Neurogenesis and Hippocampal Plasticity in Adult Brain

Yan Gu, Stephen Janoschka and Shaoyu Ge

Abstract Plasticity in the adult brain enables lifelong learning. The fundamental mechanism of adult neural plasticity is activity-dependent reorganization of pre-existing structure, in contrast to the widespread cellular proliferation and migration that occurs during development. Whereas adult hippocampal dentate gyrus continuously generates cohorts of neurons, and newborn neurons integrate into the existing neural circuit under the regulation of existing global and local neural activity, demonstrating a unique cellular and synaptic flexibility in adult brain. Exhibiting an enhanced structural and synaptic plasticity during the maturation, adult-born hippocampal neurons may represent a unique population for hippocampal function. Current evidence indicates that lifelong addition of new hippocampal neurons may extend early developmental plasticity to adulthood, which continuously rejuvenates adult brain. We reviewed most recent advancements in exploring the circuit and behavioral role of adult-born hippocampal neurons.

Keywords Adult neurogenesis · Hippocampus · Dentate gyrus · Plasticity

Abbreviations

DG	Dentate gyrus
DGCs	Dentate granule cells
SGZ	Subgranular zone
LTP	Long-term potentiation
GABA	Gamma-amino butyric acid

Y. Gu (✉) · S. Janoschka · S. Ge (✉)
Department of Neurobiology and Behavior, Stony Brook University,
100 Nicolls Road, Stony Brook, NY 11794, USA
e-mail: yangu@notes.cc.sunysb.edu

S. Ge
e-mail: sge@notes.cc.sunysb.edu

Curr Topics Behav Neurosci (2013) 15: 31–48
DOI: 10.1007/7854_2012_217

Published Online: 10 August 2012

NMDA N-Methyl-D-aspartate
AMPA Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid

Contents

1 Introduction: Hippocampus and Adult Neurogenesis

The hippocampus is one of the most extensively studied brain regions for synaptic plasticity and experience-modulated behavior. Numerous circuit tracing, targeted lesioning, and functional imaging studies have shown that the hippocampus is required for short-term declarative memory (Squire 1992), contextual associational memory (Rudy and Sutherland 1995), episodic memory (Vargha-Khadem et al. 1997), olfactory discrimination (Eichenbaum et al. 1989), and spatial navigation (O'Keefe and Dostrovsky 1971). A remarkable level of hippocampal plasticity has been proposed as a key factor in these functions. Central and long-standing hypotheses of the molecular and cellular mechanism of learning propose that memory formation relies on changes in synaptic strength and activity-dependent synaptic modification (Martin and Morris 2002; Neves et al. 2008).

Historically, the dentate gyrus (DG) has been characterized as the 'gate' of the *trisynaptic* hippocampal circuit (Hsu 2007), receiving perforant path projections from the neighboring neocortex and passing integrated information to the hippocampal CA3 subfield. Plasticity in this region has been found important for the function of hippocampus in many species including human. Based on anatomical, electrophysiological, and computer simulation data, it has been suggested that the DG plays an important role in learning and memory, including processing and representing spatial information on the basis of conjunctive encoding of multiple sensory inputs, pattern separation of spatial (especially metric) information, and temporal event integration in conjunction with the CA3 (Kesner 2007).

The subgranular zone (SGZ) of the DG is one of the only two widely acknowledged regions to date that retain neurogenesis under physiological conditions (Altman and Das 1965; Zhao et al. 2008). Continuous integration of new dentate granule cells (DGCs) provides another form of plasticity to the hippocampus in addition to the activity-dependent sub-cellular plasticity.

2 Structural and Functional Integration of Adult-Born DGCs

2.1 Structural Plasticity by Addition of New Neurons

In adult rodents, there are several thousand new neurons generated every day in the DG, modifying approximately 6 % of the total DGC population per month (Cameron and McKay 2001). Although most of these newborn DG cells (60–80 %) undergo programed cell death within 1 month following birth (Cameron and McKay 2001; Dayer et al. 2003), a remarkable number of new neurons survive and functionally integrate into the existing neural circuits (Ramirez-Amaya et al. 2006).

Hippocampal neurogenesis declines with age in mammals. It remains controversial whether ongoing adult neurogenesis provides a net increase in functional adult capacity or steady-state turnover of dying cells in the DG. Some studies have shown that the total number of DGCs does not increase with age in rat (Merrill et al. 2003; Rapp and Gallagher 1996; Rasmussen et al. 1996), whereas others indicate an increase in mice under different experimental conditions (Kempermann and Gage 1999; Kempermann et al. 1997). However, it is generally acknowledged that the elevated cell death observed in neurogenic active sites, including the DG, suggests that existing DGCs may be replaced or compete with newborn DGCs for survival (Biebl et al. 2000), and the rate of newborn cell addition is highly variable based on ontogenetic factors and behavioral activity.

A substantial number of newborn neurons integrate into the existing hippocampal neural circuits, suggesting that they are likely to play functional roles within local brain circuits and regional associated behavior. As new neurons integrate into the existing neural circuit for survival and function, they form new connections with afferent projections and efferent targets within the neural circuit. Therefore, continuous addition of new neurons in the DG introduces structural plasticity throughout the adulthood.

