HHS Public Access

Author manuscript

Cell Tissue Res. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Cell Tissue Res. 2018 January ; 371(1): 33–46. doi:10.1007/s00441-017-2668-y.

Neural mechanisms underlying GABAergic regulation of adult hippocampal neurogenesis

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Abstract

Within the dentate gyrus of the adult hippocampus is the subgranular zone, which contains a neurogenic niche for radial-like glial cells, the most primitive neural stem cells in the adult brain. The quiescence of this neural stem cell pool is maintained by tonic GABA release from interneurons. Once these cells differentiate into neural progenitor cells, GABA continues to regulate their development into mature granule cells, the principle cell type of the dentate gyrus. Here we review the role of GABA circuits, signaling, and receptors in regulation of the development of adult-born neurons, as well as the molecular players that modulate GABA signaling. Furthermore, we review recent findings linking the dysregulation of adult hippocampal neurogenesis to the altered GABAergic circuitry and signaling found in various pathological conditions.

Introduction

Dentate granule cells in the hippocampus are continuously generated from neural stem cells throughout life in all mammals. Adult neurogenesis recapitulates the whole process of neuronal development in a mature central nervous system, from proliferation and fate specification of adult neural progenitors, morphogenesis, migration, axon/dendritic development, and finally synapse formation, culminating in the full integration of new neurons into the existing circuitry. Cumulative evidence suggests that new neurons participate in specific brain functions, such as learning and memory, mood regulation, and stress response (Snyder et al. 2005; Becker and Wojtowicz 2007; Bruel-Jungerman et al. 2007; Deng et al. 2010; Parihar et al. 2011; Marín-Burgin and Schinder 2012). In adult humans, it is estimated that 700 adult-born neurons are added to the hippocampus daily, accounting for an annual turnover rate of 1.75% (Spalding et al. 2013). The dentate gyrus (DG) is believed to control the flow of cortical information into the hippocampus. It organizes sensory input arising from the perforant path of the entorhinal cortex and sends its excitatory output to the CA3 region of the hippocampus. This unilateral flow of information

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has been proposed to underlie the storage of episodic memory (Amaral et al. 2007). Adult-born granule cells (GCs) are commonly implicated in pattern separation, the process by which similar input patterns of neuronal activity can result in different output. Thus, pattern separation is believed to underlie the formation of new memories without the interference of old memories. Adult-born GCs have also been speculated to contribute to sparse coding in the DG, as well to act as individual coding units. In a recent review by Johnston *et al.*, it is proposed that pattern separation and sparse coding of adult-born GCs regulate memory resolution and robustness while avoiding memory interference (Johnston et al. 2016).

Gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the adult brain, activates synaptic and extrasynaptic $GABA_A$ receptors, causing hyperpolarization of mature neurons. In the adult brain, as in the embryonic nervous system, GABA depolarizes neural progenitors and immature neurons. GABA regulates the quiescence of the hippocampal stem cell pool, the differentiation of radial-glial like stem cells into neural progenitor cells (NPCs), maturation of NPCs into granule cells, and synaptic integration of adult-born granule cells into the existing circuitry of the hippocampus. Here we review the existing literature on the role of GABA circuits, signaling and receptors in regulation of the development of adult-born neurons, the molecular players that modulate GABA signaling, and recent findings linking aberrant GABA circuits and signaling in various pathological conditions to dysregulation of adult hippocampal neurogenesis.

Development of adult-born neurons in the hippocampus

The DG contains a neurogenic niche called the subgranular zone (SGZ) that is located between the hilus and granule cell layers. Quiescent neural stem cells (NSCs) with radial morphology in the SGZ are essential substrates for continuous neurogenesis throughout life. Radial NSCs (rNSCs) are largely quiescent and they shuttle between quiescence and activation. When rNSCs become activated, they make neurogenic or gliagenic fate choices. Upon neurogenic division, rNSCs give rise to Tbr2+MCM2+ intermediate progenitors, which in turn generate DCX+MCM2+ neuroblasts. to become DCX+ immature neurons, and finally DCX-NeuN+ mature dentate granule cells. During gliagenic division, rNSCs give rise to astroglia which further differentiate into astrocytes (Figure 1) (Eriksson et al. 1998; Johansson et al. 1999; Lagace et al. 2007; Bonaguidi et al. 2011). Electrophysiological studies have revealed a stereotyped process by which newborn neurons are integrated into existing hippocampal circuitry. Newborn neurons undergo an initial phase of tonic GABA activation (Ge, Goh et al. 2006), followed by the emergence of depolarizing GABAergic synaptic inputs, and finally receive glutamatergic synaptic inputs as GABAergic responses become hyperpolarizing (Tozuka et al. 2005; Overstreet-Wadiche et al. 2005; Song et al. 2013). The quiescence of rNSCs is maintained by tonic (nonsynaptic) GABA current from parvalbumin (PV+) interneurons (Song et al. 2012). Furthermore, GABA signaling has been shown to be important for rNSCs to choose the proper fate upon their activation.

GABAergic synaptic inputs onto NPCs induces neuronal differentiation (Tozuka et al. 2005). Fate choice occurs within the first week of cell birth. During the second week, immature granule cells begin extending dendrites into the molecular layer while migrating toward the granule cell layer. Throughout this period, GABA is depolarizing to adult-born cells due to

expression of the Na^+-K^+-Cl^- co-transporter NKCC1, which maintains a high intracellular chloride concentration. NKCC1 knockdown reduces proliferation of the stem cell pool and delays dendritic development on adult-born NPCs (Ge et al. 2006; Young et al. 2012).

Young adult born granule cells undergo a multi-week maturation process post-birth influenced by both GABAergic and glutamatergic input. It is estimated that the entire developmental process takes eight weeks for adult-born granule cells to reach plasticity similar to that of mature granule cells, although it has been noted that more than eight weeks are needed for new axon terminals to reach comparable sizes and densities (Esposito et al. 2005; Zhao et al. 2006; Kempermann et al., 2015; Toni and Schinder, 2015; Toni and Sultan 2011). Interestingly, Toni et al. found that full maturation of adult-born neurons in terms of connectivity is reached 60–180 days post cell birth (Toni et al. 2008).

