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Adult Neurogenesis and Hippocampal Memory Function: New Cells, More Plasticity, New Memories?

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Memory consists of several separate entities that depend on various brain systems [1]. Clinical and behavioral evidence suggests that the hippocampus and the surrounding anatomically associated regions serve a critical role in learning and memory [2]. In the 1960s, the outlines of the essential neural substrates of memory were gradually elucidated based on analyzing the effects of therapeutic surgical lesions of the bilateral medial temporal lobes to suppress uncontrollable epilepsy in a patient [3]. Although the operation was effective in controlling the patient's epilepsy, one unexpected consequence was that he became profoundly amnesic while retaining his intelligence and perceptual and motor functions. Similar cases were also seen in other patients with damage to the hippocampal formation and surrounding medial temporal lobe structures [4]. These individuals had severe amnesia for episodic events, although other forms of learning and memory—semantic, perceptual, procedural, and simple forms of conditioning—were spared. It is now believed that the hippocampal formation has a central role in declarative memory, the ability to recollect everyday facts and events consciously [5]. The unique anatomy, electrophysiologic characteristics, and key roles in memory formation have made the hippocampus an attractive target of research for neuroscientists.

For decades, it was believed that neurogenesis only occurred during embryonic stages in the mammalian central nervous system (CNS), making the brain one of the few mammalian organs incapable of replenishing its functional cell population throughout life [6]. In the 1960s, seminal studies by Altman and Das [7–9] provided the first evidence that new neurons were generated in the postnatal mammalian brain. In 1992, Reynolds and Weiss [10] isolated multipotent neural stem/progenitor cells (NSCs) from the adult rodent brain and characterized them in vitro. Studies in the 1990s confirmed that, contrary to long-held dogma, NSCs reside in the adult CNS and active neurogenesis occurs in discrete regions of the adult brain across various mammalian species, including mice, rats, monkeys, and humans [11–14]. Only recently has it been recognized that adult neurogenesis replicates the complex process of neuronal development to generate functionally integrated new neurons (Fig. 1) [15–17]. A role for these postnatally generated cells in learning was first suggested by Altman and Das in the 1960s [7–9,18]. Later, Nottebohm [19] directly tested the role of

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adult-generated neurons in song learning in birds. Subsequent work in rodents has led to the idea that adult neurogenesis is important for learning and memory of spatial information.

The discovery of adult neurogenesis has generated significant interest, especially in regard to the hippocampus, not only for neuroscientists but for physicians who are engaged in treating various neurologic diseases. Although interest in adult neurogenesis has grown exponentially in recent years, evidence for a role of adult-generated granule cells in learning and memory remains limited and, in most cases, indirect. In this review, the authors summarize the current body of research on mechanisms of adult neurogenesis in the hippocampus and then discuss research in the field, focusing on possible functions of adult neurogenesis in memory and learning, with comments on future directions.

Basic processes of adult neurogenesis

Adult neurogenesis is an evolutionary conserved process in various species, including birds [20], rodents [21], primates [22,23], and human beings [24]. In mammals, under normal conditions, active adult neurogenesis is primarily restricted to two brain regions, the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles [16]. The SGZ is located at the interface between the granule cell layer (GCL) and the hilus of the DG, deep within the parenchyma (see Fig. 1). A subpopulation of glial fibrillary acidic protein (GFAP)–expressing cells in this region has been proposed to be the resident NSCs [25,26]. These NSCs proliferate and give rise to new granule cells through five developmental stages (see Fig. 1): proliferation, fate specification, migration, axon/dendrite targeting, and synaptic integration [16]. These stages can be readily identified on the basis of cell morphology, mitotic capability, electrophysiological characteristics, and expression of developmentally regulated markers [27]. NSCs generate significant numbers of progeny in young adult rats, with approximately 9000 new cells, or 0.1% of the granule cell population, being replaced daily [28]. Approximately 50% of the neuronal progeny survive, and new granule cells populate the inner third of the GCL. Within 4 to 10 days after birth, new granule cells send their axonal projections toward the CA3 region and spineless dendritic arbors into the molecular layer (see Fig. 1). Their dendrites concomitantly become more complex and extend deeper into the molecular cell layer as new granule cells differentiate [29,30]. As the dendrites grow, they receive synaptic contacts and become integrated into the preexisting circuitry within 2 to 4 weeks after their birth (see Fig. 1). These new granule neurons continue their maturation process for at least another 2 months and are then maintained for a long duration in the hippocampus [31].

