SYMPOSIUM REPORT

Synaptic integration and plasticity of new neurons in the adult hippocampus

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Adult neurogenesis, a developmental process encompassing the birth of new neurons from adult neural stem cells and their integration into the existing neuronal circuitry, highlights the plasticity and regenerative capacity of the adult mammalian brain. Substantial evidence suggests essential roles of newborn neurons in specific brain functions; yet it remains unclear how these new neurons make their unique contribution. Recently, a series of studies have delineated the basic steps of the adult neurogenesis process and shown that many of the distinct steps are dynamically regulated by the activity of the existing circuitry. Here we review recent findings on the synaptic integration and plasticity of newborn neurons in the adult hippocampus, including the basic biological process, unique characteristics, critical periods, and activity-dependent regulation by the neurotransmitters GABA and glutamate. We propose that adult neurogenesis represents not merely a replacement mechanism for lost neurons, but also an ongoing developmental process in the adult brain that offers an expanded capacity for plasticity for shaping the existing circuitry in response to experience throughout life.

Since the time of Cajal, it was generally believed that the mature central nervous system lacks regenerative capacity, including the inability to re-grow injured axons and to generate new neurons. The dogma that no new neurons are generated after birth in mammals was overturned during the last decade by clear demonstrations of newly generated neurons in discrete regions of adult mammalian brains, including humans (Eriksson *et al.* 1998). Adult neurogenesis represents a developmental process that encompasses the proliferation and fate specification of adult neural stem cells along with their differentiation, maturation, migration and incorporation into the existing neural circuitry of their progeny in the mature nervous system (Ming & Song, 2005). A variety of physiological, pathological and pharmacological stimuli have been shown to regulate distinct steps of adult neurogenesis (Ming & Song, 2005). Rapidly accumulating evidence also suggests essential roles of

adult-born neurons in specific brain functions, such as learning, memory and mood regulation (Kempermann *et al.* 2004*b*; Kitabatake *et al.* 2007; Zhao *et al.* 2008). Aided by new methodologies for birth-dating and tracking new neurons in the adult brain, recent studies have elucidated the basic process of adult neurogenesis (Alvarez-Buylla & Lim, 2004; Ming & Song, 2005; Lledo et al. 2006; Zhao *et al.* 2008). In particular, studies using bromodeoxyuridine (BrdU)-based birth-dating and immunohistochemistry of cell type specific markers have identified a series of intermediate developmental stages during adult neurogenesis (Kempermann *et al.* 2004*a*). In addition, electrophysiology and imaging studies of new neurons labelled with retroviruses and in transgenic reporter mice have characterized the maturation and integration of new neurons in the adult brain (Duan *et al.* 2008). Furthermore, genetic manipulation of adult neural stem cells and their local environment, or 'neurogenic niche', is starting to reveal key molecular mechanisms underlying adult neurogenesis and activity-dependent regulation (Ge *et al.* 2006; Tashiro *et al.* 2006; Duan *et al.* 2007). Here we review recent findings on the synaptic integration and plasticity of newborn dentate granule cells in the adult hippocampus. We discuss activity-dependent regulation of adult hippocampal neurogenesis involving

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γ-aminobutyric acid (GABA) and glutamate, two major neurotransmitters in the adult brain. We also discuss how new neurons may contribute to specific functions of the adult brain.

Synaptic integration of adult-born dentate granule cells into the existing circuitry