Two to three weeks after birth, adult-born cells must compete for synaptic integration. Over 50% of adult-born cells are lost during this time (Dayer et al. 2003). Glutamatergic signaling begins during this time period, as NMDA receptor-mediated integration begins (Tashiro et al. 2006). Mossy cells and possibly mature granule cells provide glutamatergic input to adult-born cells (Kumamoto et al. 2012; Vivar et al. 2012). Young adult-born granule cells have greater dendritic Ca^{2+} signaling compared to mature granule cells, which contributes to the cells' activity-dependent growth (Stocca et al. 2008). Heigele et al. recently showed that GABAergic interneurons have bidirectional control of young granule cell activity, promoting or inhibiting maturation of adult-born cells in a network activity-dependent manner. In young granule cells 1.5–3 weeks post mitosis, GABA acts as an excitatory neurotransmitter, and supports spike initiation during moderate hippocampal network activity. However, during strong network activity, GABAergic stimulation can cause a membrane leakage conductance that shunts inhibition and halts action potential firing (Heigele et al. 2016). This work builds on evidence that excitatory GABA mediates the rate of activity-dependent growth in adult hippocampal neurogenesis (Ge et al. 2007).

During week three of development, NKCC1 expression declines and expression of the potassium-chloride co-transporter KCC2 increases, such that GABA begins to exert a hyperpolarizing force on immature GCs due to decreased intracellular Cl^- concentration (Kanaka et al. 2001; Wang et al. 2002). Four weeks post-birth, the dendritic arborization of adult-born cells expands, and synaptogenesis occurs at the axon, dendrite, and spine (Toni et al. 2007, 2008). Glutamatergic innervation by neurons in the entorhinal cortex, hilar cells, and mossy cells begin to integrate adult-born GCs. During adult neurogenesis, not all adult-born neurons survive and are integrated into the existing hippocampal circuitry. It is not well understood how behavior influences integration, although evidence points to the role of GABAergic input. During development there is a critical period in which GABA depolarization and NMDA receptor activation is required for experience-dependent synapse unsilencing (Chancey et al. 2013). NMDA receptor activation follows glutamatergic input and contributes to the maturation of the adult-born GC (Tashiro et al. 2006). The unique synaptic properties of young GCs may be important for understanding integration into the existing hippocampal circuitry, as well as competition with mature GCs in influencing hippocampal activity. For example, immature adult-born GCs have high intrinsic excitability balanced by low excitatory synaptic innervation which prevents them from responding to

broad cortical activity (Dieni et al. 2016). Four weeks after birth, young adult- born granule cells are capable of firing action potentials and show increased synaptic potentiation compared to mature granule cells and are preferentially recruited by existing circuits (Ge et al. 2007; Kee et al. 2007). Furthermore, Gu et al. demonstrated that optogenetic inhibition of adult-born neurons at 4–6 weeks (but not 2 weeks) post-birth modulate spatial and contextual leaning (Gu et al., 2012). In addition, Zhuo et al. showed that in young adult-born GCs five-ten weeks post-birth can promote location discrimination, but only if the cells undergo maturation during the task acquisition (Zhuo et al. 2016). An additional layer of complexity in understanding integration was elucidated in a study characterizing individual adult-born GCs from three- ten weeks of age. From this study, two functionally distinct states of adult-born GCs have emerged; each state being independent of cellular age and maturity (Brunner et al. 2014). One population of adult-born GCs was sensitive to a narrow range of input intensities, while the other population broadly responded to input strength in a linear fashion. Input onto mature GCs also mediates the competition with adult-born GCs. By modulating spine dynamics of mature GCs, researchers showed a decrease in mature GC spine density promotes integration of adult-born GCs (McAvoy et al. 2016). It has also been shown that pre-existing presynaptic terminals are redistributed to newly integrating GCs, therefore modifying excitatory synaptic transmission of existing neurons (Adlaf et al. 2017).

Local GABA interneurons and adult hippocampal neurogenesis

In addition to excitatory principal cells such as dentate granule cells and entorhinal cortex pyramidal cells, hippocampal microcircuits recruit different types of local GABAergic interneurons, which exert inhibitory control at the soma, proximal dendrites, distal dendrites, and the axonal initial segment of the principal cells (Halasy et al. 1992, Freund and Buzsáki 1996, Houser 2007). The populations of hippocampal interneurons are remarkably diverse in their location, morphology, targets, and gene expression (Freund and Buzsáki 1996; Maccaferri and Lacaille 2003). A number of interneurons with their axons in close proximity to the SGZ neurogenic niche can potentially exert a functional impact on adult neurogenesis. These interneurons include molecular layer perforant path (MOPP) interneurons, hilar commissural-associational pathway related (HICAP) interneurons, hilar perforant path-associated (HIPP) interneurons, stratum lacunosum-moleculare (L–M) interneurons, and basket cells (Figure. 1) (Han et al. 1993, Freund and Buzsáki 1996, Houser 2007).

Studies have just begun to characterize the interaction between local interneurons and adult precursors and their progeny, ranging from radial glia-like NSCs, proliferating intermediate NPCs and neuroblasts, post-mitotic immature neurons, to mature neurons(reviewed in Song et al., 2016). Previously, manipulations were mostly done in a cell autonomous fashion through the “single-cell knockdown” approach that uses a retrovirus expressing a short-hairpin RNA (shRNA) to infect proliferating NPCs, sometimes in combination with pharmacological manipulations. Moreover, due to the inability to use traditional electrodes to stimulate specific neuronal populations in these experiments, precise analyses of circuit function and dynamics were not feasible. With recent technical advancements in circuitry manipulation via optogenetics, DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), and cross-synaptic tracing technology, the field is in a unique position to

address fundamental questions underlying activity-dependent regulation of adult neurogenesis.

