WHEN DISCUSSING A BRAIN FUNCTION SUCH AS MEMORY, one should relate it to brain plasticity. One definition of plasticity is an alternative way of performing the same function. Anecdotal evidence suggests that the human brain can perform amazing memory feats in unexpected, alternative ways. For example, the established ability of savants (individuals with partial brain damage) to memorize events, sequences of numbers, letters, or musical notes, and to perform arithmetical calculations, suggests that compensatory rewiring of brain circuits after injury can affect learning. Which particular form of brain plasticity could be responsible for such astounding learning abilities as those seen in Kim Peek (“Rain Man”) and Daniel Tammet (“Brainman”), two individuals diagnosed as autistic savants (www.savantsyndrome.com)? In this chapter, we describe a radical form of plasticity, adult neurogenesis, in hippocampal formation (HF). The discovery of adult neurogenesis (production of new neurons in adult brain) has radically changed our ideas of how the brain can adapt to physiological and environmental challenges. The process of neuronal production is highly regulated and is involved in hippocampal functions under physiological conditions. In some cases, neurogenesis can
respond to hippocampus-related pathologies such as epilepsy, ischemia, mood disorders, and addiction. Understanding neurogenesis, along with other forms of brain plasticity, may help us to understand normal memory and perhaps the enhanced memory such as that seen in individuals with the Savant Syndrome (Treffert and Christensen 2005).

LESIONS OF THE NEUROGENIC REGION

The HF is part of an integrated network involved in learning and memory (Eichenbaum 2000, 2001; Morris 2006). However, the precise functional role of the HF is still a matter of debate, this entity being involved in cognitive mapping, relational memory, configural associations, episodic-like memories, etc. (for review, see Morris 2006). Given this complexity, the contribution of the different hippocampal subregions also remains a matter of dispute. However, to understand the role of adult neurogenesis, one may ask what can be expected from lesions of the whole dentate gyrus (DG). Borrowing from a recent article outlining a neurobiological theory of hippocampal function, we suggest that the DG is not equally involved in all types of hippocampus-dependent memories (Morris 2006). This follows from a parallel arrangement of the two main inputs into the hippocampus, the medial and lateral entorhinal cortices projecting to CA1 and CA3/DG (Fig. 1) (Witter 1993). A lesion in the DG would be expected to disrupt only one of these inputs originating from layer II in the entorhinal cortices. At the functional level, various forms of memory can be disrupted by colchicine lesions of the DG, i.e., encoding reference spatial memory (Nanry et al. 1989; Xavier et al. 1999; Jeltsch et al. 2001; Nakayama and Sawada 2002), retrieval of reference spatial memory (Nanry et al. 1989), and working memory (Xavier et al. 1999). However, the role of DG is not absolute, and some spatial-related tasks, such as odor-place or object-place paired associations, are spared (Gilbert and Kesner 2003). Furthermore, the distinction between the roles of DG and CA1 becomes subtle when behavioral tasks involve temporal or spatial pattern separation (Gilbert et al. 2001). All such experiments involving lesions must take into consideration that in cases when one region is damaged, the other pathway may compensate for the loss. In support of this explanation, the CA1 place cells, which are corollary of spatial learning, can be formed despite selective lesions of the DG (McNaughton et al. 1989; Morris 2006). However, this evidence does not disprove an argument for the involvement of the DG-CA3 pathway, together with the CA3 collateral system, in optimal, normal memory processes (Nakazawa et al. 2002). In summary, taking into account the complexity of hippocampal
functioning and considering that newly born granule neurons within DG are a small minority (perhaps 10%) of the total population, the behavioral consequences of their depletion cannot be easily predicted (Snyder et al. 2001). However, given their strategic location in the gateway of the HF, they may have a pivotal role.

A TWO-WAY INTERRELATIONSHIP BETWEEN NEUROGENESIS AND LEARNING

There are at least two ways in which neurogenesis and learning have been linked: (1) The rate of neurogenesis determines learning performance and memory and (2) learning tasks enhance neurogenesis by enhancing survival of adult-born neurons at a particular stage of their development.

