are mirrored in vivo. An autocrine cofactor of FGF-2, a glycosylated form of cystatin C, is necessary for its proliferative effects in vitro and in vivo (Taupin et al., 2000). Furthermore, the rate of hippocampal neurogenesis declines with age (Kuhn et al., 1996), and intracerebroventricular FGF-2 infusion counteracts this reduced neurogenesis (Jin et al., 2003). Additionally, FGF-2 and epidermal growth factor (EGF) infusions led to proliferation of an apparently new population of neural progenitors in the posterior

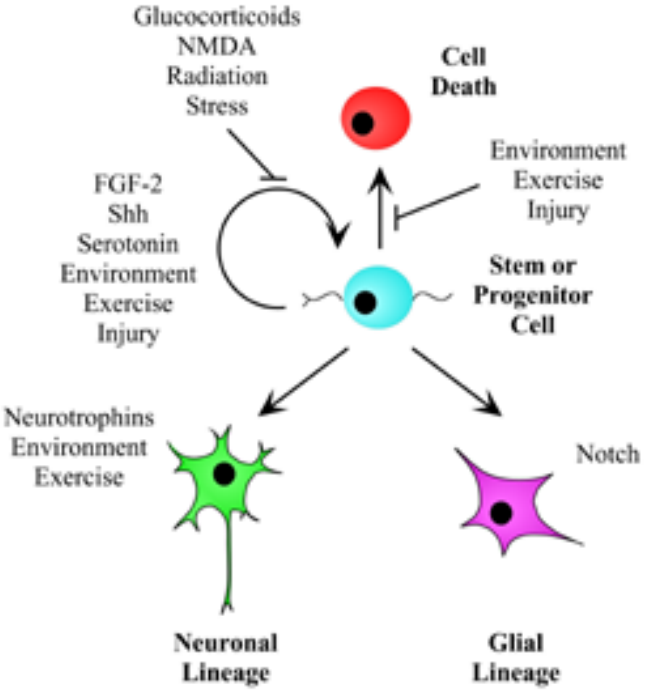

Fig. 1. A summary of molecular and systemic factors that regulate the different stages of a hippocampal stem cell's life cycle. Only those factors discussed in this article are detailed. Color image available for viewing at **www.humanapress.com**.

periventricle of the hippocampus, leading to generation of new CA1 neurons after global ischemia (Nakatomi et al., 2002). Finally, FGF-2 may mediate some of the effects of exercise, seizure, and ischemic injury on neurogenesis, as discussed in the section on Ischemic Injury and Seizure.

In addition to FGF-2, the authors have recently shown that Sonic hedgehog (Shh), a factor well known for its many roles in neural development, also promotes neural progenitor proliferation in vitro. Additionally, adeno-associated viral vector delivery of Shh more than tripled hippocampal progenitor proliferation and neurogenesis in vivo (Lai et al., 2003). Interestingly, Shh is not detected in the adult hippocampus but is expressed at high levels in basal forebrain (Traiffort et al., 1999). The basal forebrain sends numerous projections to the hippocampus, and Shh undergoes anterograde axonal transport (Traiffort et al., 2001). This raises the possibility that the basal forebrain may regulate hippocampal neurogenesis through Shh anterograde transport, and, in support of this possibility, fimbria-fornix lesion significantly reduces neurogenesis to a level not further reduced by a Shh signaling inhibitor (Lai et al., 2003). Not much is known about the regulation of Shh expression beyond development, because it was only recently shown to be expressed in adulthood (Traiffort et al., 1999). Therefore, further studies may reveal factors that regulate basal forebrain regulation of Shh, thereby yielding further insights into neurogenesis.

In addition to proliferation, another point of cellular regulation is differentiation, a process that is better characterized for SVZ stem cells than for hippocampal cells. Bone morphogenetic proteins (BMPs) promote astrocytic differentiation of embryonic SVZ progenitors (Gross et al., 1996). Furthermore, noggin binds to and inhibits BMP activity, thereby permitting neuronal differentiation. Alvarez-Buylla and colleagues found that the addition of recombinant noggin in vitro, as well as the ectopic overexpression of noggin in the adult striatum,promoted the neuronal differentiation of SVZ progenitors (Lim et al., 2000). Although noggin's role has not been explicitly studied in the adult hippocampus, several studies suggest its importance. First, both the adult olfactory bulb and the hippocampus express high noggin levels (Lim et al., 2000; Chmielnicki and Goldman, 2002). Furthermore, a recent study reports that Morris water maze training apparently increases noggin expression in the hippocampus (Fan et al., 2003), indicating a potential role for noggin in the effects of physical exercise and learning on hippocampal neurogenesis, as discussed further in the section on Learning and Exercise.