2.2 Functional Integration of Adult-Born Neurons

In 1984, Paton and Nottebohm for the first time characterized the synaptic activities of adult-born neurons in vivo in song birds, demonstrating that the newly generated neurons functionally integrate into the neural circuits and respond to

learned auditory stimuli (Paton and Nottebohm 1984). However, the sparse distribution and difficulty in direct visualization of these newborn neurons hindered the conclusive determination of many of their synaptic and functional properties. With the discovery that murine retrovirus selectively infects mitotic cells, it became possible to label and birth-date newborn neurons by virally introducing fluorescent protein genes into dividing neural stem cells in the DG. Pioneering work using this new technique was carried out by Gage's group on fluorescently labeled adult-born DGCs in live brain tissue in a series of elegant analyses on the morphological development and integration of the adult-born neurons (van Praag et al. 2002; Zhao et al. 2006).

Approximately, 80 % of dividing progenitors in the SGZ are directed to the neuronal fate and develop into dentate granule neurons. Cells targeted to the neuronal fate are highly plastic and active during the following several weeks as they migrate radially into the inner third of the granular layer. The extent of neuroblast tangential migration is currently unknown, although clonal analysis suggests such migration is minimal (Bonaguidi et al. 2011).

After complete development, newborn DGCs display typical morphology of dentate granule neurons, including apical dendritic trees projecting to the dentate gyrus molecular layer which form synaptic inputs from entorhinal cortical projections, and mature axons which contact neurons of the hilus and CA3 region.

2.2.1 Development of Adult-Born Neurons: Morphology and Membrane Properties

Recapitulating embryonic development, newborn DGCs in the adult brain follow a precise sequence of neuronal membrane development and synaptic connectivity before they become fully mature (Esposito et al. 2005; van Praag et al. 2002; Zhao et al. 2006).

During the first week, newborn DGCs have limited processes, spanning the granule cell layer toward molecular layer. All cellular properties resemble those of typical immature neurons of the developing brain, as they start to express neuronal sodium channels and fire immature action potentials.

At 2 weeks, new neurons have begun to migrate into the granule cell layer and to display typical granule cell morphology, with more numerous and elaborate dendrites traversing the molecular layer. No dendritic spines are observed at this stage. Membrane properties become more mature but still retain the characteristics of immature neurons.

At 4 weeks, newborn DGCs display morphology of mature granule neurons, including spiny dendrites that halt at the outer border of the molecular layer and axons that project to the CA3 region. Basic physiological properties mimic mature neurons at this stage, exhibiting mature action potentials and all known types of DGC synaptic connections, although synaptic plasticity continues to mature, as discussed below.

2.2.2 Formation of GABAergic Inputs

GABA has been shown to play crucial roles in regulating the development and synaptic integration of newborn neurons (Ge et al. 2007a).

Lacking synaptic inputs in the first week, newborn DGCs in the adult brain are tonically activated by ambient GABA. Functional GABAergic synapses that receive phasic GABAergic inputs from local interneurons start to form 1 week after birth (Ge et al. 2006), with the slow kinetics of GABA-activated currents indicating the initial formation of dendritic rather than perisomatic GABAergic synapses, which start to form 2 weeks later (Esposito et al. 2005; Ge et al. 2008). Physiologically, these GABAergic inputs to adult-born DGCs share the same characteristics of mature DGCs born in embryonic and early postnatal stages, and have similar functional properties (Laplagne et al. 2007).

GABA has an excitatory action owing to the high cytoplasmic chloride ion content of newborn DGCs in the first 2–3 weeks, and plays crucial role in regulating migration, development, and synaptic integration of newborn neurons (Ge et al. 2007a). Tonic GABA activation depolarizes newborn DGCs, and more importantly, it constitutes the majority of GABA-induced activation during the initial integration process when phasic GABA activation either does not exist or is weaker than tonic activation. Experimental conversion of GABA-induced depolarization (excitation) into hyperpolarization (inhibition) in newborn neurons leads to marked defects in synapse formation and dendritic development (Ge et al. 2006). Both the voltage-dependent and independent Ca^{2+}-permeable channels could be involved. Newborn DGCs in the adult brain express high levels of low-voltage-activated T-type Ca^{2+} channels which are activated below - 57 mV. Thus, tonic depolarization by GABA may lead to an activation of these Ca^{2+} channels and subsequent Ca^{2+} influx, leading to activity-dependent regulation of the development and integration of newborn neurons. However, detailed study will be needed to further determine the mechanism by which tonic GABA activation regulates these processes.

2.2.3 Formation of Glutamatergic Inputs

Following the formation of GABAergic synapses, glutamatergic inputs from the entorhinal cortex initiate synaptic connections on to the growing dendrites of adult-born DGCs. Although the first spines are formed approximately 2 weeks after birth and spine growth peaks at 3–4 weeks, further structural modifications continue for months (Zhao et al. 2006).