The Rate of Neurogenesis Determines Learning and Memory Abilities

Three categories of correlative evidence suggest involvement of adult-born neurons in memory: (1) conditions that enhance neurogenesis also improve learning, (2) conditions that decrease neurogenesis also impair learning, and (3) quantitative correlation between neurogenesis and...
learning performances. We only focus on those studies in which memory abilities and neurogenesis have been conducted in the same animals (within-subjects designs).

**Conditions Increasing Neurogenesis Enhance Learning Abilities**

Most studies evaluating effects of an enriched environment and/or physical activity support the contention that within a physiological adaptive range, the addition of adult-born neurons may be beneficial for adult brain functioning, particularly for spatial memory. Exposure of mice to an enriched environment or to a running wheel increases both the spatial memory ability in the water maze and the number of adult-born neurons in DG (Kempermann et al. 1997, 1998a; van Praag et al. 1999b). This beneficial effect of environmental experience also ameliorates reduced brain functioning during aging. Indeed, both neurogenesis and spatial memory performances are improved in senescent or middle-aged mice raised in an enriched environment (Kempermann et al. 1998b, 2002) or in senescent mice housed with access to a running wheel (van Praag et al. 2005). Furthermore, exposure of rats to an enriched environment during the prenatal period, the early postnatal period (Koo et al. 2003), and adulthood (Nilsson et al. 1999) also increased both neurogenesis and spatial learning abilities in the water maze.

Another set of experiments supports the hypothesis that improvement in memory abilities depends on increased production of new neurons. First, lowering corticosterone secretion from midlife for the rest of the animal’s life increases behavioral performance in the water maze and also hippocampal neurogenesis at the point of senescence (Montaron et al. 2006). Second, treatment of adult rats with the cognitive enhancer ginseng enhances memory performances in the contextual fear-conditioning paradigm and increases the number of bromodeoxyuridine (BrdU)-labeled cells (Qiao et al. 2005).

**Conditions Decreasing Neurogenesis Impair Learning**

On the basis of environmental, lesioning, pharmacological, and genetic approaches, it has been suggested that a reduction of hippocampal neurogenesis leads to reduced memory abilities. First, stressful events during the prenatal period caused a lifelong reduction of neurogenesis and disrupted spatial working memory in the Y maze and/or spatial reference memory in the water maze (Lemaire et al. 2000; Koo et al. 2003). Second,
olfactory bulbectomy and lead exposure during the first three postnatal weeks induced contextual memory deficits that are associated with a decreased neurogenesis (Jaako-Movits and Zharkovsky 2005; Jaako-Movits et al. 2005). Third, FoxG1 haploinsufficiency induced impairments in contextual fear conditioning and decreased hippocampal neurogenesis (Shen et al. 2006). Fourth, mice with mutation of a member of the methylated DNA-binding protein, methyl-CpG-binding protein 1, exhibited increased genomic instability, spatial memory deficits, and reduced neurogenesis (Zhao et al. 2003). Fifth, genetically based variations of neurogenesis in mice have been related to differences in spatial memory, i.e., poor learning is associated with low levels of neurogenesis (Kempermann and Gage 2002). Sixth, neurotrophin 3 (NT3) conditional KO mice, in which the NT3 gene is selectively deleted in the brain throughout development, exhibit deficits in spatial memory and impairs neurogenesis (Shimazu et al. 2006). Finally, lesion of the cholinergic septohippocampal pathway impairs spatial learning and reduces neurogenesis (Mohapel et al. 2005).

Quantitative Correlation between Learning Abilities and Neurogenesis

A quantitative relationship between learning and the number of newly generated neurons has been shown in senescent rats by characterizing spatial memory abilities in the water maze (Drapeau et al. 2003). Animals with preserved spatial memory (i.e., aged-unimpaired rats) exhibited 1 month after training a higher level of cell proliferation and a higher number of new neurons in comparison to rats with spatial memory impairments (i.e., aged-impaired rats). Two studies, however, failed to demonstrate such correlation (Bizon and Gallagher 2003; Merrill et al. 2003). Various experimental differences in the BrdU-labeling protocol, the number of subjects, the rat strain, and the gender of the animals could explain this apparent controversy.