Brain derived neurotrophic factor promotes neuronal differentiation of hippocampal progenitors in vitro (Palmer et al., 1997; Takahashi et al., 1999), although its precise role in vivo is not yet fully elucidated. A brain-derived neurotrophic factor (BDNF) heterozygous mutant mouse exhibited a 20% reduction in hippocampal stem cell proliferation (Lee et al., 2002). Furthermore, BDNF overexpression from an adenoviral vector led to significantly enhanced neuronal differentiation from SVZ neural progenitors (Benraiss et al., 2001). However, long-term BDNF overexpression in the hippocampus counteracted the increased neurogenesis observed in ischemic injury (Larsson et al., 2002). Future studies may further clarify BDNF's contributions to hippocampal neurogenesis in the

normal vs injured brain. Also, this neurotrophin's well-recognized function as a mediator of synaptic plasticity indicates that it may act as an intriguing point of synergy between these two mechanisms of neural adaptation (Thoenen, 1995). The regulation of BDNF expression in vivo has been extensively studied, and its modulation by antidepressants and physical exercise is discussed in the section on Stress and Depression.

A final point for the regulation of neurogenesis is the survival of both newly divided and differentiated cells. Although both FGF-2 and Shh promote both progenitor proliferation and survival in vitro (Lai et al., 2003; Ray et al., 1993), molecular control over cell survival has not been widely investigated in vivo. Therefore, further studies are needed to elucidate the molecular mechanisms by which exercise and potentially learning modulate cell survival, as discussed in Learning and Exercise.

In addition to growth factors, morphogens, and neurotrophins, signaling by neurotransmitters is involved in regulating adult neurogenesis. Chronic administration of serotonin reuptake inhibitors promoted hippocampal stem cell proliferation and survival, whereas lesion of serotonergic projections from the raphe nuclei significantly reduced the accumulation of new hippocampal neurons (Brezun and Daszuta, 1999, 2000; Gould, 1999a). In addition, glutamate signaling regulates neurogenesis. Activation of *N*-methyl-D-aspartate (NMDA) receptors repressed hippocampal neural stem cell proliferation, and treatment with NMDA receptor antagonists significantly upregulated stem cell proliferation, survival, and neuronal differentiation (Cameron et al., 1995; Gould, 1997). However, in animals that are subjected to ischemic injury, NMDA receptor antagonists (but not α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptor blockers) had the opposite effect and actually counteracted the increased stem cell proliferation normally observed after ischemia (Arvidsson et al., 2001; Bernabeu and Sharp, 2000). Therefore, a complex combination of signals may regulate stem cell function during ischemic injury.

The FGF, Shh, Noggin, and BDNF studies were conducted both in vitro and in vivo to demonstrate that these factors directly regulate neural stem and progenitor cells (Laiet et al., 2003; Taupin et al., 2000; Yoshimura et al., 2001). However, work with neurotransmitters has been conducted primarily only in vivo, and, therefore, their regulatory effects on stem cells may be either direct or indirect. Further work is required to elucidate the exact mechanisms of their actions, but Lindvall and colleagues have proposed that NMDA effects may be indirect, i.e., mediated by neurotransmitter-stimulated upregulation of growth factors such as FGF-2 and BDNF (Arvidsson et al., 2001). The potential roles of neurotransmitter signaling in exercise, antidepressant effects, and stress are further discussed below.

Systems Analyses

Learning and Exercise

As a parallel and complementary approach to molecular and cellular analysis, studying the possible functional implications of hippocampal neurogenesis has yielded key information on its relationships to the processes of learning, exercise, stress responses, and injury. It has long been recognized that both general environment and specific training improve performance in various cognitive, learning, and motor tasks. For example, Hebb was among the first to show the effects of environment by demonstrating that animals' housing conditions can modulate their behavioral abilities (Hebb, 1947). The anatomical basis for such improvements was initially believed to rely solely on synaptic remodeling (reviewed in Churchill et al., 2002). Extensive work does establish synaptic plasticity as a key mechanism of neural adaptation; however, the recent recognition of adult neurogenesis has naturally spurred investigation of whether this cellular plasticity also contributes to neural adaptation.