Regulation of adult neurogenesis by learning

The basic rate of neurogenesis in the DG is thought to be genetically determined [28] but can be dramatically regulated under various conditions, including aging [32]; gender [33]; steroids [34,35]; stress [36]; enriched environment [37]; voluntary exercise [38]; and pathologic conditions, such as seizures [39] or cerebral ischemia [40].

It is widely accepted that medial temporal lobe structures, including the hippocampus and surrounding cortical areas, are critical to the processes of learning and memory [5].

Interestingly, specific learning paradigms involving the hippocampus have been shown to regulate hippocampal neurogenesis in several animal models combined with various behavioral tasks (Table 1). In particular, the survival of the newborn cells is enhanced by spatial learning tasks, and there is a correlation between an individual's learning and newborn cell survival [41–43]. For example, trace eye-blink conditioning, which depends on hippocampal function, increases the number of newly generated neurons in the DG, whereas learning that does not require the hippocampus, including delayed eye-blink conditioning and cue-maze training, does not alter the number of new granule neurons compared with naive controls [44]. This phenomenon was not observed in some experiments [38,45] and these discrepancies may be attributable to different experimental designs of the learning tasks [38,44] or to stress associated with the training possibly causing downregulation in adult neurogenesis [46]. Associative long-term potentiation (LTP), an attractive model for certain forms of learning and memory [47], has been shown to enhance neurogenesis in the adult DG [48], supporting the hypothesis that activity-dependent synaptic plasticity in the DG during learning may provide signals for promoting learning-induced neurogenesis.

Potential involvement of adult neurogenesis in learning and memory

The functional relevance of adult neurogenesis in memory processes was first suggested in studies looking at the neural basis of song learning in birds [19]. In adult song birds, the volume of song-related nuclei showed seasonal and hormonal changes, with thousands of new neurons being added daily. These putative neurons responded to sound with action potentials, and neurogenesis in the avian hippocampus was modulated by the environmental complexity and learning experience [19,49]. Since then, various studies of rodent behaviors with various manipulations to eliminate or increase adult neurogenesis have provided substantial evidence for a role of newborn neurons in learning and memory (Table 2).

The basic level of proliferation and the survival rate of newborn neurons in rodents are influenced by genetic background [50,51]. For example, among different strains of mice, including C57BL/6, BALB/c, CD1(ICR), and 129Sv/J strains, the proliferation rate of NSCs was highest in C57BL/6 mice, whereas the survival rate of newborn neurons was highest in CD1 mice [51]. Comparing differences in the ability to learn the Morris water maze task between various strains of mice, it was shown that the strain with the highest baseline level of neurogenesis performed best in the learning task and that the strain with the lowest rate of basal neurogenesis performed the poorest [52,53]. Such a positive correlation between an increased rate in the number of newly generated neurons and better efficiency at completing a learning task was supported by another study that observed a quantitative relation between spontaneous individual differences in aged subjects performing a hippocampal-dependent task and the number of newly generated neurons [54,55].