Functional incorporation of new neurons into the adult circuitry was first demonstrated over two decades ago in a landmark study where 1 month after adult canaries were injected with [³H]thymidine to label new cells, four randomly recorded neurons (out of a total of 74 neurons) within a vocal control nucleus in the telencephalon exhibited electrical responses to auditory stimulation and were positive for [³H]thymidine labelling (Paton & Nottebohm, 1984). Over the past

few years engineered oncoretrovirus (van Praag *et al.* 2002) and transgenic reporter mice (Overstreet *et al.* 2004) have greatly facilitated functional analysis of new neurons *in vivo*. Studies using these tools have revealed a stereotypic integration process in establishing connections by newborn granule cells in the adult hippocampus (Fig. 1), from initial tonic activation by ambient GABA, to dendritic GABAergic synaptic inputs, followed by dendritic glutamatergic inputs and finally perisomatic GABAergic inputs (Esposito *et al.* 2005; Overstreet Wadiche *et al.* 2005, 2006; Tozuka *et al.* 2005; Wang *et al.* 2005; Ge *et al.* 2006; Karten *et al.* 2006). After a prolonged maturation phase, adult-born neurons exhibit electrical and synaptic properties that are indistinguishable from those of neighbouring mature granule cells when examined by electrophysiology at the single-cell level (Laplagne *et al.* 2006; Ge *et al.*
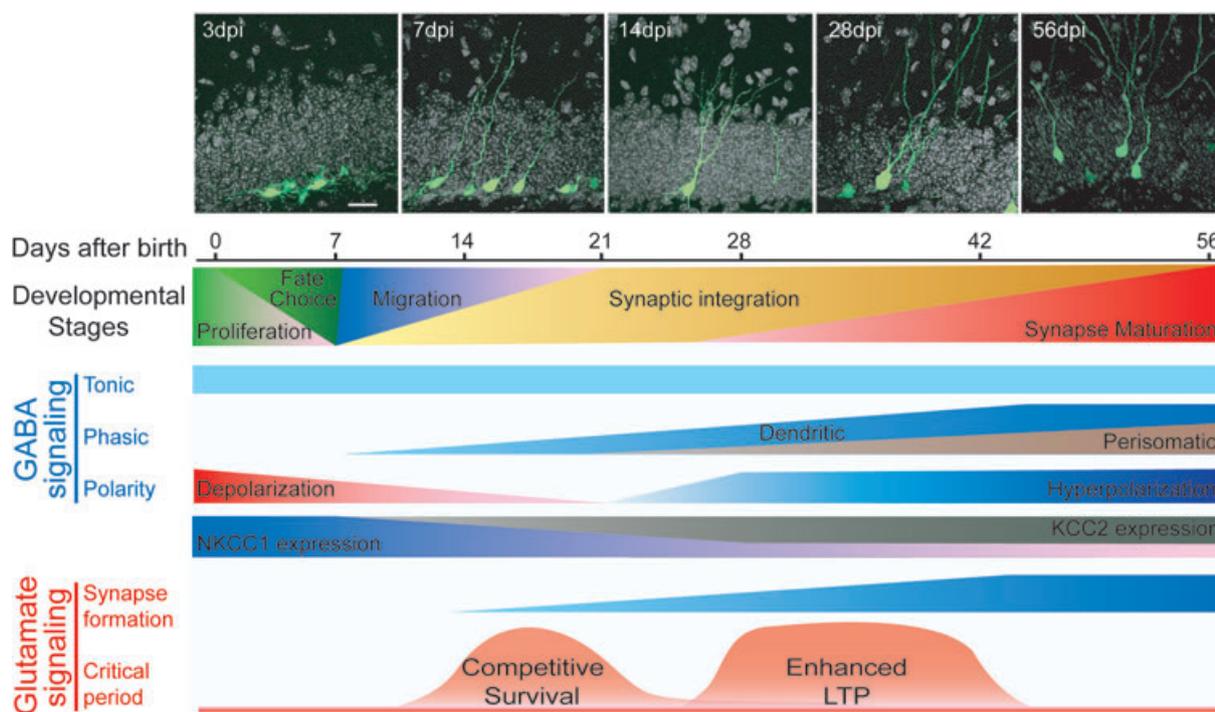

Figure 1. Synaptic integration of new granule cells in the dentate gyrus of the adult mouse hippocampus

