Adult neurogenesis and the plasticity of the dentate gyrus network

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Abstract

The granule cell layer (GCL) of the dentate gyrus contains neurons generated during embryonic, early postnatal and adult life. During adulthood there is a continuous production of neuronal cohorts that develop and functionally integrate in the preexisting circuits. This morphogenic process generates a stratified GCL, with the outermost layers containing dentate granule cells (DGCs) generated during perinatal life, and the innermost layers containing adult-born DGCs. In this review we analyse the functional profile of the different neuronal populations of the GCL, with an emphasis on adult-born neurons as they develop, mature and integrate in the dentate gyrus network. We focus on the contribution of adult-born neurons to activity-dependent synaptic modification in the dentate gyrus and, in turn, discuss how network activity modulates integration and survival of new neurons.

Introduction

The adult mammalian brain continuously generates new neurons that become integrated in the preexisting networks. Under physiological conditions adult neurogenesis is restricted to the olfactory bulb and dentate gyrus of the hippocampus. These areas produce very specific subsets of new neurons. The olfactory bulb incorporates new granule cells and periglomerular cells, both of which are inhibitory γ-aminobutyric acid (GABA)ergic interneurons (Lledo *et al.*, 2006). The dentate gyrus generates dentate granule cells (DGCs), principal neurons of glutamatergic phenotype (Zhao *et al.*, 2008). The contribution of adult-born DGCs to hippocampal function is a central question in the field of adult neurogenesis and brain plasticity.

Different approaches developed over the past 15 years have contributed to the concept that adult neurogenesis is necessary for hippocampal function. Thousands of new neurons are added every day to the dentate gyrus in young adult rodents, representing a substantial fraction of the preexisting neurons present in the granule cell layer (GCL; Cameron & McKay, 2001). This rate of neurogenesis can be substantially increased by exercise, learning or enriched environment (van Praag *et al.*, 2000; Fabel & Kempermann, 2008). Such continuous addition of new neurons should have a significant impact in the hippocampal network. Moreover, blockade of adult neurogenesis using pharmacology, irradiation or transgenesis impairs specific forms of hippocampus-dependent learning and behavior in rodents (Shors *et al.*, 2001; Santarelli *et al.*, 2003; Abrous *et al.*, 2005; Saxe *et al.*, 2006; Winocur *et al.*, 2006; Dupret *et al.*, 2008; Clelland *et al.*, 2009). These findings strongly argue that adult-born DGCs are required for information processing in the adult hippocampus, although the precise role of new DGCs remains to be understood.

What makes adult-born neurons relevant to the dentate gyrus network remains a puzzle. The continuous addition of neurons very likely represents by itself a remarkable degree of circuit plasticity. Identifying the specific set of physiological properties that new neurons bring to the network is essential for understanding their functional role in the hippocampus. These questions are the focus of this review.

From neural progenitor cells to functional neurons

Newborn DGCs of the adult dentate gyrus derive from neural progenitor cells of the subgranular zone. In the mouse, adult-born DGCs require several weeks before reaching a mature stage. Identifying the hallmarks of neuronal maturation is relevant for considering a possible role of immature neurons in information processing. During the first week of development, early neuroblasts undergo radial migration for short distances toward the inner GCL (Kempermann *et al.*, 2003; Espósito *et al.*, 2005; Zhao *et al.*, 2006). These young neurons do not receive synaptic connections but they already express GABA and glutamate receptors. The early depolarizing action of GABA acting through tonic activation of $GABA_A$ receptors can modulate the pace of neuronal development (Ge *et al.*, 2006a,b). Axon and dendrite formation begins by the second week, which is coincident with afferent synaptogenesis. Similarly to what occurs during development, early inputs are exclusively GABAergic contacts distributed in the dendrites (Espósito *et al.*, 2005; Overstreet Wadiche *et al.*, 2005; Markwardt *et al.*, 2009). Recent observations suggest that cholinergic axons from septal neurons might also contact new neurons at early stages of development, although evidence of functional synapses is still missing (Ide *et al.*, 2008).