Using rabies virus-mediated retrograde tracing in combination with retroviral approachs to label and birth-date newborn granule cells, recent studies showed that adult-generated neurons receive local connections from multiple types of GABAergic interneurons, including PV^+ basket cells, somatostatin-positive (SST^+) HIPP cells, HICAP cells, and MOPP cells, such as neurogliaform cells/Ivy cells (Fig. 1C) (Vivar et al. 2012; Deshpande et al. 2013). The rabies virus based trans-synaptic tracing tool employed in these studies is very informative in terms of defining both the organization of monosynaptic connections and how individual neurons are integrated into polysynaptic networks. However, to identify the circuit-based regulation of early stages of adult neurogenesis (e.g. the neural stem cell stage and early neural progenitor/neuroblast stages), the cross-synaptic tracing approach is not feasible as no or very few immature synapses are present at those stages of development. Therefore, electrophysiological characterization is necessary to define the nature of functional inputs during initial phases of adult neurogenesis. A recent study using paired recording in acute slices showed that interneurons of the neurogliaform cell family provide a source of GABA for immature neurons labeled with POMC-EGFP that are about 11–12 days after birth (Overstreet et al. 2004) in the adult mouse dentate gyrus (Markwardt et al. 2011).

Despite recent progress in identifying afferent inputs to immature neurons, the evidence for local interneuron regulation of NSCs and precursor cells is still limited, largely due to the distinct properties of those cell populations, which prevent effective functional characterization. Furthermore, *in vivo* functional studies of those local interneurons in regulation of adult neurogenesis are still lacking. Using the combination of optogenetics and lineage-tracing to target the quiescent radial glia-like NSCs, Song et al. have identified PV^+ interneurons as a cellular niche component that signals to quiescent NSCs through tonic GABA signaling in an activity-dependent fashion in the adult mouse dentate gyrus. Moreover, optogenetic control of dentate PV^+ neuron activity, but not SST^+ or vasoactive intestinal polypeptide (VIP^+) interneurons, dictates the radial glia-like neural stem cell decision between quiescence and activation (Song et al. 2012). In contrast to the direct synaptic inputs onto immature neurons in POMC-EGFP mice (Markwardt et al. 2009), no apparent functional GABAergic synaptic responses were detected when radial glia-like NSCs were recorded in this and previous studies (Wang et al. 2005), suggesting that GABA spillover from activated PV^+ interneuron-mature GC synapses indirectly regulates nearby radial stem cells by tonic GABA transmission. More recently, we showed that PV^+ interneurons make direct synaptic contacts with proliferating neuroblasts and regulate their survival and development in the adult dentate gyrus (Song et al. 2012, 2013). Together, these results reveal a striking diametric regulation of two early critical steps of adult neurogenesis via PV^+ neuron activity: in the dentate gyrus with heightened activity, activation of PV^+ neurons inhibits quiescent neural stem cell activation while promoting the survival of proliferating NPCs already born; conversely, when the activity in the dentate gyrus is low, decreased PV^+ neuron activation promotes expansion of the quiescent neural stem cell pool via symmetric cell division and simultaneously suppresses the survival of proliferating NPCs (Song et al. 2012, 2013). Interestingly, some local interneurons co-release GABA and

neuropeptides, such as interneurons expressing markers of SST+, VIP+, cholecystokinin (CCK+), and neuropeptide Y (NPY), which adds another layer of complexity to interneuron-mediated regulation of adult hippocampal neurogenesis. For instance, NPY+ interneurons have been shown to mediate adult neurogenesis by promoting proliferation of the stem cell pool, at the baseline and after seizure activity (Howell et al. 2003, 2007; Cardoso et al. 2010); VIP+ interneurons in the DG have been implicated in adult neurogenesis, as signaling through the VIP receptor VPAC1 influences neuronal fate of stem cells in the SGZ, while activation of the VPAC2 receptor has been shown to increase symmetric division of the stem cell pool (Zaben et al. 2009). Given that GABA signaling plays a role in maintaining rNSC quiescence, these studies suggest that neuropeptides (vs. GABA) released from GABA interneurons may play a potential role in activating NSCs. Together, these studies provide a point of entry for understanding how circuit dynamics may impact different phases of adult neurogenesis. Future studies with detailed characterization of various synaptic inputs onto adult-born neurons at different developmental stages will provide insights into spatial and temporal organization of various local circuitry niche components in relation to sequential stages of adult neurogenesis.

In addition to the direct interaction between local interneurons and adult-born cells, local interneurons also interact with mature granule cells to control hippocampal network activity. More research is needed to examine if these circuits affect development of adult-born neurons. Moreover, in the past several years the role of PV+ interneurons in regulating adult hippocampal neurogenesis has been revealed; however, to date, PV+ interneurons seem to be the most well characterized interneurons compared to the roles of CCK+, VIP+, calretinin (CR+), SST+, and NPY+ interneurons. Whether these diverse GABAergic interneuron subtypes uniquely contribute to adult hippocampal neurogenesis remains unknown. Furthermore, GABA release from local GABAergic interneurons can be regulated by a wide variety of neurotransmitters and neuromodulators, including glutamate from the entorhinal cortex, serotonin from the raphe nuclei (Matsuyama et al. 1997) and acetylcholine from the medial septum/diagonal band of Broca (Tozuka et al. 2005; Griguoli and Cherubini 2012; Teles-Grilo Ruivo and Mellor 2013). Therefore, local GABA interneurons may receive afferent inputs from distal brain regions. Indeed, electron microscopy and electrophysiology have showed that local GABA neurons receive both GABAergic and cholinergic inputs from medial septum (Freund and Antal 1988; Pabst et al. 2016). How distal inputs impacts adult hippocampal neurogenesis through local interneurons remains to be explored.