Recently, spine development on dendrites of newborn DGCs has been analyzed by 3D reconstruction of serial-section electron microscopy images (Toni et al. 2007). Filopodia—immature, motile protrusions that probe for potential synapse partners—extend very close to preexisting synaptic connections (within 200 nm) but not randomly, suggesting they are attracted to preexisting synapses, potentially by spillover glutamate from the active synapses (Kullmann and Asztely 1998;

Portera-Cailliau et al. 2003). Consistently, new dendritic spines are found in contact with multiple-synapse boutons, which contacts more than one postsynaptic spines. At 1 month, one-third of newborn spines contact single-synapse boutons, whereas all others contact multiple-synapse boutons. By the mature stage, two-thirds contact single-synapse boutons. These data suggests that newborn DGC spines initially form an preexisting synapses and later competitively replace preexisting postsynaptic spines as they stabilize (Toni et al. 2007), updating preexisting hippocampal neural circuit. By 4–8 weeks, adult-born DGCs display functional glutamatergic synaptic inputs similar to mature neurons (van Praag et al. 2002).

Glutamatergic inputs also regulate neurogenesis in the adult hippocampus, presumably by modulating neuronal integration and survival during development. Some studies have shown that AMPA receptor potentiation increases adult neurogenesis (Bai et al. 2003), while loss of NMDA receptor activity decreases newborn neuron survival (Tashiro et al. 2006). Seemingly, in contradiction, application of NMDA or AMPA receptor antagonists increase adult neurogenesis in the DG mainly by the regulation of cell proliferation (Bernabeu and Sharp 2000; Cameron et al. 1995; Gould et al. 1997). These results suggest that the regulation of adult neurogenesis by glutamatergic activity is complex, possibly through different downstream signaling pathways, or sensitive to environment or behavioral changes following treatment.

2.2.4 Formation of Synaptic Outputs

As newborn DGCs extend dendrites into the molecular layer, they extend axons rapidly toward the CA3 region. One week after birth, newborn axons pass through the hilus and reach the proximal CA3 region; by 2 weeks, they begin to form *en passant* expansions (Faulkner et al. 2008; Hastings and Gould 1999; Markakis and Gage 1999; Zhao et al. 2006). Axons continue to grow along the CA3 within 3–4 weeks while their expansions grow into larger, mossy fiber boutons (Faulkner et al. 2008). Newborn DGC axons do not extend beyond CA3, so they ultimately share the same trajectory as preexisting mature mossy fibers. According to the evidence provided by confocal and electronic microscopy studies, the earliest output synaptic contacts form on the dendritic shafts of target neurons by 2 weeks. Boutons grow in size and form spinous synaptic contacts, or share/compete spines with preexisting boutons (Faulkner et al. 2008; Toni et al. 2008). It takes 8–16 weeks for these new mossy fiber boutons to reach full maturity, with multiple invading dendritic spines and a stable number of synaptic contacts (Faulkner et al. 2008).

Recently, the excitatory optogene channelrhodopsin has been targeted into adult-born DGCs using retrovirus to study the functional synaptic output of these newborn neurons following light stimulation. The results indicate that mature adult-born DGCs establish functional synapses with hilar interneurons, mossy cells, and CA3 pyramidal cells and release glutamate as their main neurotransmitter, as do mature

DGCs (Toni et al. 2008). However, the complete process of axonal integration and maturation remains unclear. Furthermore, it will be interesting to determine whether the unusual diversity of interneuron targets reported as a distinguishing factor of adult-born olfactory neurons is also a feature of hippocampal neurogenesis (Bardy et al. 2010).

3 Circuit and Behavioral Roles of Adult-Born Neurons

3.1 Functional Relevance of Adult-Born Neurons

Since newborn neurons are continuously integrated into the existing hippocampal circuits throughout the adulthood, a key question is: do they contribute to known hippocampal function? Numerous studies using diverse approaches have shown the involvement of adult-born DGCs in hippocampal-dependent behaviors (Kee et al. 2007; Ramirez-Amaya et al. 2006; Tashiro et al. 2007).

Resulting from voluntary exercise (Farmer et al. 2004; van Praag et al. 1999), enriched environment (Nilsson et al. 1999), enhanced neurogenesis is usually associated with elevated synaptic plasticity in the DG and/or improved hippocampal-dependent learning and memory. A recent study also demonstrated that genetically increasing DG neurogenesis by specific inhibition of newborn cell death sufficiently improves hippocampal-dependent pattern separation (Sahay et al. 2011). Consistent with the hypothesis that neurogenesis has a positive role in learning and memory, decreased neurogenesis in either transgenic mouse lines, such as Methyl-CpG binding protein 1 knockout (MBD1-/-) mice, or ablation of neurogenesis by genetic methods or irradiation results in decreased synaptic plasticity in the DG and/or deficits in some forms of hippocampal-dependent learning and memory (Arruda-Carvalho et al. 2011; Drew et al. 2010; Imayoshi et al. 2008; Saxe et al. 2006; Snyder et al. 2001; Zhao et al. 2003).

Furthermore, Drapeau et al. observed a quantitative relationship between water maze performance, and the number of newborn neurons in the hippocampus of aged animals, in which animals that retained spatial memory exhibited a higher level of cell proliferation and a higher number of new neurons in comparison to those with spatial memory impairments (Drapeau et al. 2003).