The main excitatory drive that activates new DGCs arises from glutamatergic axons of the perforant pathway, which begin to establish

functional contacts during the third week of maturation (Espósito *et al.*, 2005; Ge *et al.*, 2006a; Zhao *et al.*, 2006; Toni *et al.*, 2007). During the fourth week the strength of excitatory afferents increases considerably while membrane input resistance still remains elevated (a characteristic signature of immature neurons). This balance between input strength and membrane excitability allows developing DGCs to generate spikes in response to the activation of perforant path axons (Mongiat *et al.*, 2009). In this period, axonal terminals of new DGCs begin to contact interneurons in the hilar region as well as dendritic shafts of CA3 pyramidal cells (Faulkner *et al.*, 2008; Ide *et al.*, 2008; Toni *et al.*, 2008). Structural and functional maturation of new DGCs is reached after about 6–8 weeks (van Praag *et al.*, 2002; Laplagne *et al.*, 2006, 2007; Zhao *et al.*, 2006). While the timing described above has been consistently observed in mice studies, maturation seems to occur at a faster pace in the rat hippocampus (Snyder *et al.*, 2009). The timing for development and functional integration of newborn cells is a key issue to understand the biological significance of adult neurogenesis and for the proper design of behavioral experiments aimed to investigate the role of neurogenesis in hippocampal function. In the following sections we discuss the emerging notion that new DGCs may be crucial for information processing before reaching a fully mature stage.

Continuous remodeling of the inner GCL

Neurons develop and mature as they migrate radially through the GCL, with the axon growing through the hilus towards CA3 and the dendrites reaching the outer molecular layer (Piatti *et al.*, 2006). Adult-born neurons do not migrate to reach random positions in the GCL but, instead, they remain within the inner layers. Such heterogeneous layering plan is similar to that generated during perinatal development. Morphogenesis of the rodent GCL begins during embryonic development and is finalized during the early postnatal weeks. Early studies have shown that DGCs born in the embryo assemble the outer GCL, while cells born postnatally migrate through the hilus toward the preexistent GCL and fill the layer in an outside-in pattern (Angevine, 1965; Altman & Bayer, 1990). Adult neurogenesis seems to contribute to maintain that pattern, as adult-born DGCs migrate radially from the subgranular zone, but they remain primarily positioned within the inner third of the GCL (Kempermann *et al.*, 2003; Espósito *et al.*, 2005). Recent studies have revised the outside-in layering model taking adult neurogenesis into account (Muramatsu *et al.*, 2007; Mathews *et al.*, 2010). Retroviruses or bromodeoxyuridine were used to label DGCs born during embryonic or early postnatal development as well as in the adult dentate gyrus, and their localization was analysed in the adult GCL at later time points. The conclusion was that DGCs born in the embryo contribute to all layers of the GCL, but very few of the outer GCL neurons are generated during postnatal development. Thus, most neurons born in the adult dentate gyrus remain within the innermost third of the GCL even after several months. Therefore, the outcome of adult neurogenesis is the generation of a highly heterogeneous GCL, with the inner layers containing a high proportion of adult-born DGCs (both developing and mature), and the outer layers containing mostly mature DGCs generated during development. Ectopic migration towards the molecular layer occurring in DISC1 loss of function (Duan *et al.*, 2007) or toward the hilus after epileptic seizures (Scharfman *et al.*, 2003; Jessberger *et al.*, 2007; Kron *et al.*, 2010) indicates that newborn DGCs do have the potential to migrate further away from the subgranular zone and in both directions, but this process is tightly regulated. This anatomical gradient is also consistent with electrophysiological studies showing that neurons with immature functional properties and with an increased degree of activity-dependent synaptic plasticity are primarily located in the innermost layers of the GCL (Wang *et al.*, 2000; Ambrogini *et al.*, 2004; Schmidt-Hieber *et al.*, 2004; Espósito *et al.*, 2005). Thus, the inner regions of the adult GCL are very dynamic and undergo continuous addition of neuronal populations, whereas the outer GCL seems to remain unchanged (Fig. 1). The mechanisms whereby adult-born neurons do not reach the outer GCL under physiological conditions and the functional implications of such stratified layering remain unclear.