It was first shown in 1997 that an enriched environment, one in which animals live in larger cages with several objects that are changed and moved often, dramatically enhances both the proliferation and the survival of neural stem cells (Kempermann, 1997b). Interestingly, these two effects also varied significantly with animal strain, emphasizing the importance of genetic background (Kempermann, 1997a). In parallel with increased neurogenesis, the animals performed better in a hippocampal-dependent spatial learning task, the Morris water maze. Furthermore, a subsequent study showed that after an extended period in an enriched environment (10 mo), animals still exhibit a steady state two-fold higher rate of proliferation and three-fold higher

ratio of neuronal to astrocytic differentiation as compared control animals (Kempermann, 2002). This result demonstrates that enhanced neurogenesis in response to environmental enrichment is not a transient phenomenon.

These studies establish a strong correlation between neurogenesis, potential adaptive responses to novel experiences, and subsequent performance on learning tasks. However, the work raises three additional questions: What component(s) of the enriched environment stimulate(s) neurogenesis? Are neurogenesis and environment causally linked or simply correlated? and What molecular mechanisms underlie this cellular plasticity? To address the first issue, van Praag et al. exposed mice to numerous conditions, including the full enriched environment, as well as focused training on a spatial learning task (water maze), a nonlearning swimming control condition, and voluntary exercise (running wheel). Intriguingly, voluntary running increased both hippocampal stem cell proliferation and survival, whereas learning had no effect on either (van Praag et al., 1999). By contrast, a study with rats found that training in a hippocampus-dependent learning task did not affect cell proliferation, but it doubled the survival of neurons born before training began (Gould, 1999b). The contrasting results may be caused byexperimental differences, specifically the timing between injections and training, which future work may resolve.

To directly demonstrate a causal link between neurogenesis and enhanced performance in hippocampal-dependent tasks, it would be ideal to have the capability to specifically block neurogenesis and observe the consequences on learning. For example, a mitotic toxin (a DNA methylating agent) was injected into rats at a dose that apparently depleted newly born cells without seriously affecting overall health. The animals suffered deficits in trace conditioning, a hippocampal-dependent association of stimuli separated in time (Shors, 2001). This work was a first step toward establishing causal ties between neurogenesis and learning, but the methodology used may have affected all proliferating cell populations in the body; therefore, it was unclear if the results were due to specific effects of the toxin on hippocampal stem cells. An alternate and somewhat more specific method to ablate proliferating cells from a more localized region was used to probe the relationships between antidepressants and neurogenesis (Santarelli et al., 2003), as discussed in Stress and Depression.

Finally, numerous results have begun to bridge the molecular and the systems approaches to analyzing neurogenesis, thereby yielding further insights into both sets of studies. Exercise increases FGF-2 expression in the hippocampus (Gomez-Pinilla et al., 1997), implicating this stem cell mitogen as a possible mediator of the effects of voluntary running on neurogenesis. Likewise, insulin-like growth factor I (IGF-I) promotes hippocampal stem cell proliferation in culture and when injected intravenously (reviewed in Anderson et al., 2002). Serum IGF-I levels are elevated by exercise, indicating that it also may mediate the effects of physical activity on hippocampal neurogenesis (Trejo et al., 2001). Furthermore, BDNF is upregulated in an enriched environment and associated with improved spatial memory (Falkenberg et al., 1992). Finally, serotonin levels are also upregulated by exercise (Blomstrand et al., 1989); therefore, the synergistic effects of multiple neurotransmitter and growth factor signaling systems may mediate the effects of environmental enrichment and exercise on neurogenesis.

Stress and Depression

Neurogenesis is enhanced by physical activity and potentially by learning; however, it is reduced by stress. In one study showing that neurogenesis could be modulated by environmental and physiological conditions, Gould et al. subjected tree shrews to psychosocial stress, specifically the establishment of a dominant/subordinate relationship between two competing males, and found that this stress reduced hippocampal stem cell proliferation dramatically (Gould et al., 1997). Subsequent work indicated that such effects may be mediated by stress-induced increases in serum glucocorticoids (Tanapat et al., 1998). Furthermore, BDNF may also be involved in this regulation, because its expression is reduced in the hippocampus in response to stress and glucocorticoids (Smith et al., 1995).