Combining BrdU labeling of newborn neurons and immediate-early gene expression in active neurons, Frankland's group revealed the activity of adult-born DGCs in mice during behavioral tasks, indicating the incorporation of adult-born DGCs into special memory circuits (Kee et al. 2007). A recent study by his group selectively ablated a population of predominantly mature, adult-born neurons using a diphtheria toxin-based strategy without affecting ongoing neurogenesis. Removal of these integrated, adult-born neurons after learning degraded existing hippocampal-dependent contextual fear and water maze memories, suggesting that

adult-born neurons form a critical and enduring component of hippocampal memory traces (Arruda-Carvalho et al. 2011).

Together, these studies suggest that adult-born DGCs are involved in and required for normal hippocampal function. So the following question would be: do the adult-born neurons have unique properties and thus play unique roles in the hippocampal circuit?

3.2 Synaptic Plasticity of New Neurons

Synaptic plasticity such as long-term potentiation (LTP) has been thought to be the primary cellular basis of hippocampus-dependent learning and memory.

Wojtowicz's group found that immature DGCs in the inner granular layer, as determined by immature neuron marker TOAD-64 expression, are completely unaffected by GABAa inhibition and always display robust LTP with a lower induction threshold (Wang et al. 2000). This was confirmed by another group who found that DGCs expressing PSA-NCAM, another immature neuron marker, display immature properties, and have lower threshold for LTP induction and enhanced LTP (Schmidt-Hieber et al. 2004). Furthermore, by recording the evoked field potentials of populations of DGCs, Snyder et al. found a form of LTP could be induced in absence of GABAa receptor blocker picrotoxin. This LTP was selectively blocked by gamma irradiation 3 weeks before recording (Snyder et al. 2001), suggesting that this form of LTP is mediated by newly generated young neurons. Whereas the LTP mediated by mature neuron could only be observed in the presence of picrotoxin to block the local GABAergic inhibition.

Under physiological conditions, in intact neural circuit with GABAa inhibition in the adult brain, synaptic LTP plasticity in the DG appears to be largely dependent on young adult-born neurons. In contrast, mature DGCs display much less LTP in the same condition (Wang et al. 2000), or have higher threshold for LTP induction (Schmidt-Hieber et al. 2004).

3.3 Critical Window of Enhanced Synaptic Plasticity of Adult-Born Neurons

In classic experiments on the visual cortex, Hubel and Wiesel established the term "critical period" to describe a specific time window in which neuronal properties are particularly susceptible to modification by experience, concurrent with large-scale anatomical changes that become irreversible after closure of the time window (Hubel and Wiesel 1962; Wiesel and Hubel 1963). During this period, neurons display enhanced morphological and synaptic plasticity, and critical

period plasticity is now considered a central mechanism for establishing fine-tuned neuronal circuits in the developing brain (Hensch 2004).

Newborn neurons in the adult brain recapitulate embryonic neuronal developmental processes (Esposito et al. 2005), including proliferation, differentiation, functional integration, and maturation. During integration, these neurons start to receive experience-driven inputs from existing neural circuits. Do adult-born neurons also experience a critical period with enhanced synaptic plasticity, or are their synaptic properties maintained over a long period of time?

Using a retroviral approach for labeling and birth-dating adult-born DGCs, it became possible to study the plasticity of newborn neurons at specific ages. Ge et al. recorded from adult-born DGCs of different ages while stimulating the medial perforant pathway, followed by LTP induction using theta-burst stimulation. They found an enhanced LTP with decreased induction threshold in young adult-born DGCs at the age of 4–6 weeks that rapidly drops by 8 weeks of age (Ge et al. 2007b), indicating a critical period with enhanced synaptic plasticity. This is in consistent with other studies showing adult-born neurons display a high level of anatomical plasticity during this period which decreases thereafter, such as spine motility (Zhao et al. 2006), suggesting that the newborn DGCs undergo a short period of fine-tuning while integrating into existing circuits.

3.4 Molecular Mechanisms of Enhanced Synaptic Plasticity in Young Neurons

How are new neurons more plastic during this period? Lines of studies have shown that immature adult-born DGCs display distinct active and passive membrane properties such as high input resistance (van Praag et al. 2002). Moreover, in young neurons, high levels of T-type Ca^{2+} channels can generate isolated Ca^{2+} spikes and boost fast Na^{+} action potentials, contributing to the induction of synaptic plasticity (Schmidt-Hieber et al. 2004).

Another key mediator of plasticity is the N-methyl-D-aspartate (NMDA) type of glutamate receptors (NMDARs). During adult neurogenesis, NMDARs are expressed early, starting from immature neuronal stages (Carleton et al. 2003; Nacher et al. 2007).

It is known that during early postnatal neuronal development, switching of NMDARs subtypes from NR2B to NR2A changes the direction and degree of synaptic plasticity (Barria and Malinow 2005; Kim et al. 2005; Liu et al. 2004; Tang et al. 1999; Zhao et al. 2005). NMDARs containing NR2B subunit are expressed early during postnatal development and appear to be associated with enhanced synaptic plasticity during the critical period (Barria and Malinow 2005; Cull-Candy and Leszkiewicz 2004), while NMDARs containing NR2A, which are expressed and dominant later, mediate dramatically decreased LTP after the critical period (Barria and Malinow 2005).