Functional integration of adult-born neurons

It has been proposed that the adult hippocampus continuously generates new neurons to provide the preexisting network with functional properties that are required for information processing in the hippocampus, but are absent in all other cells of the layer generated during development (Schinder & Gage, 2004; Ming & Song, 2005). The substrates for neuronal growth in the perinatal and adult brain are very distinct. The perinatal hippocampus undergoes massive neurogenesis and wiring (networks are beginning to assemble), and the activity is dominated by GABAergic interneurons exerting depolarizing actions. The adult hippocampus is a mature substrate where glutamatergic and GABAergic networks are completely established, and new DGCs must integrate in a functional network immersed in a highly complex environment. Thus, DGCs generated at either stage could, in principle, develop towards different functional phenotypes. This notion was addressed by comparing the electrophysiological properties of fully mature DGCs (> 6 weeks old) born in embryonic, early postnatal and adult mice (Laplagne *et al.*, 2006, 2007). All mature DGCs exhibited a striking similarity in amplitude and kinetics for glutamatergic and GABAergic postsynaptic currents, including short-term plasticity of excitatory inputs, regardless of the time when neurogenesis occurred. Moreover, adult-born DGCs could trigger action potentials in response to stimulation of excitatory afferents, displaying a similar spiking probability to neurons born in the early postnatal period. In agreement with this functional convergence, electron and confocal microscopy analysis in dendritic spines demonstrated that the overall number of excitatory synapses onto mature DGCs born in the perinatal and adult dentate gyrus is similar (Toni *et al.*, 2007). Therefore, no unique properties were found for fully mature DGCs born in the adult hippocampus with regard to the major excitatory and inhibitory inputs. However, among all of those functional similarities it was found that DGCs generated during embryonic development are less excitable, as reflected by the larger inward current required for triggering a spike (Laplagne *et al.*, 2007). These data predict a very sparse activation of this neuronal population and, consequently, low levels of neuronal activity to be detected in the outer GCL in behaving animals. In contrast, all mature DGCs generated postnatally seem to be largely equivalent in regard to their physiological characteristics independently of the developmental stage in which they were produced, the early neonate or the adult hippocampus.