To examine the influence of new neurons on the learning process, alterations of adult neurogenesis have been induced intentionally in various animal models (see Table 2). Environmental enrichment [56] and increased physical activity [38,56] enhance neurogenesis in the DG, and combining both stimuli leads to improved performance in a water maze test [37,57,58]. Conversely, administration of antimitotic agents and irradiation are two of the approaches to reduce the number of adult-generated cells [59–61]. Treatment

with a toxin for proliferating cells, the DNA methylating agent methylazoxymethanol acetate (MAM), reduced the number of newly generated cells in the DG without impairing overall health. Ionizing irradiation of the adult hippocampus also caused deletion of proliferating cells in the DG, leaving other cells apparently unchanged [62]. The effect of radiation was dose dependent, with cell death in the proliferating cells occurring within 3 to 6 hours after treatment, and lasted at least up to 120 days after irradiation [63]. In the learning tasks that are known to require hippocampus-controlled memory function (eg, place-recognition task [64], spatial learning in the Barnes maze [65]), the mice with reduced hippocampal neurogenesis performed more poorly than controls, whereas they were not impaired in hippocampus-independent learning (eg, object-recognition task [64], elevated plus maze [65]). Similar dependency on hippocampus-related function was observed in trace conditioning tasks [60,61] and in the basic non–matching-to-sample (NMTS) task, in which an animal must associate stimuli that are separated in time. Reduced neurogenesis caused no impairment in these tasks when the interval between the cue and the test trials were short. However, when the interval was relatively long, thereby increasing the demand on hippocampus-associated memory function, the decreased neurogenesis caused a significant impairment on learning [66].

Although these studies suggest a significant role for adult neurogenesis in some types of learning, this finding is nowhere conclusive because of the nonspecific nature of these manipulations. Irradiation can cause an inflammatory response despite no obvious morphologic changes or alterations in the tissue. Activated microglia and infiltrating peripheral monocytes seen in the tissue of irradiated animals indicate that reduced neurogenesis may be associated with alterations in the neurogenic microenvironment, leading to persistent inflammation [43,67]. This prolonged inflammation can cause side effects that do not seem to be directly involved in cell death, such as weight loss [68]. MAM treatment, per se, does not alter general activity, pain sensitivity, or stress levels or cause structural changes in the hippocampus other than a reduction in the number of new cells, but MAM reduces cell proliferation systemically; thus, its influence is not exclusively limited to the hippocampus. Despite no side effects at low doses, which were often used, slightly higher doses caused weight loss and reduced locomotion [69].

Genetic modifications, including gene knockout and transgenic techniques, have been used to study the involvement of adult neurogenesis in learning (see Table 2). Overexpression of vascular endothelial growth factor (VEGF) in the hippocampus using recombinant adenoassociated viral vectors led to a twofold increase in neurogenesis, and inhibition of VEGF expression by RNA interference completely blocked the environmental induction of neurogenesis [70]. This animal model of VEGF overexpression also showed a positive correlation between increases in adult neurogenesis and improved cognitive function in the water maze and passive avoidance tasks [70]. In another example, deletion of methyl-CpG binding protein 1 (MBD1), a member of the methylated DNA-binding protein family, increased genomic instability in adult NSCs and caused a reduction in hippocampal DG neurogenesis. MBD1 knockout mice exhibited impaired spatial learning and had a significant reduction in LTP [71]. In another example, the conditional knockout mice of presenilin-1 (PS1), which is known to be associated with the early onset of Alzheimer’s disease, showed a pronounced deficiency in enrichment-induced neurogenesis in the DG,

and this phenomenon was accompanied by prolonged long-term memory retention as seen with the contextual fear-conditioning task. This study suggests an association between hippocampal neurogenesis and the clearance of old memory traces after cortical memory consolidation [72].

Animal models with genetic modifications can provide new clues to discover associations with other biologic activities that originally seemed unrelated and have become powerful tools for studying adult neurogenesis. Current animal models are not specific enough to select for newborn neurons exclusively and the influence of genetic mutation on other tissues or cell types and compensation mechanisms cannot be excluded. Future development of more cell type–specific and inducible animal models is essential to provide definitive evidence for the role of adult neurogenesis in mammals.