Adult Neurogenesis and Hippocampal Activity

Substantial evidence has suggested that these adult-born new neurons are involved in cognition, stress response and mood regulation(Harrison 2004; Kempermann et al. 2008, Le Strat et al. 2009, Song et al., 2012; Zhou et al. 2013); and aberrant adult neurogenesis contributes to brain disorders, such as epilepsy and mental disorders, suggesting that adult neurogenesis may be a crucial substrate that can contribute to the onset of these disorders. This raises a fundamental question: how is hippocampal activity modulated by continuous addition of newborn neurons? Adult-born neurons could impact brain functions directly via two modes: first, as an additional information-processing unit and, second, as an active modulator of local circuitry to shape mature neuron firing, synchronization, and network

oscillations. One hallmark of the dentate gyrus is its sparse activation as shown by both *in vivo* recording of putative granule cells (Neunuebel and Knierim 2012) and immediate early gene expression (Ramirez-Amaya et al. 2005). Although these adult-born neurons are small in absolute number, preferential recruitment of excitable immature neurons with enhanced plasticity would allow this population to be a major player in information processing within the trisynaptic hippocampal circuit. The contribution of the local hippocampal circuitry in regulating adult-born GCs has also been addressed in computational models as it relates to information-processing and pattern separation (Myers and Scharfman 2009; Li et al. 2012; Temprana et al. 2015) In the second mode, newborn neurons could actively modulate local circuit activity, for example, maintaining a basal tone of excitation/inhibition or facilitating information encoding by increasing signal to noise in the region and/or by priming circuits to respond (Freund 2003; Lacefield et al. 2010). Such activity modulation could have direct impact on the local hippocampal circuit through axonal projections from newborn neurons to their downstream hippocampal targets (CA3 to CA1), or indirect impact on the global neural network through axonal projections of newborn neurons to the local neurons that project to other brain regions. These possibilities have not been tested experimentally until recently. Temprana et al. recently showed that immature GCs receive weak feed-back inhibition, however once mature, these adult-born cells activate GABAergic parvalbumin (PV+) interneurons involved in feedback loops that restrict spiking of nearby GCs. The functional significance of this, as predicted by a computational model, is that the delayed-coupling of feedback inhibition during integration of adult-born GCs promotes sparse coding in the DG (Temprana et al. 2015). Furthermore, it has been shown that environmental enrichment promotes integration of adult-born GCs by activating mature GCs, which recruit PV+ interneurons that target immature GCs (Alvarez et al. 2016). In addition, GABAergic interneurons in the DG have also been found to modulate sensorimotor gating during adolescence. Though further studies are needed, the authors speculate that changes in adult neurogenesis during adolescence may affect the survival of GABAergic interneurons (Guo et al. 2013). Moreover, adult-born granule cells have been shown to contribute to the excitatory-inhibitory balance of the DG by GABAergic synaptic input (Li et al. 2012; Ikrar et al. 2013). Park et al. found that adult-born granule cells indirectly contribute to memory discrimination by regulating this balance (Park et al. 2015). While it is clear that the excitation-inhibition balance in the dentate gyrus is crucial for hippocampal activity, the total contribution of hippocampal network control of adult neurogenesis and adult-born granule cells is yet to be determined. An interesting review by Piatti et al. raises the question: are adult-born granule cells carrying the message or dictating the tone within the hippocampus? Further studies are needed to characterize the unique properties of immature neurons and how they contribute to signaling in the dentate gyrus (Piatti et al. 2013).

GABA Receptor Mechanisms in Adult Neurogenesis

Current knowledge on GABA receptor mechanisms underlying adult hippocampal neurogenesis is sparse. $GABA_A$ receptors ($GABA_ARs$) are fast, ionotropic, heteropentameric channels permeable to Cl^- and HCO_3^+. The quiescence of the SGZ stem cell pool is mediated by tonic GABA currents through the $GABA_ARs$ of the $\alpha5\beta3\gamma2$ composition (Song et al. 2012). Tozuka et al. demonstrated that excitatory GABAergic input through $GABA_ARs$ induces activity-dependent differentiation of NPCs (Tozuka et al. 2005).

Duveau et al. found that distinct $GABA_AR$ subtypes dictate spatiotemporal regulation of adult neurogenesis (Duveau et al. 2011). In their studies, tonic GABAergic transmission occurred through α4 and δ subunits, while phasic transmission occurred through α2. In addition, they showed that $GABA_ARs$ containing α4, but not δ, subunits modulate cell proliferation, early migration, and early dendritic development. They also found that α2-containing $GABA_ARs$ determine positioning of adult-born GCs and mediate late dendritic arborization. Extrasynaptic $GABA_ARs$ containing the δ subunit are highly expressed throughout the DG, and mice that lack this receptor display aberrant migration and development of adult-born neurons, as well as enhanced fear acquisition, impaired fear extinction, and impaired recognition memory (Whissell et al. 2013).

In contrast to $GABA_ARs$, $GABA_B$ receptors ($GABA_BRs$) are metabotropic and have been associated with suppressed proliferation of adult neurogenesis in the DG (Felice et al. 2012). O'Leary et al. found that reductions in the $GABA_BR$ 1a isoform are associated with increased susceptibility to stress-induced anhedonia, while reductions in the 1b isoform are associated with resilience and increased adult neurogenesis (O'Leary et al. 2014). Since $GABA_BRs$ are expressed in SGZ stem cells as well as throughout the adult hippocampal neurogenic lineage, it is possible that $GABA_AR$ and $GABA_BR$ signaling act synergistically to regulate adult neurogenesis (Giachino et al. 2013). Compared to $GABA_ARs$, relatively little is known about the mechanism through which $GABA_BRs$ regulate adult neurogenesis.