The implications of these and similar findings have been broadened into the concept that reduced hippocampal neurogenesis may underlie periodic episodes of depression (reviewed in Jacobs et al., 2000, and Kempermann, 2002). Stress, which is often associated with depression, reduces neurogenesis (Gould et al., 1997; Tanapat et al., 1998). Conversely,

exercise, which promotes neurogenesis (van Praag et al., 1999), counteracts depression. In addition, increasing brain serotonergic signaling is currently the most effective treatment for depression, and numerous pharmacological interventions for depression aim to do so by inhibiting serotonin reuptake. As discussed above, serotonergic signaling is associated with enhanced neurogenesis (Brezun and Daszuta, 1999, 2000; Gould, 1999a). Furthermore, antidepressants upregulate hippocampal expression of BDNF, and exercise enhances this effect (Russo-Neustadt et al., 2001). BDNF regulates neural stem cell proliferation (Lee et al., 2002) and neuronal differentiation (Palmer et al., 1997).

Again, an effective approach to establish a causal link between neurogenesis and a behavior would be to analyze the effects of a hippocampal stem cell inhibition or ablation on that behavior. An intriguing recent study presented more direct evidence for the role of neurogenesis in mediating the effects of antidepressants (Santarelli et al., 2003). The serotonin reuptake inhibitor fluoxetine (Prozac) promotes neurogenesis and reduced anxiety, but serotonin 1A receptor mutant mice were incapable of exhibiting either of these responses. Furthermore, X-ray irradiation of the hippocampus, which kills hippocampal progenitors (Parent et al., 1999), blocked the antidepressants' effects. This study adds to the strong evidence supporting a role for reduced neurogenesis in depression. However, radiation results in a general hippocampal dysfunction, including reduced progenitor proliferation, increased glial differentiation, and disruption of angiogenesis (Monje et al., 2002). Therefore, an even more direct and causal demonstration must await the development of more specific means to manipulate neural stem cell function *in situ*.

Ischemic Injury and Seizure

Neurogenesis is upregulated in response to hippocampal ischemia and seizure, raising speculation that it may be involved in neural regeneration from these injuries. Transient, global forebrain ischemia significantly stimulated SGZ stem cell proliferation, survival, and neuronal differentiation (Liu et al., 1998; Takagi et al., 1999). SGZ stem cell proliferation was also significantly upregulated after stroke induced by middle cerebral artery occlusion (Arvidsson et al., 2001; Komitova et al., 2002). In another injury model, hippocampal seizure induced by compounds including pilocarpine and kainic acid also significantly increase proliferation and, in some cases, neuronal differentiation (Gray and Sundstrom, 1998; Parent and Yu et al., 1997; Parent and Tada et al., 1999).

Several potential molecular mediators of these responses to injury have been implicated. First, FGF-2 expression is upregulated in the hippocampus upon seizure or ischemic injury, and upregulation of neurogenesis upon brain injury is not observed in FGF-2 mutant mice (Yoshimura et al., 2001). Second, erythropoietin, which is upregulated as part of the normal hypoxic response, promotes the neuronal differentiation of SVZ progenitors in vitro and increases the number of olfactory bulb interneurons at the cost of proliferating progenitors in the SVZ (Shingo et al., 2001). However, erythropoietin has not been studied in the hippocampus.

Despite this ample evidence of upregulated stem cell proliferation, survival, and neuronal differentiation in the injured brain, it is unclear whether these effects serve as a specific mechanism for injury recovery or are simply a byproduct of widespread growth factor and cytokine secretion during injury. In one study, neurogenesis replaced only a small fraction of dead neurons (0.2%), and most of the new cells died within several weeks (Arvidsson et al., 2002), indicating that neurogenesis may be a potentially serendipitous side effect. However, regardless of whether the phenomenon is specific or inadvertent, the effect could be further enhanced and harnessed for neuroregeneration efforts.