The studies discussed above indicate that all mature DGCs receive a similar quality and quantity of excitation and inhibition. This conclusion is based on postsynaptic responses generated by the activation of many axons, without distinguishing possible differences in specific populations of presynaptic neurons. If axons impinging onto adult-born DGCs belonged to restricted subpopulations of entorhinal neurons, unique pathways for information processing would be assembled by adult neurogenesis. Toni *et al.* (2007) combined retroviral labeling with electron tomography and serial
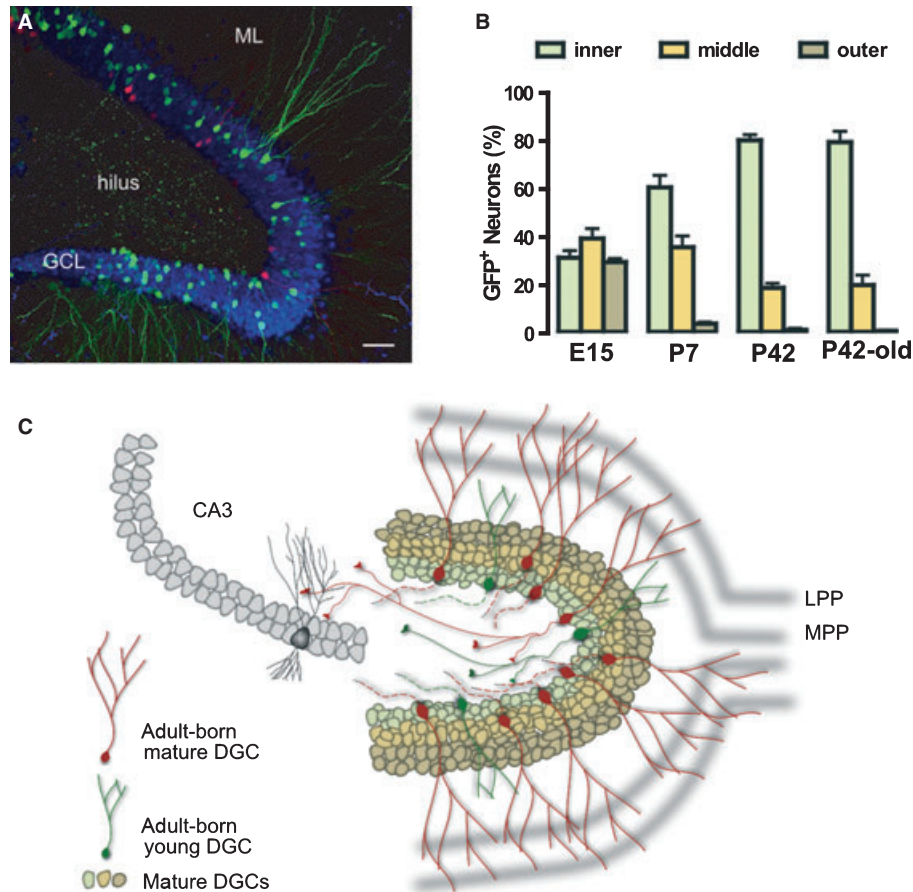
FIG. 1. Restricted remodeling of the inner GCL by adult-born DGCs. (A) Fluorescent confocal image showing the dentate gyrus of a 3-month-old mouse depicting the distribution of DGCs born during embryonic development (E15, green) and during adulthood (P42, red). The mouse received a retroviral injection at E15 to deliver a GFP-expressing retrovirus, and a second injection at P42 with a retrovirus encoding for RFP. GCL, granule cell layer; ML, molecular layer. DGCs are labeled for NeuN (blue). Scale bar: 50 μm. (Image reproduced with permission from Laplagne *et al.* (2007). (B) Distribution of DGCs born at different developmental stages. The chart shows the proportion of DGCs located in the inner, middle and outer third of the GCL of adult mice. 'P42 old' describes the distribution of DGCs born in young adult mice measured approximately 1 year later. GFP, green fluorescent protein. (Adapted with permission from Mathews *et al.* (2010). (C) Schematic representation depicting the active remodeling of the inner GCL (light green) of the adult dentate gyrus. Newborn DGCs of immature age are primarily located in the inner GCL, whereas some mature newborn cells may also reach the middle layer (yellow). The outer layer (brown) remains largely static throughout life. Notably, continuous network remodeling and the concomitant enhanced synaptic plasticity are mostly restricted to the inner GCL. DGC, dentate granule cell; LPP, lateral perforant pathway; MPP, medial perforant pathway.

section electron microscopy to study the time course of axo-spinous (excitatory) synaptogenesis in adult-born DGCs. In this thorough work they found that dendritic spines are initially involved in multiple-synapse boutons. At later time points, boutons become exclusive to the new neuron, devoid of additional postsynaptic partners. The emerging model is that dendritic protrusions of developing DGCs initially approach boutons already involved in a synapse (that most likely belongs to a different neuron) and compete to expel additional partners, maintaining the bouton. This evidence would suggest that adult-born DGCs receive glutamatergic synapses from the same population of axons that connect preexisting DGCs in the circuit. Further addressing this question requires retrograde labeling to distinguish neurons that are presynaptic to DGCs born at different developmental stages.