Molecular players that interact with GABA signaling for adult hippocampal neurogenesis regulation

Various molecules have been shown to mediate adult neurogenesis by modulating PV+ interneuron mediated GABA signaling. NFATc4 is an activity-dependent transcription factor of $GABA_AR$ α2 and α4 subunits (Quadrato et al. 2014). NFATc4 transduces BDNF signaling in adult-born GCs and regulates synaptic plasticity (Quadrato et al. 2012). BDNF synthesized in GC dendrites enhances GABA release in the SGZ, resulting in increased differentiation and maturation of progenitor cells partly from PV+ interneurons (Waterhouse et al. 2012). Cav1.2, a subunit of L-type calcium channels, is needed for BDNF expression and promotes survival of young hippocampal neurons (Lee et al. 2016). The chemokine stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 up-regulate PV+ interneuron GABAergic innervation of NPCs (Bhattacharyya et al. 2008; Kolodziej et al. 2008). The extracellular matrix glycoprotein tenascin-R (TNR) is expressed by PV+ interneurons in the DG as well as in differentiating NPCs (Xu et al. 2014). TNR −/− mice have an increase in PV+ interneurons, which results in increased GABAergic transmission to cells in the SGZ and subsequently inhibits proliferation of NPCs (Xu et al. 2014).

Numerous other molecules have been implicated in GABA signaling. NSCs express the Diazepam Binding Inhibitor (DBI) protein which dampens GABA signaling through $GABA_A$ receptors and acts as an adaptive mechanism in response to environmental changes such as physical exercise and environmental enrichment. DBI regulates balance between quiescence and proliferation (Dumitru et al., 2017). Overexpression of neuroligin-2A, a synaptic adhesion molecule, in young GCs increases GABAergic innervation as well as spine density and size (Krzisch et al. 2016). This suggests neuroligin-2a has a role in

integration of adult-born GCs. Cdk5 has also been shown to affect development of adult-born GCs by mediating transmisison through $GABA_A$Rs containing the α5 subunit (Deprez et al. 2016). Neuregulin-2 (NRG2) has a dual role in synaptogenesis of adult-born GCs. The extracellular domain of NRG2 acts as a ligand for GABAR and therefore promotes GABAergic synaptogenesis in developing adult-born GCs, while the intracellular domain mediates dendritic growth and maturation of glutamatergic synapses (Lee et al. 2015). GABA-induced depolarization that is mediated by NKCC1 expression regulates Disrupted-in-Schizophrenia 1(DISC1) through the AKT-mTOR pathway (Kim et al. 2012). DISC1 knockdown also induces early dendritic growth enhanced by GABA signaling through $GABA_A$Rs.

Dysfunction of GABA signaling in causing adult neurogenesis deficits in diseased conditions

Different from other somatic stem cell compartments where morphogens and growth factors generally serve as niche signals, adult neurogenesis is well known to be dynamically regulated by neuronal activity and experience. Accumulating evidence suggests that adult neurogenesis is differentially regulated by various physiological and pathological stimuli (Crowther and Song, 2014). As adult hippocampal neurogenesis occurs within a dynamic neuronal network, it is conceivable that the neural circuit activity could serve as an effective readout of current tissue demands and provide a signal to tune new neuron production and integration in response to experiences, environmental influence, and pathological conditions (Figure 2). Here we review recent findings correlating aberrant GABA circuits and signaling in various pathological conditions to dysregulation of adult hippocampal neurogenesis.

Alzheimer’s Disease

Aberrant adult hippocampal neurogenesis has been noted in numerous diseased conditions. In Alzheimer’s disease (AD), an excitatory-inhibitory imbalance impairs adult neurogenesis (Sun et al. 2009). The amyloid precursor protein, the precursor to amyloid plaques associated with AD, is normally highly expressed in dentate GABAergic interneurons and controls adult neurogenesis by maintaining the excitatory-inhibitory balance (Wang et al. 2014). It has been shown that the genetic polymorphism apolipoprotein E4, a risk factor for AD, is associated with reduced GABAergic interneuron input to developing GCs and disrupted maturation (Li et al. 2009). In a triple transgenic mouse model of AD, selective loss of medium septum (MS) GABAergic neurons and dentate interneurons including PV^+ neurons were observed, which was accompanied with cognitive deficits (Loreth et al. 2012). Furthermore, aberrant hippocampal neurogenesis was observed in the AD mouse model with an initial increase followed by a decrease of adult hippocampal neurogenesis at the later stage (reviewed in (Kuhn et al. 2007; Lazarov and Marr 2010)). These data suggest that disruption of the MS-DG GABAergic circuit may correlate with impaired adult hippocampal neurogenesis under the pathological condition of AD. Future studies using circuit-based approaches to directly test this link will be of great interest to determine the significance of disrupted adult neurogenesis in AD.

Epilepsy

Epilepsy has also been associated with disrupted adult neurogenesis. The accumulation of abnormal adult-born GCs predicts seizure frequency and severity (Hester and Danzer 2013). Interestingly, one study found that ablating adult-born GCs could reduce seizure frequency and duration (Hosford et al. 2016). One hypothesized mechanism of epilepsy is reduction of GABAergic interneuron signaling in regulating adult neurogenesis (Scharfman and Brooks-Kayal 2014). Yutsudo et al. found that fosB-null mice are a plausible model for the comorbidity of spontaneous epilepsy and depressive behavior. These mice had fewer PV+ interneurons and reduced thyroid-releasing hormone associated with GABA release (Yutsudo et al. 2013). Temporal lobe epilepsy is also associated with an initial loss of both glutamatergic and GABAergic synapses with GCs after status epilepticus, followed by the return to baseline of excitatory synapses and an overshoot in the number of inhibitory synapses (Thind et al. 2010). This builds on evidence that temporal lobe epilepsy is followed by an increase in proliferation of adult-born GCs (Parent et al. 1997). The mechanism of how this change in excitatory-inhibitory balance regulates adult neurogenesis and integration of immature GCs is unclear. For a more detailed review of GABAergic mechanisms in epilepsy relevant to adult neurogenesis, see review by Scharfman and Brooks-Kayal (Scharfman and Brooks-Kayal 2014).