Summary

Neurogenesis is a potentially powerful mechanism of cellular plasticity that complements synaptic plasticity as means for neuroadaptation. Research in this area has nucleated with two efforts: the identification of signaling factors that control neural stem and progenitor cell survival, proliferation, and differentiation, and the relationships among neurogenesis, learning, exercise, depression, and injury. These endeavors have converged with the identification of molecular signals that may underlie the effects of exercise and injury on neurogenesis. Furthermore, the spectrum of efforts will continue to expand. For example, little is known about the intra-

cellular signal transduction mechanisms that control stem cell functions, and the development of techniques, such as inducible recombination, to directly manipulate neural stem cells *in situ* may be valuable for establishing causal links between neurogenesis and behavioral adaptation (Kaspar et al., 2002). Finally, this basic work will likely lead to both behavioral and molecular therapies in order to harness and manipulate this mechanism of neuroadaptation for both neural regeneration and counteracting the effects of aging.

Acknowledgments

The authors thank Analeah O'Neill for helpful technical comments. This work was supported by an Office of Naval Research Young Investigator Program Award (N000140110812) to DVS and by support from Project ALS, the Lookout Fund, and NIH (NIA) to FHG.

References

Altman, J., and Das, G. D. (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J. Comp. Neurol.* **124,** 319–335.

Anderson, M. F., Aberg, M. A., Nilsson, M., Eriksson, P. S. (2002) Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Res. Dev. Brain Res.* **134,** 115–122.

Arvidsson, A., Kokaia, Z., Lindvall, O. (2001) N-methyl-D-aspartate receptor-mediated increase of neurogenesis in adult rat dentate gyrus following stroke. *Eur. J. Neurosci.* **14,** 10–18.

Arvidsson, A., Collin, T., Kirik, D., Kokaia, Z., Lindvall, O. (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat. Med.* **8,** 963–970.

Benraiss, A., Chmielnicki, E., Lerner, K., Roh, D., Goldman, S. A. (2001) Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *J. Neurosci.* **21,** 6718–6731.

Bernabeu, R., and Sharp, F. R. (2000) NMDA and AMPA/kainate glutamate receptors modulate dentate neurogenesis and CA3 synapsin-I in normal and ischemic hippocampus. *J. Cereb. Blood Flow Metab.* **20,** 1669–1680.

Blomstrand, E., Perrett, D., Parry-Billings, M., Newsholme, E. A. (1989) Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. *Acta. Physiol. Scand.* **136,** 473–481.

Brezun, J. M., and Daszuta, A. (1999) Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. *Neuroscience* **89,** 999–1002.

Brezun, J. M., and Daszuta, A. (2000) Serotonin may stimulate granule cell proliferation in the adult hippocampus, as observed in rats grafted with foetal raphe neurons. *Eur. J. Neurosci.* **12,** 391–396.

Cameron, H. A., McEwen, B. S., Gould, E. (1995) Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. *J. Neurosci.* **15,** 4687–4692.

Chmielnicki, E., and Goldman, S. A. (2002) Induced neurogenesis by endogenous progenitor cells in the adult mammalian brain. *Prog. Brain Res.* **138,** 451–464.

Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., Greenough, W. T. (2002) Exercise, experience and the aging brain. *Neurobiol. Aging* **23,** 941–955.

Eriksson, P. S., Perfilieva, E., Bjork-Eriksson, T., et al. (1998) Neurogenesis in the adult human hippocampus. *Nat. Med.* **4,** 1313–1317.

Falkenberg, T., Mohammed, A. K., Henriksson, B., Persson, H., Winblad, B., Lindefors, N. (1992) Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. *Neurosci. Lett.* **138,** 153–156.

Fan, X. T., Cai, W. Q., Yang, Z., Xu, H. W., Zhang, J. H. (2003) Effect of antisense oligonucleotide of noggin on spatial learning and memory of rats. *Acta. Pharmacol. Sin.* **24,** 394–397.

Gomez-Pinilla, F., Dao, L., So, V. (1997) Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res.* **764,** 1–8.

Gould, E., McEwen, B. S., Tanapat, P., Galea, L. A., Fuchs, E. (1997) Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J. Neurosci.* **17,** 2492–2498.

Gould, E. (1999a) Serotonin and hippocampal neurogenesis. *Neuropsychopharmacology* **21,** 46S–51S.

Gould, E., Beylin, A., Tanapat, P., Reeves, A., Shors, T. J. (1999b) Learning enhances adult neurogenesis in

the hippocampal formation. *Nat. Neurosci.* **2,** 260–265.

Gould, E., Reeves, A. J., Fallah, M., Tanapat, P., Gross, C. G., Fuchs, E. (1999c) Hippocampal neurogenesis in adult Old World primates. *Proc. Natl. Acad. Sci. USA.* **96,** 5263–5267.