To be functionally relevant, new DGCs must integrate excitatory and inhibitory inputs, generate a spike, and release neurotransmitters onto postsynaptic neurons. While it was well known that adult-born DGCs project their axons through the hilus and toward the CA3 region of the hippocampus (Hastings & Gould, 1999; Markakis & Gage,

1999; Zhao *et al.*, 2006), functional and structural evidence for synaptic output was revealed only recently. The technical challenge for electrophysiological studies was to specifically stimulate axons of newborn neurons to measure responses from postsynaptically connected hippocampal target cells. This problem was approached using retroviral expression of the light-activated cation channel channelrhodopsin-2 in newly generated neurons of the adult mouse dentate gyrus (Toni *et al.*, 2008). Flashing a blue light onto acute hippocampal slices generated spikes in adult-born neurons that have reached maturity, allowing to obtain postsynaptic glutamatergic responses in hilar interneurons and CA3 pyramidal cells that were randomly selected for whole-cell recordings. Structural evidence for synaptic output was obtained by immuno-electron microscopy and serial sectioning of retrovirally labeled neurons (Faulkner *et al.*, 2008; Toni *et al.*, 2008). Axons of newborn cells formed synapses onto thorny excrescences, dendritic spines and aspiny dendrites in the hilus and CA3. Interestingly, synapses formed onto CA3 pyramidal cells, the main output of the dentate gyrus, reached a fully mature structure only after 8 weeks. Taken together, morphological and physiological studies

have demonstrated that adult-born DGCs display all the characteristics required to receive, process and convey information within the hippocampal network.

Unique functional properties of immature neurons

Adult-born neurons develop for several weeks to acquire functional properties, afferents and output connectivity that are similar to those of DGCs generated during perinatal development. While developing, newborn cells express physiological characteristics that are typical of immature neurons, such as high input resistance, increased intrinsic excitability and reduced GABAergic inhibition, making them functionally unique (Fig. 2; Espósito *et al.*, 2005; Couillard-Despres *et al.*, 2006; Ge *et al.*, 2006a). Due to their enhanced excitability, it has been proposed that immature DGCs might become highly engaged in information processing in the dentate gyrus, encoding the memory of events occurring within a narrow window of time (Aimone *et al.*, 2006; Deng *et al.*, 2010). Indeed, immature neurons might be ready to participate in information processing before their development is complete. In the adult mouse dentate gyrus 3-week-old neurons receive strong enough glutamatergic afferents to generate spikes in response to the activation of perforant path axons in acute slices (Mongiat *et al.*, 2009). *In vivo* studies have interrogated firing of newborn cells using the expression of immediate-early genes as indicators of neuronal activity after spatial learning and exploration (Jessberger & Kempermann, 2003; Ramirez-Amaya *et al.*, 2006; Kee *et al.*, 2007; Tashiro *et al.*, 2007). Although this is an indirect approach to measuring neuronal spiking, it is powerful in that it allows identifying DGCs that were active *in vivo*. For instance, new DGCs of mice exposed to an enriched environment at 2 weeks of age were more likely to become activated at later times by the same environment than by a different one, suggesting that immature neurons processed spatial information (Tashiro *et al.*, 2007). Consistent with this notion, 4-week-old neurons were activated by a spatial learning task (Kee *et al.*, 2007). As neurons matured, activation became even more prominent than all mature DGCs in the GCL, suggesting that adult-born DGCs are more likely to be engaged in information processing during spatial learning. A remarkable bias towards the activation of newborn cells was also reported for > 5-month-old DGCs after spatial exploration in adult rats (Ramirez-Amaya *et al.*, 2006). Addressing whether new DGCs are preferentially recruited by hippocampal activity or, for instance, whether the expression of immediate-early genes is more sensitive to activity in these cells will require further experimental evidence. Yet, these findings reveal a preferential recruitment of adult-born DGCs with an early onset during immature developmental stages that continues for several months, long after new DGCs have reached a mature phenotype. In this context, it seems plausible to envision a specific biological role for immature DGCs and a different one for mature DGCs.