Stress, Anxiety, and Depression

As adult hippocampal neurogenesis occurs within a dynamic neuronal network, it is conceivable that the local circuit activity could serve as an effective readout of current tissue demands and provide a signal to tune new neuron production in stressed, anxious, and depressed states. GABAergic regulation of adult neurogenesis has been implicated in these neuropsychiatric states. Song et al. recently showed that PV^+ neurons serve as a unique niche component to couple social isolation stimuli to the regulation of adult NSCs in the hippocampus (Song et al. 2012). Specifically, decreased PV^+ neuron activity by chronic social isolation promotes excessive activation and symmetric cell division of rNSCs at the expenses of decreased neuronal production. In addition to reduced GABA interneuron activity, chronic stress has also been shown to reduce the number of GABAergic interneurons in a region-specific manner, so it is suspected that adult hippocampal neurogenesis is affected (Czéh et al. 2015). Moreover, PV+ and CR+ interneurons are reduced in the dorsal hippocampus and ventral CA1 following chronic stress, while NPY+ and SST+ interneurons are reduced throughout almost all regions of the dorsal and ventral hippocampus. Earnheart et al. found that inactivation of $GABA_A$Rs containing the $\gamma 2$ subunit in the adult forebrain reduced adult hippocampal neurogenesis, and increased behavioral inhibition to stressful situations (Earnheart et al. 2007). Shen et al. found that a deficit in GABAergic control of adult neurogenesis alone is insufficient to cause anxiety and depression (Shen et al. 2012). Interestingly, chronic fluoxetine (an SSRI commonly prescribed for anxiety and depression) reduces the number of PV+ interneurons and increases stem cell proliferation in the SGZ (Ohira et al. 2013).

Autism

Disrupted adult neurogenesis has also been noted in animal models of Autism Spectrum Disorder. Exposure to valproic acid has been used to induce autism-like phenotypes in animal models (Mabunga et al. 2015). Watanabe et al. recently reported that exposure to valproic acid from gestational day 6 to postnatal day 21 targets GAD67+ interneurons and has late effects on granule cell lineage due to altered proliferation and synaptic plasticity. MECP2 duplication syndrome, also associated with autism-like phenotypes, has been reported to significantly decrease GABAergic PV+ interneurons, resulting in reduced adult hippocampal dividing cells and an accumulation of quiescent neural stems in transgenic mice overexpressing MECP2, suggesting MECP2 is important for differentiation of neuronal progenitor cells (Chen et al. 2017). The neuronal splicing regulator RBFOX3 (also known as neuronal marker NeuN) has been implicated in ASD, epilepsy, and cognitive disability, and has been suggested to promote adult neurogenesis and synaptogenesis by GABAergic interneurons (Lin et al. 2016).

GABA regulation of adult hippocampal neurogenesis as a potential therapeutic target

Various neuropsychiatric and neurodegenerative disorders are associated with hippocampal dysfunction, learning and memory deficits, and impaired adult hippocampal neurogenesis. Although adult hippocampal neurogenesis is not thought to occur at a rate great enough to regenerate the hippocampus, targeting NSCs and their progeny could possibly restore some aspects of the cognitive functions. $GABA_A$ and $GABA_B$ receptors are potential drug targets for this purpose given their role in preserving the neural stem cell pool and promoting adult hippocampal neurogenesis. In addition, with the recent progress in identifying the specific interneuron types in regulating NSCs and hippocampal neurogenesis, there is great potential in targeting specific GABAergic interneuron populations, the sources of GABA signaling, in modulating hippocampal circuit and hippocampal dependent functions. Indeed, loss or dysfunction of GABAergic interneurons is commonly seen in various neurodegenerative and neuropsychiatric disorders linking to aberrant adult hippocampal neurogenesis (Marin, 2012).

There have been variable outcomes regarding adult hippocampal neurogenesis in various AD mouse models depending on promoters, transgene expression, and age of onset (Winner and Winkler, 2015, Lazarov and Marr, 2010; Marlatt and Lucassen, 2010). However, Sun et al. showed an imbalance of hippocampal GABAergic and glutamatergic signaling disrupts adult neurogenesis in an hAPP (human amyloid precursor protein) transgenic mouse model; this imbalance can be rescued by inhibition of $GABA_A$ receptors in early neurogenesis to suppress GABA signaling (Sun et al., 2009). A recent study by Muñoz et al. showed a new mouse model of Parkinson's disease that could also be rescued by targeting $GABA_A$ receptors. Smad3 deficient mice fail to induce LTP in the dentate gyrus due to enhanced $GABA_A$ receptor-mediated activity, in addition to decreased adult neurogenesis and dysregulated hippocampal function (Muñoz et al., 2016). Picrotoxin, a $GABA_A$ antagonist,

rescued this phenotype. These studies demonstrate the potential in targeting $GABA_A$ receptors and adult hippocampal neurogenesis in neurodegenerative diseases.

$GABA_A$ receptor-modulatory actions of neurosteroids such as allopregnanolone (also known as 5α3α-THPROG) have shown promising neurogenic outcomes as a potential therapies for AD and depressive-like behaviors (Wang et al., 2005; Wang et al., 2008; Wang et al., 2010; Gunn et al., 2015). In 2010, Wang et al. showed 5α3α-THPROG, can reverse the hippocampal-dependent cognitive deficits in the 3xTgAD mouse model of AD. Evans et al. also showed exogenous 5α3α-THPROG administration could prevent impaired adult hippocampal neurogenesis and depressive- and anxiety-like behaviors in a social isolation rat model of chronic stress (Evans et al., 2012).