Gray, W. P., and Sundstrom, L. E. (1998) Kainic acid increases the proliferation of granule cell progenitors in the dentate gyrus of the adult rat. *Brain Res.* **790,** 52–59.

Gross, R. E., Mehler, M. F., Mabie, P. C., Zang, Z., Santschi, L., Kessler J. A. (1996) Bone morphogenetic proteins promote astroglial lineage commitment by mammalian subventricular zone progenitor cells. *Neuron* **17,** 595–606.

Hebb, D. O. (1947) The effects of early experience on problem solving at maturity. *Am. Psychol.* **2,** 306–307.

Jacobs, B. L., Praag, H., Gage, F. H. (2000) Adult brain neurogenesis and psychiatry: A novel theory of depression. *Mol. Psychiatry* **5,** 262–269.

Jin, K., Sun, Y., Xie, L., et al. (2003) Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. *Aging Cell* **2,** 175–183.

Kaspar, B. K., Vissel, B., Bengoechea, T., et al. (2002) Adeno-associated virus effectively mediates conditional gene modification in the brain. *Proc. Natl. Acad. Sci. USA.* **99,** 2320–2325.

Kempermann, G. (2002) Regulation of adult hippocampal neurogenesis—implications for novel theories of major depression. *Bipolar Disord.* **4,** 17–33.

Kempermann, G., Kuhn, H. G., Gage, F. H. (1997a) Genetic influence on neurogenesis in the dentate gyrus of adult mice. *Proc. Natl. Acad. Sci. USA.* **94,** 10409–10414.

Kempermann, G., Kuhn, H. G., Gage, F. H. (1997b) More hippocampal neurons in adult mice living in an enriched environment. *Nature* **386,** 493–495.

Kempermann, G., Gast, D., Gage, F. H. (2002) Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann. Neurol.* **52,** 135–143.

Komitova, M., Perfilieva, E., Mattsson, B., Eriksson, P. S., Johansson, B. B. (2002) Effects of cortical ischemia and postischemic environmental enrichment on hippocampal cell genesis and differentiation in the adult rat. *J. Cereb. Blood Flow Metab.* **22,** 852–860.

Kuhn, H. G., Dickinson-Anson, H., Gage, F. H. (1996) Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J. Neurosci.* **16,** 2027–2033.

Lai, K., Kaspar, B. K., Gage, F. H., Schaffer, D. V. (2003) Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. *Nat. Neurosci.* **6,** 21–27.

Larsson, E., Mandel, R. J., Klein, R. L., Muzyczka, N., Lindvall, O., Kokaia, Z. (2002) Suppression of insult-induced neurogenesis in adult rat brain by brain-derived neurotrophic factor. *Exp. Neurol.* **177,** 1–8.

Lee, J., Duan, W., Mattson, M. P. (2002) 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.* **82,** 1367–1375.

Lim, D. A., Tramontin, A. D., Trevejo, J. M., Herrera, D. G., Garcia-Verdugo, J. M., Alvarez-Buylla, A. (2000) Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron* **28,** 713–726.

Liu, J., Solway, K., Messing, R. O., Sharp, F. R. (1998) Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J. Neurosci.* **18,** 7768–7778.

Liu, S., Wang, J., Zhu, D., Fu, Y., Lukowiak, K., Lu, Y. M. (2003) Generation of functional inhibitory neurons in the adult rat hippocampus. *J. Neurosci.* **23,** 732–736.

Lois, C., Alvarez-Buylla, A. (1993) Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. *Proc. Natl. Acad. Sci. USA.* **90,** 2074–2077.

Markakis, E. A., and Gage, F. H. (1999) Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. *J. Comp. Neurol.* **406,** 449–460.

Monje, M. L., Mizumatsu, S., Fike, J. R., Palmer, T. D. (2002) Irradiation induces neural precursor-cell dysfunction. *Nat. Med.* **8,** 955–962.

Nakatomi, H., Kuriu, T., Okabe, S., et al. (2002) Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* **110,** 429–441.

Palmer, T. D., Ray, J., Gage, F. H. (1995) FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. *Mol. Cell Neurosci.* **6,** 474–486.

Palmer, T. D., Takahashi, J., Gage, F. H. (1997) The adult rat hippocampus contains primordial neural stem cells. *Mol. Cell Neurosci.* **8,** 389–404.