Potential mechanisms underlying the contribution of adult neurogenesis on learning and memory

Despite some unresolved issues, if adult hippocampal neurogenesis can be assumed to play a critical role in learning and memory, how do these new cells contribute to the process? It takes approximately 2 to 4 weeks before the newly generated neurons are functionally integrated and start modifying active hippocampal circuits. Thus, it seems that mere replacement of the old neuronal population with newly generated cells is too slow and cannot explain the mechanism of plasticity alone. In addition to their morphologic changes, single cell–recording studies have revealed that newly formed neurons have electrophysiological properties that are distinct from those of mature neurons but resemble immature neurons formed during embryonic development [73,74]. At 1 to 3 weeks after mitosis, these cells showed a higher input resistance, a markedly lower threshold for triggering action potentials, and a much slower membrane time constant that favored action potential generation with extremely small current stimuli [73]. This enhanced excitability may be important for young neurons, because only a few excitatory contacts have been formed early in their incorporation process. More significantly, newborn immature granule cells at 1 to 3 weeks after birth exhibit a lower threshold for LTP induction than mature neurons [73,74]. Recent studies have further demonstrated that a critical period exists up to 6 weeks after birth, when newborn neurons exhibit significantly greater LTP and a lower threshold for induction than those of new neurons after maturation (S. Ge, H. Song, unpublished data, 2006). These studies suggest that newly generated neurons in the adult hippocampus can enhance the synaptic plasticity and modulate the neural network through their unique physiologic properties. Enhanced LTP that causes an increase in hippocampal neurogenesis has also been observed in several animal models [58,75]. Conversely, inhibition of neurogenesis leads to reduced LTP [71,76,77] (also, see the article by Shors and colleagues [60]). Hence, promoting the survival of newly generated neurons in the process of learning may be useful and effective to shift the neural population from the existing status, in which old neurons are tightly incorporated with each other, to a more flexible condition, with increased excitability and synaptic plasticity (Fig. 2). It can be reasoned that it is faster, and more biologically cost-effective, to reconstruct the neural network by increasing the “plasticity index” of the hippocampus by increasing the number

of young neurons causing elevated regional plasticity rather than by remodeling the developmentally born, old established network.

Summary and future directions

Although profound progress has been made in understanding and characterizing the mechanisms of adult neurogenesis, current studies are still insufficient to establish the true functional relevance of newborn neurons in adult mammalian brain. Learning and memory consist of extremely complicated and tightly orchestrated functions causing complex higher order behavior. It seems that the classic assumption in learning-induced structural plasticity —"more neurons are better"—may not address this mechanism correctly. Adult neurogenesis seems to contribute to this critical function not only by increasing the number of neurons but by adding "immaturity" to the region, meaning more excitability (higher sensitivity to γ-aminobutyric acid [GABA] and a lower threshold for the activity) and more fate options (neuron, glia, or cell death). Identification of the stage of newborn neurons that may make special contributions to hippocampal function is critical.

Currently, however, all manipulations may directly or indirectly change the properties of these new neurons, and none of the experimental models are sufficient to investigate how, when, and to what extent adult neurogenesis contributes to this profound function. New animal models are needed to test a role of adult neurogenesis directly. In this regard, establishment of refined genetic models in which neurogenesis exclusively in the DG can be regulated at suitable time points and in the suitable region, so that learning and memory can be studied in its depth, is needed. In addition, behavior tests that have better sensitivity are needed to detect subtle changes in learning and memory with respect to changes in adult neurogenesis. Although it took a century to establish the existence of adult neurogenesis fully, recent rapid progress in the field has led to confidence that the true physiologic significance of this evolutionally conserved phenomenon is likely to be revealed in the near future.