The crucial role of immature neurons in activity-dependent synaptic modification

All principal synapses in the trisynaptic hippocampal circuit are highly plastic, as they can be strengthened (potentiated) or weakened (depressed) by activity (Neves *et al.*, 2008). Such a remarkable level of plasticity has been proposed as a key player in hippocampal function. In fact, a central and long-standing hypothesis on the cellular basis of learning proposes that memory formation in the hippocampus relies on changes in synaptic strength and, therefore, it involves

activity-dependent synaptic modification (Martin & Morris, 2002; Neves *et al.*, 2008). While the synaptic plasticity and memory hypothesis still await definitive causal proof, it has provided a valuable framework to investigate the biological relevance of adult hippocampal neurogenesis.

The importance of adult neurogenesis in the plasticity of the dentate gyrus network was discovered by the pioneering studies of Wojtowicz and collaborators. They first characterized long-term potentiation (LTP) of excitatory afferents of young and mature DGCs, which they identified by their location in the GCL, expression of neuronal markers, morphology and input resistance (Wang *et al.*, 2000; Fig. 1). In mature neurons, high-frequency stimulation of the medial perforant path induced LTP of glutamatergic synapses only if GABAergic inhibition was blocked in the hippocampal slice. In striking contrast, postsynaptic responses recorded in young DGCs exhibited LTP even when GABAergic inhibition was left intact. It was then proposed for the first time that young neurons would display a lower threshold for LTP induction and/or reduced GABAergic inhibition when compared with mature DGCs.

In a later work, the same group went a step further to study LTP in large populations of DGCs by measuring local field potentials in acute slices of the adult rat hippocampus (Snyder *et al.*, 2001). In the presence of GABAergic inhibition LTP was small but highly consistent, displayed a low threshold of induction, and required activation of the NR2B type of *N*-methyl-D-aspartate (NMDA) receptor. When GABAergic transmission was pharmacologically blocked, LTP was large, exhibited a higher threshold for induction and required activation of the NR2A type of NMDA receptor. Notably, LTP evoked in the presence of GABAergic transmission was completely and specifically abolished by blocking adult neurogenesis with gamma irradiation 3 weeks prior to electrophysiological recordings. This work demonstrated that under physiological conditions (i.e. with GABAergic inhibition left intact), dentate gyrus LTP in acute slices from adult rats requires young neurons that are < 3 weeks old. These early observations and predictions by Wojtowicz and colleagues have been thoroughly confirmed by other laboratories.

The lower threshold for LTP induction in immature DGCs was corroborated by a later study using perforated patch recordings in immature neurons of the inner GCL, identified by their high input resistance (Schmidt-Hieber *et al.*, 2004). In these experiments, LTP was induced in the presence of GABA receptor blockers using theta-burst stimulation to simulate *in vivo* activity in the perforant path. Under these conditions a weak stimulation protocol was sufficient to evoke LTP in immature but not mature DGCs. More recently, a retroviral labeling approach was undertaken to show that LTP in perforant path inputs onto newborn DGCs almost doubles that of synapses onto mature DGCs, is mediated by NMDA receptors containing the NR2B subunit, and was unaffected by the presence or absence of GABAergic inhibition (Fig. 2; Ge *et al.*, 2007, 2008). Moreover, retroviral birth dating was used to establish precisely that LTP was enhanced during a narrow time window of the cell age, ranging from 4 to 6 weeks old in the adult mouse.