Summary

There is a general consensus that neurogenesis is related to learning and memory abilities. However, it is not yet clear how this is accomplished. In young animals that are capable of high rates of neurogenesis and hence high rates of neuronal turnover, new neurons could participate in day-to-day memory acquisitions as implied by the experiments described
below. However, in older animals, the rates may be too low for such function, and gradual structural changes in network connectivity are more likely. Such adaptive restructuring of the hippocampus may be species-dependent and probably occurs on a much larger scale in animals living in a natural environment instead of contrived laboratory conditions. Furthermore, hippocampal function (improved or decreased memory) is not solely due to neurogenesis (high or low rate of production). Modifications in synaptic and structural plasticity at the level of the dendrites and spines, for example, in vascularization and in metabolic adaptation, occurring within and outside the HF could change memory independently of neurogenesis. Experimental dissection of these factors will be required to establish a causal role of new neurons in memory.

Influence of Learning on Neurogenesis

Training on learning tasks requiring the HF has been shown to exert a complex influence on distinct steps of neurogenesis: cell survival, cell proliferation, and cell death. We review the influence of learning on each of these steps separately, keeping in mind that these might be intermingled processes.

Effect on Cell Survival

The effect of associative (trace eye-blink conditioning) or spatial learning has been examined on survival of newly born cells. To this end, animals received a single BrdU injection and were submitted to the tasks 1 week later. The 1-week delay allows for cell differentiation into neurons but not to their full maturation since at this time, the axons and dendritic trees are still under development (Piatti et al. 2006). Animals sacrificed immediately following trace eye-blink conditioning showed an increase in the number of BrdU-labeled cells (Gould et al. 1999). One week after completion of the task, most newly born cells colabeled with neuronal markers (Gould et al. 1999). The learning-induced increase in neurogenesis was maintained for 2 months after completion of the task (Leuner et al. 2004). The behavioral performances positively correlated with the number of surviving cells, indicating that learning, and not training, rescued the adult-born cells (Leuner et al. 2004). The observed enhancement of cell survival was specific to hippocampus-dependent associative learning, as neurogenesis remained unchanged in rats following delay-eye-blink conditioning (classically attributed to the cerebellum; Gould et al. 1999) or to active shock avoidance (another classical Pavlovian conditioning
task that does not strictly depend on the HF; Van der Borght et al. 2005a). The degree of task difficulty also seems to be an important factor for obtaining a learning-promoting effect on cell survival. Indeed, establishing a contextual conditioned stimulus representation acquired in a single training trial is not sufficient to change the survival of cells born 10 days before exposure to the task (Pham et al. 2005).

A positive effect of learning on cell survival has also been described in the water maze task. The number of newly born cells, labeled with BrdU 1 week before exposure to the task, was increased following 4 days of training (Gould et al. 1999; Hairston et al. 2005). The observed enhancement of cell survival was specific to spatial learning, as neurogenesis remained unchanged in rats exposed to the task without a platform, but producing the same amount of motor responses (stress group). Furthermore, learning-induced up-regulation of neurogenesis has been specifically attributed to hippocampal functioning, as training on a cued test in the water maze, a hippocampus-independent type of learning, does not modify neurogenesis (Gould et al. 1999). Most recent evidence shows that the survival-promoting effects of training are strongest in the animals that learn the task well (Sisti and Shors 2006). Several studies did not observe a survival-promoting effect in the water maze (Ambrogini et al. 2000; Van der Borght et al. 2005b). These discrepancies may be due to restricting the counting of BrdU cell numbers to the dorsal DG (Ambrogini et al. 2000), and/or the platform location being changed during the course of training (Van der Borght et al. 2005b), and/or differences in the number of daily trials (Snyder et al. 2005).