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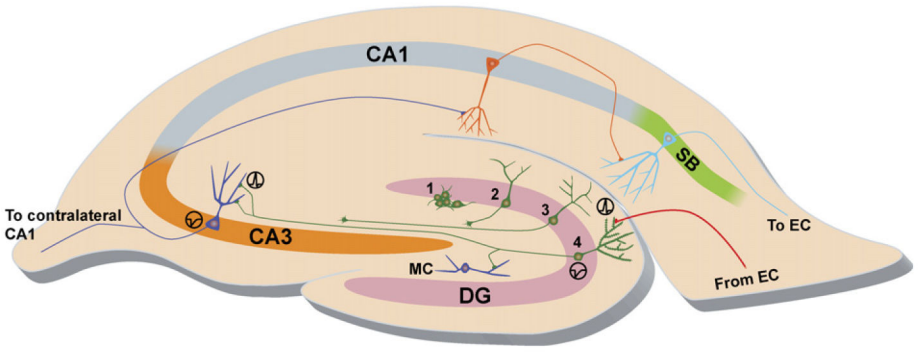

Fig. 1.

DG neurogenesis incorporation of new neurons. Neurogenesis in the hippocampus occurs in the SGZ of the DG, wherein neural progenitor cells reside (1). Within the first week after birth, these progenitors undergo a fate choice, in this case, becoming an immature neuron (2) with developing neurites. The axons of these new granule neurons are guided through the hilus of the DG, with long-distance branches targeting the CA3 (3) and the dendrites extending into the molecular layer (3). After 3 to 4 weeks, these cells form a mature phenotype, with their dendrites containing spines that receive input primarily from the entorhinal cortex (EC) by way of the perforant pathway (*red axon*) and their highly branched axons that output to CA3 pyramidal neurons (4) and hilar mossy cells (MC) by way of the mossy fiber pathway (*green axon*). Continuing the hippocampal circuitry, the CA3 pyramidal neurons output to the CA1 ipsilateral pyramidal neurons by way of the Schaffer collateral pathway or contralaterally by way of the associational commissural pathway (*blue axon*). The CA1 pyramidal neurons output (*orange axon*) to pyramidal neurons of the subiculum (SB), which output (*cyan axon*) to the EC, and these neurons eventually output to the parahippocampal and perirhinal cortex. Ultimately, the circuitry connects to the association cortices.

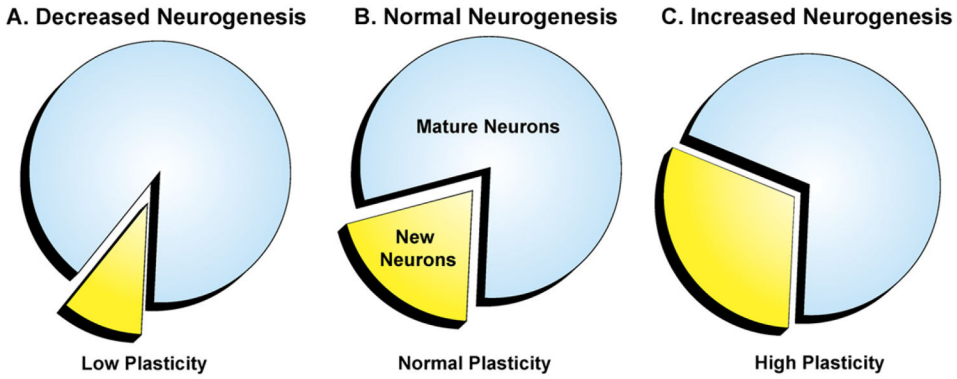

Fig. 2.

Theory of hippocampal neurogenesis in learning and memory. In normal neurogenesis (*B*), it appears that new neurons are constantly replacing a small portion of the existing population at a basal rate without a significant overall increase in the number of total granule neurons in the DG over time. Under certain conditions that cause a decrease in neurogenesis (*A*), it is assumed that this rate of replacement is significantly decreased and that with stimulation, this rate of replacement increases (*C*). Compared with the mature neuron population, the proportion of new neurons may cause a shift into an elevated plastic state. An increase in neurogenesis, and thus an increase in plasticity, may cause improvement in learning and memory tasks. Therefore, conversely, blocking neurogenesis and decreasing the plasticity index may be the cause of the observable decline in performance with various learning- and memory-related tasks.