The works discussed above demonstrated that adult-born neurons of immature age play a crucial role in activity-dependent synaptic plasticity in the adult dentate gyrus. It is important to note that the experimental condition that most likely resembles the *in vivo* scenario is that in which GABAergic inhibitory circuits are left fully functional. Under these conditions, LTP can only occur in the presence but not the absence of adult neurogenesis (Snyder *et al.*, 2001). This observation opens the provocative possibility that activity-dependent plasticity in synaptic inputs to the dentate gyrus requires adult neurogenesis. It is also likely that, under specific circumstances, neuromodulators would
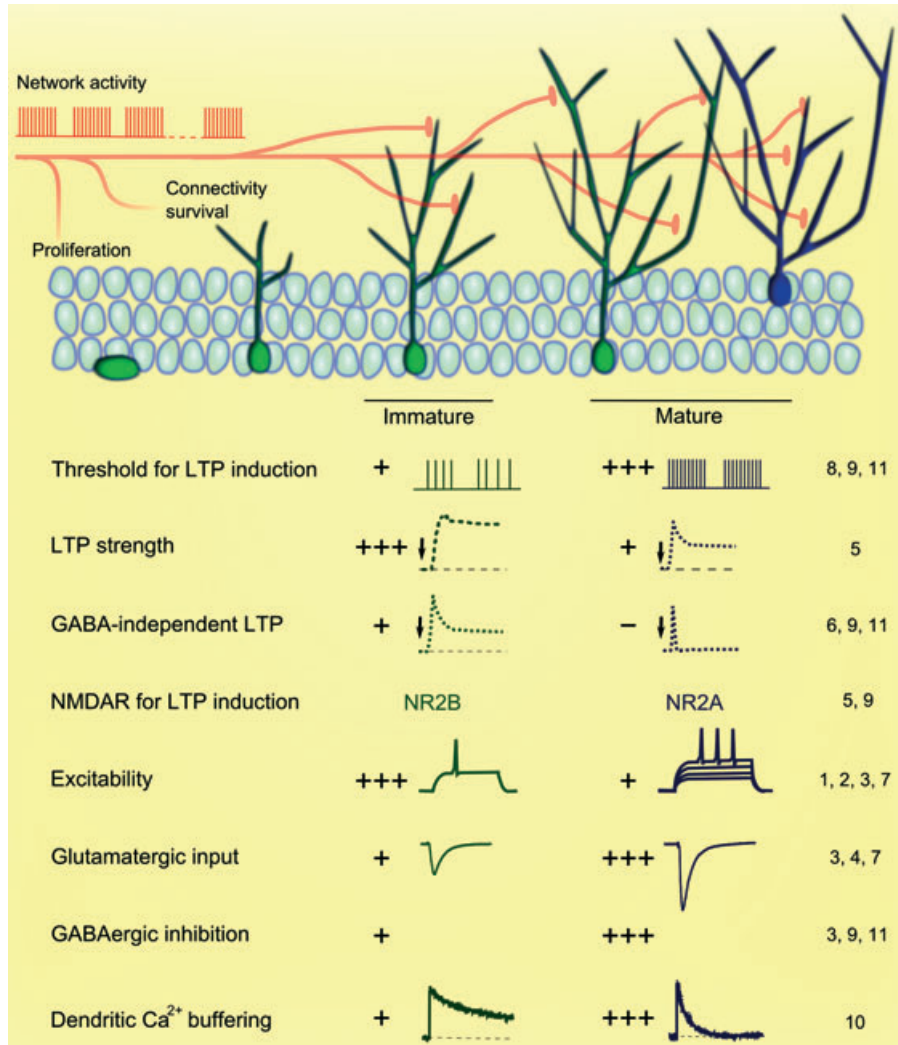
FIG. 2. Interplay between adult neurogenesis and network activity. (Top panel) The schematic drawing depicts newborn DGCs of different ages (green), as they develop, integrate and mature in the GCL. A DGC generated during embryonic development is drawn in blue. Axons projecting from the entorhinal cortex and from local interneurons make glutamatergic and GABAergic synapses onto DGCs. Network activity (depicted as spike trains) modulates adult neurogenesis by increasing progenitor cell proliferation, shaping the connectivity of neuronal inputs and determining the survival of adult-born DGCs. (Bottom panel) Summary of the most relevant properties of immature DGCs that provide a distinctive functionality to the dentate gyrus. Threshold for LTP induction: the stimulus required to evoke LTP is represented as afferent spike trains. LTP strength and GABA-independent LTP: the drawings represent a time course of evoked excitatory postsynaptic currents before and after theta burst stimulation (arrow). Excitability: the traces depict action potentials elicited by current injection. Glutamatergic input: drawings denote excitatory postsynaptic current traces evoked by similar stimuli. Dendritic Ca^{2+} buffering: time course of intracellular Ca^{2+} levels. The numbers on the right indicate the references containing experimental data summarized in the figure: 1, Ambrogini *et al.* (2004); 2, Couillard-Despres *et al.* (2006); 3, Espósito *et al.* (2005); 4, Ge *et al.* (2006a); 5, Ge *et al.* (2007); 6, Ge *et al.* (2008); 7, Mongiat *et al.* (2009); 8, Schmidt-Hieber *et al.* (2004); 9, Snyder *et al.* (2001); 10, Stocca *et al.* (2008); 11, Wang *et al.* (2000). GABA, γ-aminobutyric acid; LTP, long-term potentiation; NMDAR, *N*-methyl-D-aspartate receptor.