Using field potential recordings, Snyder et al. revealed that LTP in the DG with intact GABAergic inhibition, which is potentially mediated by young adult-born neurons, could be specifically blocked by NR2B antagonist ifenprodil (Snyder et al. 2001). By specifically targeting adult-born DGCs, Ge et al. showed ifenprodil completely abolished LTP on DGCs of 4-weeks old, but not 8-weeks old or mature DGCs, providing a temporal correlation between synaptic expression of NR2B subtypes and critical period plasticity. They also found that the plasticity of newborn DGCs within the critical period rely significantly more on NR2B-containing NMDARs than on pan-NMDARs, suggesting that NR2B, which is the major NMDARs subtype expressed during the critical period, plays an instructive role in the enhanced synaptic plasticity of adult-born DGCs within this time window (Ge et al. 2007b). These studies suggest that adult-born neurons in the critical period undergo molecular mechanisms similar to neurons in the early postnatal critical period.

3.5 Contribution of Young Adult-Born DGCs to Hippocampal Functions

Since adult-born DGCs integrate into existing neural circuits of the hippocampus, and they express an enhanced synaptic and anatomic plasticity during the critical period in response to experience other than mature neurons that have passed the critical period (Ge et al. 2007b; Hensch 2004; Katz and Shatz 1996), do they make unique contributions to hippocampal function?

Emerging evidence suggests that adult-born DGCs might be preferentially recruited into hippocampal neural circuits that mediate novelty recognition, contextual fear conditioning, spatial information processing and memory formation (Denny et al. 2011; Kee et al. 2007; Ramirez-Amaya et al. 2006). This preferential recruitment appears at 4–6 weeks after birth, which is consistent with the critical period of the adult-born DGCs (Denny et al. 2012; Kee et al. 2007).

Owing to their high excitability (Mongiat et al. 2009; van Praag et al. 2002) and critical period plasticity for the fine-tuning of synaptic incorporation in the neural circuitry in response to experience, adult-born DGCs of the critical period are more readily recruited into the hippocampal circuit for the encoding of novel information. As modeled by Aimone et al., the special properties of young adult-born neurons are required for the formation of temporal clusters which associate individual elements of long-term episodic memories (Aimone et al. 2006).

Overall, the available evidence strongly indicates that young adult-born neurons play an important role in participating in certain types of hippocampus-related behaviors, particularly learning and memory. Based on the expression of doublecortin (DCX) or CRMP4, proteins specific to immature neurons, the population of young adult-born neurons could correspond up to 10 % of all granule cells of the DG, and are likely to have a broad impact on the entire hippocampus.

Therefore, by continuously generating cohorts of new neurons, adult hippocampus is able to retain an enhanced form of plasticity in a population of DGCs for the function of hippocampus throughout the adulthood.

4 Regulation by Local and Global Neural Activity

Activity-dependent anatomical reorganization is widely regarded as a fundamental mechanism of developmental and adult neural plasticity. Adult neurogenesis is similarly dynamic and highly dependent on the activity of the neural circuits. As DG receives various innervations from multiple brain regions, adult-born neuron development at distinct stages is regulated by numerous factors related to global and local neuronal activities.

As previously mentioned, neurogenesis in the adult hippocampus is significantly enhanced by an enriched environment (Brown et al. 2003; Kempermann et al. 2002; Kempermann et al. 1997), and physical activity (running) (Brown et al. 2003; Farmer et al. 2004; Rhodes et al. 2003; van Praag et al. 1999). Gould and colleagues reported that spatial learning activity increased the number of newborn neurons in the adult hippocampus (Gould et al. 1999). Electric stimulation in the entorhinal cortex or LTP induction in the DG enhanced both proliferation and survival of adult-born neurons (Bruel-Jungerman et al. 2006; Stone et al. 2011). Recent evidence showed different activity level in the septal and temporal pole of the hippocampus results in the difference of the integration and maturation of newborn neurons. Newborn neurons in the septal pole of DG display higher rate of maturation as indicated by intermediate early and neuronal marker gene expression, morphology, and electrophysiological properties, possibly due to higher septal pole basal network activity (Piatti et al. 2011). NMDA receptor-dependent hippocampal learning activity has been shown to promote the survival of specific populations of adult-born neurons (Dupret et al. 2007; Gould et al. 1999). In fact, loss of NMDA receptor activities decreases the survival of adult-born neurons (Tashiro et al. 2006). In general, neural circuit activity regulates adult neurogenesis in the brain, and NMDA receptor activation appears to be critical for not only proliferation of newborn neurons, but also successful integration and survival of new neurons by strengthening the correct functional glutamatergic synaptic connections through activity-dependent synaptic modification.

On the other hand, ambient GABA levels, regulated by interneuron activities, may also serve as a general indicator of dynamic neuronal network activity in a sparsely activated DG. Before receiving any synaptic innervations, newborn neurons may sense local neuronal network activities through ambient GABA. The maturation of GABAergic synapses is associated with the critical developmental period of adult-born DGCs. Thus, the tempo of the synaptic integration and the critical period of the newborn neurons are regulated by local GABAergic inputs (Ge et al. 2008).