Table 1

Influences of learning on the hippocampal neurogenesis

Tasks		Proliferation	Survival	References
Water maze	(2 trials per day × 4 days)		nc	Gould, et al [44]
	(4 trials per day × 4 days)		+	
Water maze	(10 trials per day × 5 days)		+	Ambrogini, et al [41]
Water maze	(6 trials per day × 3 days)		+	Rola, et al [43]
Water maze	(8 trials per day × 4 days)		+	Hairston, et al [42]
Water maze	(2 trials per day × 30 days)	nc	nc	van Praag, et al [58]
Water maze	(4 trials per day × 8 days)			Dobrossy, et al [78]
	(early phase)	nc, then decreased by later learning		
	(late phase)	+	+	
Water maze	(4 trials per day)			Drapeau, et al [55]
	(old animals)	+	+	
	(young animals)		nc	
Water maze	(1 or 2 trials per day × 10 days)		nc	Merrill, et al [45]
Water maze	(6 trials per day × 4 days)			Ehninger and Kempermann [46]
	(type 3 cells)		−	
	(type 2 cells)		−, then +	
Trace eye-blink conditioning		nc	+	Gould, et al [44]
Trace eye-blink			+	Leuner, et al [79]
STFP task	(1 day of training)		+	
	(2 days of training)		−	Olariu, et al [80]
Contextual fear conditioning		−	nc	Pham, et al [81]

Unmarked indicates not examined in proliferation column.

Abbreviations: nc, no change; STFP, social transmission of food preference; +, increase; −, decrease.

Table 2

Influences of altered neurogenesis on learning performance

Factors	Neurogenesis	Learning task	Learning	References
Aging		Water maze	Positive correlation	Bizon and Gallagher [54]
Strain		Water maze	Positive correlation	Kempermann and Gage [53]
Running	+	Water maze	Improved	van Praag, et al [58]
Enriched environment	+	Water maze	Improved	Nilsson, et al [37]
Stress	−	Water maze	Impaired	Lemaire, et al [82]
Irradiation	−	Water maze	nc	Madsen, et al [64]
		Object recognition task	nc	
		Place recognition task	Impaired	
		Barnes maze	Impaired	
Irradiation	−	Water maze	nc	Raber, et al [65]
		Elevated plus maze	nc	
Irradiation	−	Water maze	Impaired	Rola, et al [43]
		Barnes maze	nc	
Irradiation	−	Water maze	Impaired	Snyder, et al [68]
Irradiation + enrichment	−	Water maze	nc	Meshi, et al [57]
Irradiation	−	NMTS task	Impaired	Winocur, et al [66]
		Contextual fear conditioning	Impaired	
MAM	−	Trace-eyeblink	Impaired	Shores, et al [60]
MAM	−	Water maze	nc	Shores, et al [61]
	−	Elevated plus maze	nc	
		Trace fear conditioning	Impaired	
MAM	−	Novel object recognition task	nc	Bruel-Jungerman, et al [59]
Enriched environment	+	Novel object recognition task	Improved	
MAM+enriched environment	−	Novel object recognition task	Impaired	
Deletion of MBD1	−	Water maze	Impaired	Zhao, et al [71]
Deletion of NT-3	−	Water maze	Impaired	Shimazu, et al [76]
VEGF overexpression	+	Water maze	Improved	Cao, et al [70]
		Passive avoidance	Improved	

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Factors	Neurogenesis	Learning task	Learning	References
Immunedeficiency	−	Water maze	Impaired	Ziv, et al [83]

Abbreviations: MAM, methylazoxymethanol acetate; MBD1, methyl-CpG binding protein 1; nc, no change; NMTS, non–matching-to-sample; NT-3, neurotrophin-3; VEGF, vascular endothelial growth factor; +, increase; −, decrease.