Palmer, T. D., Markakis, E. A., Willhoite, A. R., Safar, F., Gage F. H. (1999) Fibroblast growth factor-2 acti-

vates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *J. Neurosci.* **19,** 8487–8497.

Parent, J. M., Yu, T. W., Leibowitz, R. T., Geschwind, D. H., Sloviter, R. S., Lowenstein, D. H. (1997) Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J. Neurosci.* **17,** 3727–3738.

Parent, J. M., Tada, E., Fike, J. R., Lowenstein, D. H. (1999) Inhibition of dentate granule cell neurogenesis with brain irradiation does not prevent seizure-induced mossy fiber synaptic reorganization in the rat. *J. Neurosci.* **19,** 4508–4519.

Ray, J., Peterson, D. A., Schinstine, M., Gage, F. H. (1993) Proliferation, differentiation, and long-term culture of primary hippocampal neurons. *Proc. Natl. Acad. Sci. USA.* **90,** 3602–3606.

Reynolds, B. A., and Weiss, S. (1992) Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science* **255,** 1707–1710.

Russo-Neustadt, A., Ha, T., Ramirez, R., Kesslak, J. P. (2001) Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. *Behav. Brain Res.* **120,** 87–95.

Santarelli, L., Saxe, M., Gross, C., et al. (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301,** 805–809.

Shingo, T., Sorokan, S. T., Shimazaki, T., Weiss, S. (2001) Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells. *J. Neurosci.* **21,** 9733–9743.

Shors, T., Miesegaes, G., Beylen, A., Zhao, M., Rydel, T., Gould, E. (2001) Neurogenesis in the adult is involved in the formation of trace memories. *Nature* **410,** 372–376

Smith, M. A., Makino, S., Kvetnansky, R., Post, R. M. (1995) Effects of stress on neurotrophic factor expression in the rat brain. *Ann. NY Acad. Sci.* **771,** 234–239.

Takagi, Y., Nozaki, K., Takahashi, J., Yodoi, J., Ishikawa, M., Hashimoto, N. (1999) Proliferation of neuronal precursor cells in the dentate gyrus is accelerated after transient forebrain ischemia in mice. *Brain Res.* **831,** 283–287.

Takahashi, J., Palmer, T. D., Gage, F. H. (1999) Retinoic acid and neurotrophins collaborate to regulate neurogenesis in adult-derived neural stem cell cultures. *J. Neurobiol.* **38,** 65–81.

Tanapat, P., Galea, L. A., Gould, E. (1998) Stress inhibits the proliferation of granule cell precursors in the developing dentate gyrus. *Intl. J. Dev. Neurosci.* **16,** 235–239.

Taupin, P., Ray, J., Fischer, W. H., et al. (2000) FGF-2-responsive neural stem cell proliferation requires CCg, a novel autocrine/paracrine cofactor. *Neuron* **28,** 385–397.

Thoenen, H. (1995) Neurotrophins and neuronal plasticity. *Science* **270,** 593–598.

Traiffort, E., Charytoniuk, D., Watroba, L., Faure, H., Sales, N., Ruat, M. (1999) Discrete localizations of hedgehog signalling components in the developing and adult rat nervous system. *Eur. J. Neurosci.* **11,** 3199–3214.

Traiffort, E., Moya, K. L., Faure, H., Hassig, R., Ruat, M. (2001) High expression and anterograde axonal transport of aminoterminal sonic hedgehog in the adult hamster brain. *Eur. J. Neurosci.* **14,** 839–850.

Trejo, J. L., Carro, E., Torres-Aleman, I. (2001) Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J. Neurosci.* **21,** 1628–1634.

van Praag, H., Kempermann, G., Gage, F. H. (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* **2,** 266–270.

van Praag, H., Schinder, A. F., Christie, B. R., Toni, N., Palmer, T. D., Gage, F. H. (2002) Functional neurogenesis in the adult hippocampus. *Nature* **415,** 1030–1034.

Yoshimura, S., Takagi, Y., Harada, J., et al. (2001) FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. *Proc. Natl. Acad. Sci. USA.* **98,** 5874–5879.

Zhao, X., Schaffer, D. V., Gage F. H. (2003) Neurogenesis in the adult brain: understanding its mechanism and regulation. In Gage, F. H., Bjorklund, A. and Christen, Y. (Eds.), and in Research and Perspectives in Neurosciences, Foundation IPSEN, Springer-Verlag, Berlin.