Adult hippocampal neurogenesis has been implicated in the role of antidepressants. Some studies have indicated that neurogenesis is required for the behavioral effects of antidepressants (Santarelli et al., 2003; Malberg and Duman, 2003). However, there is also evidence for neurogenesis-independent antidepressant mechanisms, and that ablating adult hippocampal neurogenesis is not sufficient to induce a depressive- like state (Airan et al., 2007; Sahay and Hen 2007; David et al., 2009; Kang et al. 2016). Interestingly, SSRIs increase adult neurogenesis, but adult neurogenesis is not affected by knockout of 5-HT1A receptors (Santarelli et al., 2003). Serotonin depletion also increases survival of adult-born neurons (Diaz et al., 2013). Luscher and Fuchs suggest that antidepressants indirectly promote adult neurogenesis by acting on 5-HT1A receptors to inhibit GABAergic interneurons (Diaz et al., 2013; Luscher and Fuchs, 2013). In addition, Egeland et al. found that mice lacking p11, a protein expressed by hippocampal interneurons, are non-responsive to fluoxetine treatment (Egeland et al., 2010). The fact that BDNF is upregulated by all antidepressants currently used, combined with evidence that BDNF is needed for normal interneuron maturation, further implicates the role of GABAergic interneuron dysregulation and impaired adult hippocampal neurogenesis in depressive-like states (reviewed in Luscher and Fuchs, 2013). Changes in $GABA_B$ receptor activity have also been shown to enhance BNDF expression (Heese et al. 2000; Enna et al., 2006; Fiorentino et al., 2009). While a large body of data has suggested $GABA_B$ receptor as a therapeutic target for antidepressant drugs, how adult hippocampal neurogenesis fits into this paradigm is uncertain. A review by Ghose et al. suggests that decreased serotonergic activity enhances $GABA_B$ tone, and therefore response to antidepressants depends on reduction in $GABA_B$ receptor stimulation (Ghose et al., 2011). Overall, further research is needed to determine the potential of targeting GABAergic interneurons, $GABA_A$ receptors, and $GABA_B$ receptors to treat neuropsychiatric disorders.

Conclusion

Adult neurogenesis is a complex process that is regulated by neuronal activity. GABA is emerging as a key signal within the neurogenic niche, enabling rNSCs and their progeny to sense neuronal activity and regulate their development. Aided by methodological advancements, studies have started to extensively investigate circuit-based regulation of adult hippocampal neurogenesis at distinct developmental stages. Studies of local GABA interneuron circuits and GABA signaling in regulation of adult hippocampal neurogenesis

have so far served as an entry point for exploring the basic principles of neuronal development in the context of dynamic and distinct neural circuit activity in the mature CNS. A unique feature of the hippocampal circuit is the large-scale structural modification via the addition of newborn neurons arising from ongoing neurogenesis. The entire milieu must preserve the functional integrity of the existing circuitry, and at the same time, it needs to provide a niche to support the development of adult-born neurons and allow these cells to modify the local neuronal network. The differential modulation by various types of local and distal circuits thus may provide the fine control of synaptic integration of adult-born neurons required for specific neurogenic events in response to experiences, environmental influences, and pathological conditions. Defects in one or several of these mechanisms will lead to circuit abnormalities such as those associated with altered network excitability and behavioral defects (Zhou et al. 2013).

There are many unanswered questions regarding GABA-mediated regulation of adult neurogenesis. First, the local GABA interneuron circuit mechanisms underlying activity-dependent regulation of adult hippocampal neurogenesis remain elusive. The DG neurogenic niche consists of a diverse group of local interneurons with distinctive electrophysiological, molecular, and innervation properties. However, virtually nothing is known about how distinct interneurons regulate distinct developmental stages during adult hippocampal neurogenesis, ranging from neural stem cell fate decision and proliferation of NPCs to maturation, synaptic integration and survival of newborn neurons (Zhao et al. 2008; Ming and Song 2011). Second, some local GABA interneurons co-release GABA and neuropeptides, such as SST+, VIP+, CCK+ and NPY+ interneurons. The role of GABA in regulation of adult hippocampal neurogenesis is well-defined, but few studies have examined the role of GABA-mediated neuropeptides in adult neurogenesis regulation at the circuit level. The balance of neuropeptide and GABA signaling in regulating adult neurogenesis remains elusive. Third, GABA release from local hippocampal GABAergic interneurons can be regulated by a wide variety of neurotransmitters and neuromodulators, pointing to the possibility that local interneuron activity may be regulated by afferent inputs from distal brain regions. Future studies to identify neuronal networks linking long-distance inputs to distinct types of local interneurons for adult hippocampal neurogenesis regulation will have a number of implications for understanding basic circuit mechanisms underlying dynamic control of adult hippocampal neurogenesis and for developing strategies in treating brain disorders potentially arising from aberrant hippocampal neurogenesis, such as Alzheimer’s disease and schizophrenia.

Acknowledgments

We thank Brent Asrican for helpful comments on the review. This work was supported by grants from American Heart Association, Whitehall Foundation, and NIH (R01MH111773, R21MH106939) to J.S., and NIH (T32NS007431) to C.C.