**Effect on Cell Proliferation**

Recent evidence indicates that spatial learning also induces the proliferation of neural precursors. During learning of the water-maze task, two phases can be distinguished: an early phase, during which performance improves rapidly, and a late phase, during which performance stabilizes and reaches an asymptotic level. Döbrössy et al. (2003) have shown that the early phase of learning does not modify proliferation, whereas the late phase does. Indeed, when animals are injected with BrdU during the early phase and sacrificed at the end of this phase, learning does not modify BrdU-immunoreactive cell numbers. In contrast, when animals are injected with BrdU during the late phase of learning and sacrificed 1 day later, the number of BrdU-labeled cells is increased (Lemaire et al. 2000; Döbrössy et al. 2003). Learning-induced cell proliferation was not correlated to learning
performances (Döbrössy et al. 2003), suggesting that these newly born cells do not directly sustain ongoing learning. Their function remains to be determined. The learning-induced increase in the genesis of cells born contingently with the late phase of learning is long-lasting, persisting for at least 5 weeks after the animals had acquired the task (Döbrössy et al. 2003). However, some controversy exists, since cell proliferation, as measured with Ki-67, was not influenced following 4 days of training and decreased following 14 days in the water maze (Mohapel et al. 2006).

**Effect on Cell Death**

More surprisingly, spatial learning also decreased the number of newborn cells (Döbrössy et al. 2003; Ambrogini et al. 2004). This decline in BrdU cell numbers was not related to stress and or physical activity since (1) animals were habituated to the pool before training in order to diminish its stressful component (but see Ehninger and Kempermann 2006) and (2) no change in BrdU cell numbers was observed in yoked animals exposed to the pool but without the platform. Indeed, in animals injected with BrdU during the early phase and sacrificed at the end of the late phase, the number of BrdU-labeled cells decreased. This decrease was specifically induced by the late phase of learning and not by the passage of time (Döbrössy et al. 2003). Even more surprisingly, the decline in newly born cells was correlated with spatial abilities, as rats with the lowest number of BrdU-labeled cells (and most likely the highest rates of cell death) had the best memory performances (Döbrössy et al. 2003). This observation indicates that the decline in newly born cells is “involved” in memory and that learning, not training, decreased the number of adult-born cells. The decline in BrdU cell number most likely resulted from a cell death process, since spatial learning, but not cue training, increased cell death as evaluated with the TUNEL (terminal deoxynucleotidyl-transferease-mediated dUTP-biotin nick end-labeling) technique (Ambrogini et al. 2004). These intriguing results, together with the fact that learning also increased the number of newly born cells, may explain why no changes in BrdU cell numbers were observed in animals injected with BrdU during the entire period of training (van Praag et al. 1999a; Döbrössy et al. 2003).

**Summary**

Altogether, the reported results suggest a complex chain of changes in neurogenesis that accompanies spatial learning. The first step, occurring
during learning of the task, is characterized by an increase in the survival of cells that have been produced before the learning experience. Remarkably, the survival-promoting effect of hippocampus-dependent learning seems to occur during the second week of cellular development. During this “critical period,” cells are still immature but already differentiated as neurons and express immature neuronal markers and physiological neuronal characteristics (Kempermann et al. 2004; Piatti et al. 2006). One hypothesis is that these cells have reached an adequate developmental period to be “stabilized” by activity-dependent stimuli generated in the course of learning. This is supported by electrophysiological evidence showing that enhanced synaptic activity (obtained by the stimulation of perforant path) enhances cell survival (Bruel-Jungerman et al. 2006). An activity-dependent process might promote neurogenesis either by GABAergic depolarization (Esposito et al. 2005; Overstreet et al. 2005; Tozuka et al. 2005; Wang et al. 2005; Ge et al. 2006; Overstreet-Wadiche et al. 2006) or by glutamate activation of the L-type (Deisseroth et al. 2004) or the T-type Ca^{2+} channels (Schmidt-Hieber et al. 2004). The observation that reduction of learning-induced increase in cell survival by sleep restriction selectively impaired spatial learning (Hairston et al. 2005) suggests that the neurons rescued by learning participated in memory processes. However, at least one fundamental question remains: What is the function for these surviving neurons? One possibility is outlined by Becker and Wojtowicz (2007), who proposed that clusters of newly born neurons induce formation of functional neuronal assemblies in CA3. These assemblies could represent the memory traces available for further consolidation and ultimately retrieval.