Shown is a schematic summary of the synaptic integration and maturation process of newborn dentate granule cells in the adult mouse hippocampus. Adult neurogenesis is a developmental process consisting of proliferation and fate specification of adult neural progenitors, and migration and integration of new neurons into the existing circuitry. New neurons also follow a stereotypic process to establish different types of synaptic inputs. For GABA signalling, tonic GABA activation occurs first, followed by formation of GABAergic dendritic synaptic inputs and finally perisomatic GABAergic inputs. New neurons exhibit a gradual change in the expression of different chloride transporters. As a consequence, new neurons are initially depolarized by GABA and gradually become hyperpolarized by GABA during their maturation. For glutamate signalling, glutamatergic synapse formation starts after initial synaptogenesis of GABAergic dendritic synaptic inputs and before synaptogenesis of perisomatic GABAergic synaptic inputs. During the maturation stages, there are two critical periods when new neurons are particularly sensitive to glutamatergic signalling, the first involving NR1-dependent competitive survival of new neurons and the second involving NR2B-dependent enhanced synaptic plasticity. The images shown in the top panel were adapted from Ge *et al.* (2006, 2007*b*).

2007*b*; Laplagne *et al.* 2007). Alternative approaches with imaging of dendritic spines (Zhao *et al.* 2006) and analysis of immediate early gene expression (Jessberger & Kempermann, 2003) in adult-born granule cells suggest a similar prolonged time course of synaptic integration and maturation of adult-born neurons. These studies revealed interesting similarities and differences between adult neurogenesis and embryonic/early postnatal neurogenesis. First, incorporation of new neurons into the neuronal circuitry follows a conserved sequence in forming different types of synaptic connections throughout life. Second, the tempo of synaptic integration and maturation is significantly slower during adult neurogenesis than during embryonic and early postnatal neurogenesis.

The full integration of new neurons requires the establishment of both synaptic inputs and synaptic outputs within the neuronal circuitry. While axons of adult-born granule cells have been shown to extend into the CA3 subfield of the hippocampus (Hastings & Gould, 1999; Markakis & Gage, 1999; Zhao *et al.* 2006), little is known about properties of their synaptic outputs due to technical hurdles. Electron microscopy reconstruction of the mossy fibre synaptic boutons of retroviral-labelled adult-born neurons suggests that their synaptic outputs exhibit a similar time course of synaptogenesis and maturation to their synaptic inputs (authors' unpublished observations). Future development of novel tools, such as selective optical or chemical stimulation and trans-neuronal tracers, may facilitate the characterization of the development and properties of synaptic outputs of newborn neurons in the adult brain.

Role of GABA in the integration of newborn dentate granule cells in the adult brain

One hallmark of adult neurogenesis is its regulation by the activity of the existing neuronal circuitry. GABA and glutamate are the major inhibitory and excitatory neurotransmitters, respectively, for mature neurons in the adult brain. These neurotransmitters activate neurons not only locally within synaptic clefts (phasic activation), but also at a distance after diffusion out of synapses (tonic activation) (Farrant & Nusser, 2005; Ge *et al.* 2007*a*). GABA$_A$Rs are chloride (Cl$^-$) permeable channels and the polarity of GABA action depends on the Cl$^-$ gradient across the membrane, which in turn is determined by the developmentally regulated expression of Cl$^-$ transporters (Owens *et al.* 1996; Ben-Ari, 2002; Tozuka *et al.* 2005; Ge *et al.* 2006). Adult hippocampal neural progenitors and immature neurons express functional ionotropic GABA receptors (GABA$_A$Rs) (Tozuka *et al.* 2005; Wang *et al.* 2005; Ge *et al.* 2006). Newborn granule cells exhibit a gradual decrease in the expression of NKCC1, a Cl$^-$