reduce the amount of inhibition received by mature neurons, allowing the engagement of that neuronal population in information processing and plasticity.

A role for activity-dependent synaptic modification in the integration of developing DGCs

The enhanced synaptic plasticity observed in the afferent connections to developing neurons may be relevant for information processing, with young neurons providing a primary source of synaptic plasticity for inputs to the dentate gyrus network (Snyder *et al.*, 2001). In addition, such remarkable plasticity may act as a form of activity-dependent refinement for afferent connections to tailor the connectivity and integration of newborn cells to the preexisting circuit, also

defining their neuronal partners. In fact, *in vivo* induction of LTP in medial perforant path synapses of adult rats was shown to increase proliferation and survival of neurons born a few days after LTP induction (Bruel-Jungerman *et al.*, 2006). However, neurons that participated in LTP were preexistent to neurons whose survival was enhanced. Therefore, in these experiments activity could not act by strengthening afferent synapses onto developing DGCs. In contrast, it was shown that when LTP induction occurs after neurons were born, it increases survival of 1–2-week-old DGCs, but not younger or older neurons (Kitamura *et al.*, 2010). This effect was dependent on activation of NMDA receptors. It is conceivable that in these highly immature neurons activity-dependent synaptic modification strengthens incipient glutamatergic inputs, promotes a more efficient integration and, as a consequence, increases survival. In agreement with this

notion, retrovirus-mediated single-cell gene knockout has revealed a striking decrease in the survival of newborn DGCs when NMDA receptor function was impaired in a cell-autonomous fashion (Tashiro *et al.*, 2006). Notably, hippocampus-dependent learning paradigms that require NMDA receptor-mediated activity have also been shown to promote the survival of specific populations of adult-born neurons (Gould *et al.*, 1999; Dupret *et al.*, 2007). It would now be critical to establish whether survival of newborn DGCs induced by learning involves NMDA receptor-dependent synaptic modification. Finally, whether activity-dependent synaptic plasticity is necessary for the proper integration of new developing neurons, for information processing in the dentate gyrus, or for both, remains to be investigated in depth.

Concluding remarks

Adult neurogenesis increases the level of complexity of the hippocampal circuit due to the continuous addition of new computational units, which appear to be fundamental for information processing. DGCs are generated from development through adulthood and become positioned in the GCL in a manner that leads to an anatomical and functional segregation. The innermost GCL contains cohorts of immature neurons that are highly excitable, weakly inhibited and display enhanced synaptic plasticity. The possibility that immature DGCs play a critical role in hippocampal function is currently under intense investigation. Immature DGCs can be activated by weak excitatory inputs and, therefore, might be recruited by a broad variety of stimuli in the behaving animal. In addition, their enhanced activity-dependent synaptic modification seems to greatly contribute to the plasticity of the dentate gyrus network. In contrast, fully mature DGCs were recently shown to display a low firing probability during exploratory behavior and learning, leading to the notion that they constitute a barely active neuronal population (Alme *et al.*, 2010). Thus, these differences in the activation of young and mature neurons would be reflected in a functional gradient where neuronal processing preferentially occurs in the inner GCL. In this context, it will be relevant to address the specific roles that immature and mature neurons play in dentate gyrus function.

Acknowledgements

Abbreviations

DGC, dentate granule cell; GABA, γ-aminobutyric acid; GCL, granule cell layer; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate.

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