Also importantly, as adult-born DGCs begin to express muscarinic and nicotinic acetylcholine receptors and receive direct cholinergic innervations early in their development, their successful integration and function are regulated by the activity of these inputs (Campbell et al. 2010; Harrist et al. 2004; Mohapel et al. 2005). Lesion of the medial septum, which sends cholinergic projections to the DG, decreases the survival of newborn neurons (Van der Borght et al. 2005). Similarly, selective neurotoxic lesion of forebrain cholinergic input to the DG also reduces adult neurogenesis (Cooper-Kuhn et al. 2004; Mohapel et al. 2005), possibly as a result of increased apoptosis of newborn DGCs (Cooper-Kuhn et al. 2004). Consistent with these results, systemic administration of the cholinergic agonist physostigmine or acetylcholinesterase inhibitor donepezil increases neurogenesis by enhancing survival of newborn DGCs (Kaneko et al. 2006; Kotani et al. 2006). Proliferation of adult neural hippocampal progenitors is also reduced in mice lacking the beta2-subunit of the nicotinic acetylcholine receptor (Harrist et al. 2004). Likewise, knockout of the alpha7 subunit of the nicotinic acetylcholine receptor not only decreases the survival of the newborn neurons, but also affects their maturation. The neurons of both alpha7-knockout mice and those infected with retrovirus which knocks down alpha7 mRNA display a prolonged period of GABAergic depolarization characteristic of an immature state (Campbell et al. 2010).

Furthermore, increased serotonergic signaling increases adult neurogenesis (Banasr et al. 2004), while blockage decreases it (Brezun and Daszuta 1999). Adult neurogenesis is also regulated by dopaminergic, norepinephrine, and NO systems (Hoglinger et al. 2004; Jhaveri et al. 2010; Zhang et al. 2001). In addition, modulation of excitatory neurotransmission by hormonal release in certain conditions, such as stress, is known to shift hippocampal neurogenesis, dendrite remodeling, and synaptic capacity (McEwen 2007).

In summary, the generation, survival, maturation, and integration of adult-born DGCs are precisely regulated by global and local neural circuitry activities, depending on the environmental conditions and the developmental stage and receptor expression of the newborn neurons.

5 Conclusion and Open Questions: The Unique Plasticity of Hippocampal Circuits

During the initial development, adult-born neurons display distinct properties, such as high input resistance, high structural plasticity, and enhanced susceptibility for the induction of LTP before they are fully matured.

Due to the enhanced excitability and plasticity, young adult-born DGCs provide unique capability to local circuits and associated behaviors. It has been proposed that adult-born DGCs might be highly engaged as the DG integrates memory of events that occur within a narrow window of time (Aimone et al. 2006; Deng et al. 2010).

Thus adult neurogenesis may provide not only a source of replacement neurons for maintenance of hippocampal structure, synaptic connections, and steady DGC number, but also an ongoing developmental process that continuously rejuvenates the mature nervous system by offering expanded capacity of plasticity in response to experience throughout life so that the adult brain maintains the ability to adapt to new experiences.

New evidence is emerging that adult-born neurons are also important for other hippocampal-related functions. Recently, an additional temporal function was reported showing that newborn neurons modulate the transference of short-term fear memory to hippocampus-independent memory centers, a process potentiated by voluntary exercise (Kitamura et al. 2009). Interestingly, Feng et al. found that forebrain-specific presenilin-1 knockout mice, which have a deficiency in enrichment-induced neurogenesis in the DG, did not show appreciable learning deficits, but a marked increase of memory retention after post-learning enrichment, suggesting that adult dentate neurogenesis also plays a role in the periodic clearance of outdated hippocampal memory traces after cortical memory consolidation, thereby ensuring that there are young newborn DGCs in the hippocampus continuously available for processing new memories (Feng et al. 2001). New approaches are required for further clarification, particularly to disambiguate the functional contributions of the newborn neurons in the adult brain.

Evidence also shows the difference of neurogenesis along the septo-temporal axis of the hippocampus. Development of newborn neurons is accelerated at the septal pole, possibly due to higher septal pole basal network activity (Piatti et al. 2011). The septal pole of the hippocampus is known to be associated with spatial learning and memory while the temporal pole with affective behavior, but the significance of these findings is not yet fully understood, especially since this same study reported increased physiological activity due to running preferentially activates temporal pole development.

However, the full functions of adult-born DGCs are not yet fully understood, nor is it entirely clear why a cell-based reorganization strategy is retained in the hippocampal archicortex but not the neocortex. While we currently have a far stronger understanding of the diverse factors which influence this unique form of brain plasticity, further studies and new approaches, particularly, in coordination with the results of olfactory neurogenesis studies, will be required to address these important questions.