The second, even less understood, step occurring during the late phase of learning is characterized by a decrease in the number of newly produced cells, likely due to the elimination of immature newly generated cells that have not been selected (stabilized) by learning. The elimination of more immature cells may be necessary for the survival of older newly generated cells “by making room.” Indeed, newborn neurons are certainly competing for available resources to survive, and the death of one population could facilitate the survival and the integration of the remaining older ones. According to the selective stabilization theory (Changeux et al. 1973), regressive events, including cell death, will stabilize particular networks among others, thereby sculpting the circuits that are crucial for a given function. Yet another scenario has been proposed, where the selection of immature neurons is balanced by cell death of more mature newborn neurons (Ambrogini et al. 2000, 2004). Thus, although both scenarios rely on an active selection process, they differ in the age of the newly born cells that are selected or killed by learning.
A third step also takes place during the late phase of learning and is characterized by an increase in cell proliferation. It may constitute a compensatory mechanism to the selection process and consequently replace the pool of neurons that encounter death.

IS NEUROGENESIS CAUSALLY RELATED TO MEMORY ABILITIES?

One of the most important challenges in the field of hippocampal neurogenesis is to demonstrate a causal relationship between memory and neurogenesis. So far, only three methods have been used to target the neural progenitor cells in the DG. Two of the methods have been borrowed from cancer research, in particular from cancer treatment using high-energy irradiation and chemotherapy. These methods take advantage of the known sensitivity of rapidly dividing cells to γ-rays and to various chemical agents that disrupt the mitotic cell cycle. The most recent approach consists of development of inducible glial fibrillary acidic protein (GFAP)-thymidine kinase (TK) transgenic (TG) mice (Garcia et al. 2004). Selectivity and possible side effects of these methods have been discussed elsewhere; here, we only deal with the interpretation of the results and not with various possible shortcomings of the methods (Monje and Palmer 2003; Wojtowicz 2006).

Analysis of the literature indicates that the road to a conclusion on the existence of a causal relationship between memory and neurogenesis is long. Indeed, treatment with the antimitotic agent MAM (methylazoxymethanol) has been shown to disrupt trace eye-blink conditioning and trace fear conditioning (Shors et al. 2001, 2002). In contrast, no deficits were observed in two other hippocampus-dependent memory tasks, i.e., contextual fear conditioning and spatial memory in the water maze (Shors et al. 2002). In the case of irradiation treatment, contextual fear conditioning (Winocur et al. 2006), place recognition in a T maze (Madsen et al. 2003), spatial learning in the Barnes maze test (Raber et al. 2004), delayed nonmatching to sample in the water maze (especially when the delay between sample and test trials is long; Winocur et al. 2006), and long-term retention in the water maze (Snyder et al. 2005) have all been demonstrated to be altered by irradiation. In contrast, spatial learning in the water maze has been reported to remain unchanged following irradiation treatment (Madsen et al. 2003; Raber et al. 2004; Snyder et al. 2005; Mashi et al. 2006; Saxe et al. 2006), with the exception of one study reporting altered spatial learning following cranial irradiation (Fan et al. 2007). Ablating neurogenesis in GFAP-TK TG mice using a subcutaneous infusion of ganciclovir led to deficits in contextual fear conditioning...
(Saxe et al. 2006). The same studies revealed that nonhippocampal tasks were not affected.