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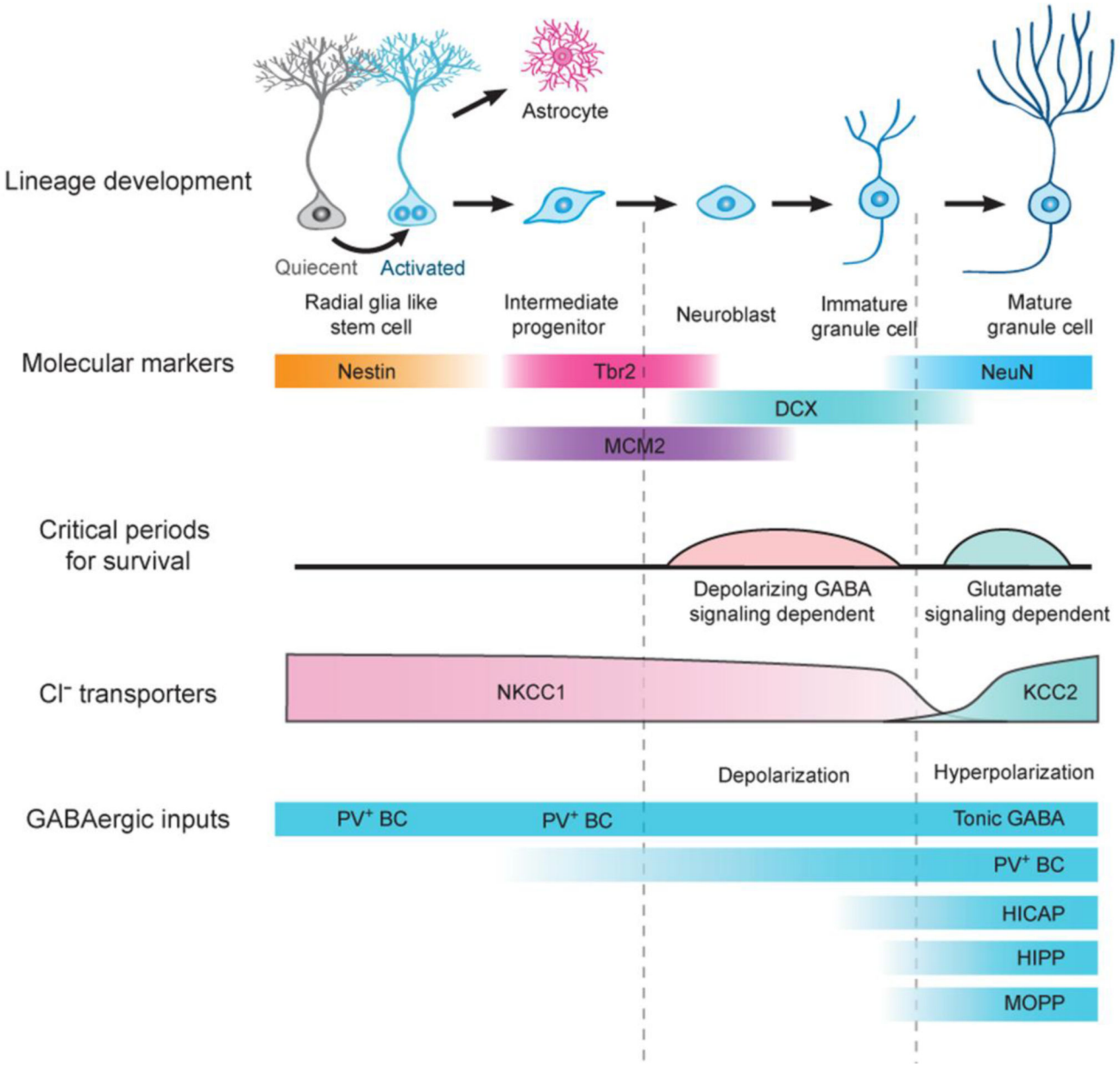

Figure 1. Adult hippocampal neurogenesis in the young adult mouse brain

Summary of the developmental processes of adult hippocampal neurogenesis, including time course of marker expression, developmental stages, critical periods for cell survival, and special neuronal properties associated with different stages. BC, basket cells; HICAP, hilar interneuron with commissural-associational pathway-associated axon terminals; HIPP, hilar perforant path-associated interneurons; MOPP, molecular-layer perforant pathway cells; PV +, parvalbumin-expressing interneurons.

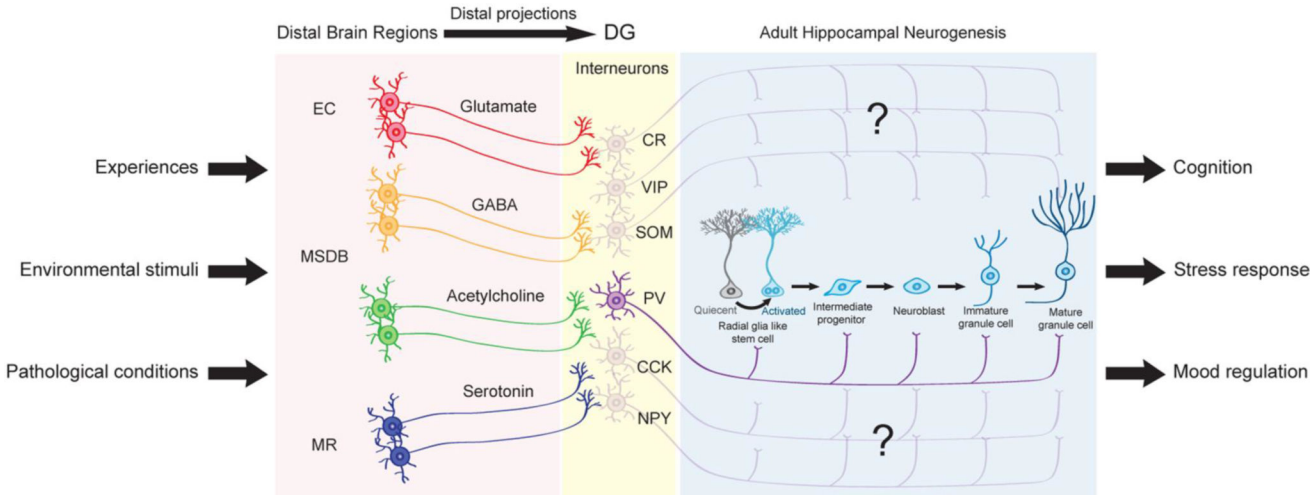

Figure 2. Experience-dependent regulation of adult hippocampal neurogenesis mediated by local interneurons

Shown is an illustration of how local interneurons may couple experiential and environmental stimuli to the regulation of adult hippocampal neurogenesis. Long-distance afferent inputs relay experiential and environmental information to the dentate interneurons to regulate various stages of adult hippocampal neurogenesis, from proliferation and fate specification of adult neural progenitors, morphogenesis, migration, axon/dendritic development, and finally synapse formation and integration. Furthermore, modified adult hippocampal neurogenesis by experiential and environmental stimuli can in turn contribute to normal and aberrant brain functions, such as learning and memory, stress response, and mood regulation. EC, entorhinal cortex; MSDB, medial septum diagonal band; MR, medial raphe; CR, calretinin; VIP, vasoactive intestinal peptide; SST, somatostatin; PV, parvalbumin; CCK, cholecystokinin; NPY, neuropeptide Y.