References

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

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

Arruda-Carvalho M, Sakaguchi M, Akers KG, Josselyn SA, Frankland PW (2011) Posttraining ablation of adult-generated neurons degrades previously acquired memories. J Neurosci 31:15113–15127

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

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

Bardy C, Alonso M, Bouthour W, Lledo PM (2010) How, when, and where new inhibitory neurons release neurotransmitters in the adult olfactory bulb. J Neurosci 30:17023–17034

Barria A, Malinow R (2005) NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. Neuron 48:289–301

Bernabeu R, Sharp FR (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

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

Bonaguidi MA, Wheeler MA, Shapiro JS, Stadel RP, Sun GJ, Ming GL, Song H (2011) In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. Cell 145:1142–1155

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

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

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

Cameron HA, McKay RD (2001) Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 435:406–417

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

Campbell NR, Fernandes CC, Halff AW, Berg DK (2010) Endogenous signaling through alpha7-containing nicotinic receptors promotes maturation and integration of adult-born neurons in the hippocampus. J Neurosci 30:8734–8744

Carleton A, Petreanu LT, Lansford R, Alvarez-Buylla A, Lledo PM (2003) Becoming a new neuron in the adult olfactory bulb. Nat Neurosci 6:507–518

Cooper-Kuhn CM, Winkler J, Kuhn HG (2004) Decreased neurogenesis after cholinergic forebrain lesion in the adult rat. J Neurosci Res 77:155–165

Cull-Candy SG, Leszkiewicz DN (2004) Role of distinct NMDA receptor subtypes at central synapses. Sci STKE:re16

Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA (2003) Short-term and long-term survival of new neurons in the rat dentate gyrus. J Comp Neurol 460:563–572

Deng W, Aimone JB, Gage FH (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11:339–350

Denny CA, Burghardt NS, Schachter DM, Hen R, Drew MR (2012) 4- to 6-week-old adult-born hippocampal neurons influence novelty-evoked exploration and contextual fear conditioning. Hippocampus 22:1188–1201

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

Drew MR, Denny CA, Hen R (2010) Arrest of adult hippocampal neurogenesis in mice impairs single- but not multiple-trial contextual fear conditioning. Behav Neurosci 124:446–454

Dupret D, Fabre A, Dobrossy MD, Panatier A, Rodriguez JJ, Lamarque S, Lemaire V, Oliet SH, Piazza PV, Abrous DN (2007) Spatial learning depends on both the addition and removal of new hippocampal neurons. PLoS Biol 5:e214

Eichenbaum H, Mathews P, Cohen NJ (1989) Further studies of hippocampal representation during odor discrimination learning. Behav Neurosci 103:1207–1216

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

Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR (2004) Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 124:71–79

Faulkner RL, Jang MH, Liu XB, Duan X, Sailor KA, Kim JY, Ge S, Jones EG, Ming GL, Song H, Cheng HJ (2008) Development of hippocampal mossy fiber synaptic outputs by new neurons in the adult brain. Proc Natl Acad Sci U S A 105:14157–14162

Feng R, Rampon C, Tang YP, Shrom D, Jin J, Kyin M, Sopher B, Miller MW, Ware CB, Martin GM, Kim SH, Langdon RB, Sisodia SS, Tsien JZ (2001) Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. Neuron 32:911–926

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

Ge S, Pradhan DA, Ming GL, Song H (2007a) GABA sets the tempo for activity-dependent adult neurogenesis. Trends Neurosci 30:1–8

Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007b) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559–566

Ge S, Sailor KA, Ming GL, Song H (2008) Synaptic integration and plasticity of new neurons in the adult hippocampus. J Physiol 586:3759–3765

Gould E, McEwen BS, Tanapat P, Galea LA, 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, Beylin A, Tanapat P, Reeves A, Shors TJ (1999) Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 2:260–265

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

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

Hensch TK (2004) Critical period regulation. Annu Rev Neurosci 27:549–579

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

Hsu D (2007) The dentate gyrus as a filter or gate: a look back and a look ahead. Prog Brain Res 163:601–613

Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106–154

Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, Mori K, Ikeda T, Itohara S, Kageyama R (2008) Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci 11:1153–1161

Jhaveri DJ, Mackay EW, Hamlin AS, Marathe SV, Nandam LS, Vaidya VA, Bartlett PF (2010) Norepinephrine directly activates adult hippocampal precursors via beta3-adrenergic receptors. J Neurosci 30:2795–2806

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

Katz LC, Shatz CJ (1996) Synaptic activity and the construction of cortical circuits. Science 274:1133–1138

Kee N, Teixeira CM, Wang AH, Frankland PW (2007) Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. Nat Neurosci 10:355–362

Kempermann G, Gage FH (1999) Experience-dependent regulation of adult hippocampal neurogenesis: effects of long-term stimulation and stimulus withdrawal. Hippocampus 9:321–332

Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. Nature 386:493–495

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

Kesner RP (2007) A behavioral analysis of dentate gyrus function. Prog Brain Res 163:567–576

Kim MJ, Dunah AW, Wang YT, Sheng M (2005) Differential roles of NR2A- and NR2B-containing NMDA receptors in Ras-ERK signaling and AMPA receptor trafficking. Neuron 46:745–760

Kitamura T, Saitoh Y, Takashima N, Murayama A, Niibori Y, Ageta H, Sekiguchi M, Sugiyama H, Inokuchi K (2009) Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. Cell 139:814–827

Kotani S, Yamauchi T, Teramoto T, Ogura H (2006) Pharmacological evidence of cholinergic involvement in adult hippocampal neurogenesis in rats. Neuroscience 142:505–514

Kullmann DM, Asztely F (1998) Extrasynaptic glutamate spillover in the hippocampus: evidence and implications. Trends Neurosci 21:8–14

Laplagne DA, Kamienkowski JE, Esposito MS, Piatti VC, Zhao C, Gage FH, Schinder AF (2007) Similar GABAergic inputs in dentate granule cells born during embryonic and adult neurogenesis. Eur J Neurosci 25:2973–2981

Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M, Auberson YP, Wang YT (2004) Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. Science 304:1021–1024

Markakis EA, Gage FH (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

Martin SJ, Morris RG (2002) New life in an old idea: the synaptic plasticity and memory hypothesis revisited. Hippocampus 12:609–636

McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87:873–904

Merrill DA, Karim R, Darraq M, Chiba AA, Tuszynski MH (2003) Hippocampal cell genesis does not correlate with spatial learning ability in aged rats. J Comp Neurol 459:201–207

Mohapel P, Leanza G, Kokaia M, Lindvall O (2005) Forebrain acetylcholine regulates adult hippocampal neurogenesis and learning. Neurobiol Aging 26:939–946

Mongiat LA, Esposito MS, Lombardi G, Schinder AF (2009) Reliable activation of immature neurons in the adult hippocampus. PLoS One 4:e5320

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

Neves G, Cooke SF, Bliss TV (2008) Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nat Rev Neurosci 9:65–75

Nilsson M, Perfilieva E, Johansson U, Orwar O, Eriksson PS (1999) Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. J Neurobiol 39:569–578

O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171–175

Paton JA, Nottebohm FN (1984) Neurons generated in the adult brain are recruited into functional circuits. Science 225:1046–1048

Piatti VC, Davies-Sala MG, Esposito MS, Mongiat LA, Trinchero MF, Schinder AF (2011) The timing for neuronal maturation in the adult hippocampus is modulated by local network activity. J Neurosci 31:7715–7728

Portera-Cailliau C, Pan DT, Yuste R (2003) Activity-regulated dynamic behavior of early dendritic protrusions: evidence for different types of dendritic filopodia. J Neurosci 23: 7129–7142

Ramirez-Amaya V, Marrone DF, Gage FH, Worley PF, Barnes CA (2006) Integration of new neurons into functional neural networks. J Neurosci 26:12237–12241

Rapp PR, Gallagher M (1996) Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. Proc Natl Acad Sci U S A 93:9926–9930

Rasmussen T, Schliemann T, Sorensen JC, Zimmer J, West MJ (1996) Memory impaired aged rats: no loss of principal hippocampal and subicular neurons. Neurobiol Aging 17:143–147

Rhodes JS, van Praag H, Jeffrey S, Girard I, Mitchell GS, Garland T Jr, Gage FH (2003) Exercise increases hippocampal neurogenesis to high levels but does not improve spatial learning in mice bred for increased voluntary wheel running. Behav Neurosci 117:1006–1016

Rudy JW, Sutherland RJ (1995) Configural association theory and the hippocampal formation: an appraisal and reconfiguration. Hippocampus 5:375–389

Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472:466–470

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

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

Snyder JS, Kee N, Wojtowicz JM (2001) Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol 85:2423–2431

Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99:195–231

Stone SS, Teixeira CM, Devito LM, Zaslavsky K, Josselyn SA, Lozano AM, Frankland PW (2011) Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J Neurosci 31:13469–13484

Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ (1999) Genetic enhancement of learning and memory in mice. Nature 401:63–69

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

Tashiro A, Makino H, Gage FH (2007) Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 27:3252–3259

Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH (2007) Synapse formation on neurons born in the adult hippocampus. Nat Neurosci 10:727–734

Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, Schinder AF (2008) Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci 11:901–907

Van der Borght K, Mulder J, Keijser JN, Eggen BJ, Luiten PG, Van der Zee EA (2005) Input from the medial septum regulates adult hippocampal neurogenesis. Brain Res Bull 67: 117–125

van Praag H, Christie BR, Sejnowski TJ, Gage FH (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 96:13427–13431

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

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277:376–380

Wang S, Scott BW, Wojtowicz JM (2000) Heterogenous properties of dentate granule neurons in the adult rat. J Neurobiol 42:248–257

Wiesel TN, Hubel DH (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 26:1003–1017

Zhang R, Zhang L, Zhang Z, Wang Y, Lu M, Lapointe M, Chopp M (2001) A nitric oxide donor induces neurogenesis and reduces functional deficits after stroke in rats. Ann Neurol 50: 602–611

Zhao X, Ueba T, Christie BR, Barkho B, McConnell MJ, Nakashima K, Lein ES, Eadie BD, Willhoite AR, Muotri AR, Summers RG, Chun J, Lee KF, Gage FH (2003) Mice lacking methyl-CpG binding protein 1 have deficits in adult neurogenesis and hippocampal function. Proc Natl Acad Sci U S A 100:6777–6782

Zhao MG, Toyoda H, Lee YS, Wu LJ, Ko SW, Zhang XH, Jia Y, Shum F, Xu H, Li BM, Kaang BK, Zhuo M (2005) Roles of NMDA NR2B subtype receptor in prefrontal long-term potentiation and contextual fear memory. Neuron 47:859–872

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

Zhao C, Deng W, Gage FH (2008) Mechanisms and functional implications of adult neurogenesis. Cell 132:645–660

http://www.springer.com/978-3-642-36231-6

Neurogenesis and Neural Plasticity
Belzung, C.; Wigmore, P. (Eds.)
2013, X, 401 p., Hardcover
ISBN: 978-3-642-36231-6