To summarize, the impact of ablating neurogenesis has been more extensively examined using contextual fear conditioning and the Morris water maze test. It appears that contextual fear memories are altered in some cases (Saxe et al. 2006; Winocur et al. 2006) but not in others (Shors et al. 2002). The data concerning the water maze are more conflicting given that spatial memory deficits were described in two studies (Snyder et al. 2005; Fan et al. 2007), but not in others (Shors et al. 2002; Madsen et al. 2003; Raber et al. 2004; Mesi et al. 2006; Saxe et al. 2006; Winocur et al. 2006). The controversy might be linked to the method used to ablate neurogenesis, the duration of the treatments before the testing procedure (and thus the age of the adult-born neurons at the time of behavioral testing), the species used (mice, rats, gerbils), the testing procedure used (configuration of the tests, training schedule, etc.), the type of memory examined (configural, relational, working), "task complexity," and/or the memory phase examined (encoding, consolidation, retrieval).

An important aspect of this work is its guidance by theoretical and computational models that can incorporate data into conceptual frameworks and formulate predictions for future experiments. A number of such theoretical models have been put forward (Becker 2005; Meltzer et al. 2005; Wiskott et al. 2006). Such interactions between experimental and theoretical approaches should prove fruitful in advancing neurogenesis research and also in its integration within the mainstream neuroscience.

CONCLUSION AND PERSPECTIVES

On the basis of evidence from several correlative studies, it has been proposed that neurogenesis is involved in hippocampus-dependent memory and in particular in spatial memory. This proposal is reinforced by the observation that, reciprocally, learning influences the rate of production and the number of surviving neurons. On the other hand, the experiments involving lesions of the neurogenic region suggest no significant role for new neurons in spatial learning. This is in contrast to the results obtained with complete DG lesions that can impair acquisition of spatial reference memory. These data may be explained by the existence of a compensatory mechanism that can sustain the apparently normal function with either the mature granule cells or other neurons of the Ammon’s Horn via the direct projections from the entorhinal cortex (see
However, the door is still open to new experiments. For example, theoretical considerations suggest that the dependence of spatial learning on new neurons may be particularly strong when several similar learning tasks are presented in sequence (Becker 2005). This and other computational predictions can be addressed with existing experimental methods. Although the present state of knowledge in this area is confusing, it provides us with certain directions for future progress.

1. Experiments should continue taking the correlative and causative approaches into account. These approaches are complementary and should ultimately lead to a unified picture of how neurogenesis participates in learning.
2. A variety of behavioral tasks should be used since neurogenesis is likely to have different roles in different behavioral circumstances.
3. Relating cells of certain ages (e.g., 1–2 weeks and 2–3 weeks old) to specific learning functions should be a priority.
4. Determining which plastic properties of new neurons are relevant to learning. Do the changes occur at the perforant path or mossy fiber synapses?
5. Development of new transgenic models to ablate adult-born neurons with emphasis on targeting different development stages of neurons (i.e., eliminating neurons at stages of proliferation, differentiation, and maturation).
6. Development of new drugs to kill neurons or to stimulate their production.

SUMMARY

The discovery of a continuous renewal of neurons in the adult mammalian brain has been a long process, one of the most controversial of modern neuroscience. The existence of de novo production of neurons in the adult hippocampus, a structure involved in memory, has stimulated research on their potential role in the physiology and pathophysiology of the hippocampus. Here, we have reviewed the current knowledge on the putative role of adult hippocampal neurogenesis in memory. In particular, we have illustrated that there is a two-way interrelationship between neurogenesis and learning: The rate of neurogenesis determines learning and memory and, reciprocally, learning influences the rate of neurogenesis. However, we have also highlighted that the state of our knowledge on the causal role of newborn neurons in memory is still controversial.
ACKNOWLEDGMENTS
D.N.A. is supported by INSERM, France. J.M.W. is supported by NSERC and CIHR, Canada.

REFERENCES


Adult Neurogenesis © 2008 Cold Spring Harbor Laboratory Press 978-087969-784-6
For conditions see www.cshlp.org/copyright.