importer, with a concurrent increase in the expression of KCC2, a Cl$^-$ exporter, during their maturation process (Fig. 1) (Ge *et al.* 2006). As a consequence, GABA initially depolarizes immature new neurons because of their high Cl$^-$ content and such depolarization is gradually converted to hyperpolarization over a period of 2–3 weeks. Interestingly, retrovirus-mediated expression of short-hairpin RNA against *nkcc1* in newborn granule cells abolishes GABA-induced depolarization and leads to significant defects in their dendritic growth and formation of both GABAergic and glutamatergic synaptic inputs. These studies provide the first *in vivo* evidence for an essential role of GABA-induced depolarization in neuronal development. A similar role of GABA has been demonstrated in the development of mouse embryonic cortical neurons (Cancedda *et al.* 2007; Wang & Kriegstein, 2008) and *Xenopus* tectum neurons (Akerman & Cline, 2006) *in vivo*.

There are several standing questions about the activity-dependent regulation of neuronal development through excitatory GABA signalling. First, it remains to be directly demonstrated that GABA, instead of Cl$^-$, is essential for neuronal development. Second, what is the relative contribution of tonic *versus* phasic GABA-induced depolarization to neuronal development? Given the extensive recurrent connections between principal neurons and interneurons within the dentate gyrus, the level of ambient GABA may serve as a general indicator of the dynamic neuronal network activity, while GABAergic phasic activation encodes input specific information. Third, how do GABAergic and glutamatergic signalling interact to regulate neuronal development? It is possible that GABA$_A$R signalling cooperates with NMDAR activation to regulate development of new neurons, as recently reported for glutamatergic synapse formation of embryonic cortical neurons (Wang & Kriegstein, 2008). Fourth, what is the downstream signalling mechanism that mediates depolarizing GABA effects in different aspects of neuronal development?

Critical periods of glutamate signalling during new neuron integration in the adult brain

Glutamate signalling has long been implicated in regulating adult hippocampus neurogenesis. Injection of NMDA rapidly decreases cell proliferation in the adult rat dentate gyrus, whereas injection of an NMDAR antagonist exhibits the opposite effect (Cameron *et al.* 1995; Nacher *et al.* 2001). On the other hand, induction of long-term potentiation at the glutamatergic medial perforant path–granule cell synapses promotes the proliferation of adult neural progenitors and survival of newborn neurons in an NMDAR-dependent fashion (Bruel-Jungerman *et al.* 2006; Chun *et al.* 2006). These findings highlight

the complexity of glutamate signalling in regulating adult neurogenesis, which is likely to involve both cell autonomous effects in immature neurons and non-cell autonomous effects through modulation of existing neuronal circuits. Electrophysiological analysis has shown the expression of ionotropic glutamate receptors in immature neurons (Ambrogini *et al.* 2004; Overstreet Wadiche *et al.* 2005; Tozuka *et al.* 2005). Immuno-histochemistry studies suggest that the NR1 and NR2B subunits are expressed at early stages during adult neurogenesis (Nacher *et al.* 2007). Genetic deletion of NR1 in proliferating adult neural progenitors reduces the survival of their neuronal progeny exclusively between 2 and 3 weeks after they are born in the adult brain (Tashiro *et al.* 2006). Interestingly, injection of an NMDAR antagonist, (+/−)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), to diminish differences in NMDAR signalling in all new neurons promotes survival of these NR1 null neurons. These findings suggest a critical period for NMDAR-dependent competitive survival of newborn neurons in the adult brain (Fig. 1). Interestingly, such a critical period is coincident with a transition from excitatory to inhibitory GABA signalling. Whether GABA cooperates with glutamate signalling in regulating the survival of new neurons during this critical period remains to be determined.

Analysis of the plasticity of glutamatergic synaptic inputs onto newborn granule cells during their maturation process has identified another critical period exhibiting enhanced long-term potentiation (LTP; Fig. 1) (Schmidt-Hieber *et al.* 2004; Ge *et al.* 2007*b*). New neurons within 4–6 weeks after they are born exhibit both reduced induction threshold and increased amplitudes of LTP in response to a physiological pattern of stimulation (Ge *et al.* 2007*b*). Interestingly, such a critical period is associated with a developmentally regulated prominent synaptic contribution of NR2B-containing NMDARs in adult-born neurons, since pharmacological inhibition of NR2B-containing NMDARs completely abolished LTP in these neurons, but not in mature neurons. In these initial LTP experiments, bicuculline was added to remove the influence of GABAergic synaptic transmission. We repeated some of these experiments in the absence of bicuculline. Interestingly, 4-week-old adult-born granule cells exhibit enhanced LTP similar to that in the presence of bicuculline (10 μM; Fig. 2*A*). In contrast, no significant
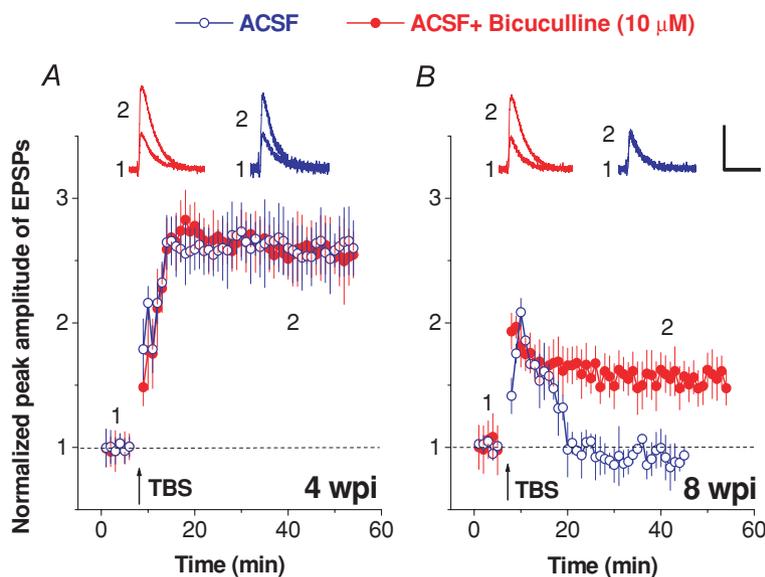

Figure 2. Differential modulation of glutamateric synaptic plasticity of adult-born dentate granule cells by GABA

LTP recorded from GFP$^+$ adult-born dentate granule cells in acute slices prepared at 4 weeks (*A*) or 8 weeks (*B*) after retrovirus-mediated birth-dating and expression of GFP as in Ge *et al.* (2007*b*). Evoked postsynaptic potentials (EPSPs) were recorded from GFP$^+$ dentate granule cells under the whole-cell current-clamp at 32–34°C and LTP was induced with a physiologically relevant theta burst stimulation (TBS) protocol consisting of four repeated episodes (at 0.1 Hz) of 10 stimuli at 100 Hz, repeated 10 times at 5 Hz and paired with a 100 pA postsynaptic current injection (as in Ge *et al.* 2007*b*). Based on the intracellular/extracellular solutions for cells recorded at both time points ([Cl$^-$]$_i$ = 19 mm; [Cl$^-$]$_o$ = 134.1 mm), the expected chloride reversal potential is −51 mV. Shown in the top row is an example of LTP of EPSPs recorded under the whole-cell current-clamp. Representative EPSPs averaged from five consecutive stimuli were taken before and after LTP induction by a physiologically relevant TBS (arrow) at the time points (1 and 2) indicated in the graph. Scale bars: 5 mV and 50 ms. Shown at the bottom are the summaries of LTP recorded in the presence or absence of bicuculline (10 μM) in the recording bath (artificial cerebrospinal fluid; ACSF). Normalized EPSP amplitudes are shown. Values represent means ± s.e.m. The summary plot for neurons recorded in the presence of bicucculline was adapted from Ge *et al.* (2007*b*).

LTP was induced by the same theta burst stimulation (TBS) in 8-week-old adult-born granule cells without the presence of bicuculline (Fig. 2*B*), a result consistent with previous field recordings (Snyder *et al.* 2001). Thus, the critical period for enhanced synaptic plasticity for these adult-born neurons would be even more striking with intact GABA signalling in the adult brain. The bicuculline insensitivity in LTP expression is not related to differences in the polarity of the GABA response, since the conversion of GABA-induced depolarization to hyper-polarization occurs between two and three weeks after the new neurons are born (Ge *et al.* 2006). Instead, the interaction between GABA signalling and LTP induction may involve the delayed establishment of perisomatic GABAergic innervations onto new neurons (Fig. 1), which exhibit powerful inhibition of neuronal excitation due to their localization.

Unique properties and potential functions of newborn neurons in the adult brain

What is the evolutionary pressure for maintaining neuro-genesis in specific brain regions? One hypothesis is that because of their unique physiological properties, developing adult-born neurons transiently serve as major mediators for experience-driven plasticity and become selectively integrated as special units within the adult circuitry where they contribute to specific brain functions over the long term.

Adult-born granule cells exhibit a number of unique properties transiently during their integration and maturation process that are distinct from the existing mature neurons, including (i) depolarization by GABA ($<$ 3 weeks old) (Ge *et al.* 2007*b*), (ii) enhanced excitability and low LTP induction threshold ($\sim$2–4 weeks old) (Schmidt-Hieber *et al.* 2004; Ge *et al.* 2007*b*), (iii) larger LTP amplitude ($\sim$4–6 weeks old) (Ge *et al.* 2007*b*), and (iv) delayed formation of perisomatic GABAergic innervations ($>$ 4 weeks old) (Esposito *et al.* 2005) (Figs 1 and 2). It is likely that synaptic outputs of new neurons also transiently exhibit unique properties during their maturation. In addition, there are also two critical periods when adult-born neurons are subjected to activity-dependent selective integration into the existing neuronal circuitry, including (i) NMDAR-dependent competitive survival among cohorts of new neurons ($\sim$2–3 weeks old), and (ii) NR2B-dependent enhanced synaptic plasticity of new neurons ($\sim$4–6 weeks old) (Fig. 1). Indeed, a number of studies based on the neuro-nal expression of the immediate early genes *c-Fos* and *Arc* suggest a selective incorporation of adult-born neurons into behaviourally relevant neuronal circuitry and preferential reactivation of these neurons in response to the same stimulation (Ramirez-Amaya *et al.* 2006; Kee *et al.* 2007; Tashiro *et al.* 2007).

Taken together, current evidence demonstrates that adult-born neurons exhibit unique properties during their maturation stages and suggests that a strategic integration of adult-born neurons into the existing circuitry may be the functional basis of their specific contribution to brain functions. We propose that adult neurogenesis represents not merely a basic replacement mechanism for lost neurons, but also is an ongoing developmental process that offers an expanded capacity of plasticity for shaping the existing circuitry in response to experience throughout life. Such a hypothesis can be directly tested in the near future using genetically modified animals with various behavioural tests, such as specific deletion of NR2B-containing NMDARs in new neurons to remove their enhanced plasticity during critical periods.

Summary

Continuous neurogenesis in the adult mammalian brain has attracted both basic and clinical research interests. On one hand, adult hippocampal neurogenesis provides a unique experimental model system to understand basic principles of neuronal development in the mature brain environment with a number of advantages, including a prolonged time course of neuronal development, a single defined neuronal subtype, and established genetic approaches to specifically manipulating new neurons. In addition, the complete neuronal developmental process proceeds within an active mature circuitry, thus offering a system to explore underlying activity-dependent mechanisms. On the other hand, adult neurogenesis highlights the regenerative capacity of the mature brain, not only in generating functional new neurons, but also in providing a permissive environment to guide functional integration. Understanding this unique regenerative process in the adult brain may shed light on strategies to promote functional regeneration after injury or degenerative neurological diseases.

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