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Neural stem cells and the regulation of neurogenesis in the adult hippocampus

Bettina Seri and Arturo Alvarez-Buylla*

Department of Neurosurgery Research, Box 0520, Brain Tumor Research Center, University of California, San Francisco, CA 94143, USA

Abstract

Neurogenesis continues in the hippocampal dentate gyrus of adult rodents and primates including humans. Neurons are born in the underlying subgranular layer (SGL) and move into the granule cell layer (GCL) to become mature granule neurons. Recent work indicates that the primary precursors for these new neurons correspond to radial astrocytes whose cell body is in the SGL and their processes traverse the GCL. These astrocytes divide to give rise to intermediate precursors, D cells that likely become mature granule neurons. Here we propose that the anatomy of radial astrocytes may allow for signals within the GCL to regulate neurogenesis in the SGL. Levels of neuronal activity within the granule cell layer may regulate the proliferation rates of radial astrocytes and determine the number of new neurons produced in the dentate gyrus.

Keywords

Neural progenitor; Neurogenesis; Plasticity; Astrocyte; Glia; Dentate gyrus

1. Introduction

It has been suspected for some time that adult neurogenesis requires the presence of primary precursors, or stem cells, within the germinal zones where new neurons are born [1–4]. Consistently, cells with neural stem cell properties in-vitro can be isolated from the adult mammalian brain using growth factors [5–7]. In adult mammals neural stem cells that continually generate new neurons are present in the subventricular zone (SVZ) of the lateral ventricle [8,9], and the subgranular layer (SGL) of the hippocampal dentate gyrus [10–13].

A critical step towards understanding adult neurogenesis and how this process is regulated is the identification of the primary precursors that generate new neurons in vivo. The identification of the stem cells is also critical for future attempts to engineer these cells for therapeutic applications. Recent work in the hippocampus indicates that new neurons are derived from dividing dentate gyrus radial astrocytes [14]. Several other studies have described experimental interventions that affect proliferation, recruitment and incorporation of new neurons in the adult dentate gyrus [15–25]. Those studies, however, were done

before the primary progenitors in the adult hippocampus were identified and could not link effects on proliferation, generation and survival of new neurons to possible alterations in the behavior of the stem cells. Here we will focus on the *in vivo* identification of the primary precursors for new neurons and on how the anatomy of these cells suggests possible mechanisms of regulation of adult neurogenesis in the adult hippocampus.

2. SGL astrocytes as neuronal progenitors

In contrast to the embryonic VZ or the SVZ in the adult, the SGL is not located close to the walls of the brain ventricles, but it exists deep within the brain parenchyma at the interface of the granule cell layer (GCL) of the dentate gyrus and the hilus in the hippocampus. Earlier work had suggested that small dark cells in the SGL corresponded to neural stem cells in the adult dentate gyrus [2,10,13]. In addition to the dark cells, several studies had shown that astrocytes continue to divide in the SGL of the adult hippocampus [13,26]. Division of astrocytes is generally attributed to ongoing local gliogenesis, a process thought necessary for the maintenance and support of neuronal function. Given recent evidence showing that SVZ-astrocytes give rise to new neurons, we investigated the possibility that astrocytes could function as the primary neuronal precursors in the dentate gyrus [14].

Astrocytes in the SGL stain prominently with antibodies to GFAP and have a radial process that traverses the granular cell layer and short tangential processes extending under the blades of the dentate gyrus [27]. At the electron microscope these cells have ultrastructural features of astrocytes. They have a light cytoplasm containing intermediate filaments and multiple processes that intercalate between neighboring cells [14]. Two hours after a BrdU (bromodeoxyuridine) or a [³H]thymidine injection, 60% of labeled cells in the SGL correspond to astrocytes. Interestingly, the number of labeled astrocytes decreases within the next 24 hours coinciding with an increase in the number of labeled GFAP negative cells which have similar characteristics to the small dark cells (D cells) previously described.

The above labeling study suggests that dividing SGL astrocytes could give rise to non-astrocytic cells. In order to determine whether these cells were producing new neurons in the dentate gyrus, a cocktail of antimitotic drugs was employed to kill the actively dividing cells in the SGL. Combined administration of Ara-C and Procarbazon kills dividing cells in the SGL resulting in the elimination of D cells and many astrocytes [14]. However, some astrocytes survive and begin dividing soon after termination of antimitotic treatment. D cells reappear four days after the termination of antimitotic treatment. Injecting [³H]thymidine or BrdU 2 days after termination of the antimitotic treatment, when only SGL astrocytes are dividing, results in labeled granule neurons, astrocytes and oligodendrocytes 1–5 months later.

After selective infection of SGL astrocytes using the RCAS-AP avian retrovirus in transgenic mice where the receptor for this retrovirus is expressed under the control of the GFAP promoter; AP-labeled neurons are found in the granule cell layer (Fig. 1C). Some of these neurons extend axonal projections that could be followed to the CA3 region of Ammon's horn, indicating that they had been incorporated into the normal circuitry of the hippocampus. Together, these experiments indicate that SGL astrocytes are the primary

precursors that give rise to new granule neurons in the adult dentate gyrus through the intermediate D cells (Fig. 1B). It is likely that SGL astrocytes also act as stem cells in vitro, but this remains to be demonstrated.

3. Regulation of adult neurogenesis

Hormones, neurotransmitters and seizures have been shown to increase or decrease the proliferation of cells in the SGL and the number of new neurons recruited in the adult GCL (Table 1). In order to suggest possible regulatory mechanisms that could explain how SGL stem cells respond to these manipulations we discuss below some of these experimental manipulations.

Consistently with the proposition that astrocytes function as the primary precursors for new granule neurons, previous studies have shown a parallel between astrocytic proliferation and neurogenesis following adrenalectomy. One week after adrenalectomy, astrocytic proliferation in the SGL increases [15] and the numbers of labeled neurons in the GCL 1 month later is four times higher than controls [28]. Interestingly, adrenal hormones induce the extracellular accumulation of glutamate in the GCL [29–31]. Therefore, we would expect that removal of adrenal steroids via adrenalectomy would cause a drop in extracellular glutamate levels. Alterations in neuronal activity in the GCL and/or a drop in glutamate levels may be detected by astrocytes inducing them to proliferate and generate more new neurons to perhaps restore GCL neuronal activity. Alternatively, adrenal hormones may have a direct effect on SGL astrocytes as it has been shown that hippocampal astrocytes express the mineralocorticoid and glucocorticoid receptors [32]. More astrocytes may become directly activated through signaling via glucocorticoid receptors to accommodate the increased demand for new neurons following adrenalectomy.

Other experimental interventions that directly alter synaptic transmission or electrophysiological activity also have profound effects on hippocampal neurogenesis. Administration of NMDA receptor antagonists produce a transient increase in dentate gyrus proliferation 2 days after treatment and an increase in the total number of new neurons in the granule cell layer 1 month later [33,34]. It has been shown that NMDA receptor antagonists block the release of glutamate in the dentate gyrus [35] and that astrocytes can modulate extracellular levels of glutamate in a Ca^{2+} -dependent manner [36–39]. Unfortunately, the response of astrocytes to the administration of NMDA antagonists has not been studied. Blockade of NMDA receptors may increase neurogenesis by inducing a larger proportion of SGL astrocytes to undergo mitosis. As suggested for the adrenalectomy case, astrocytes may regulate their proliferation based on the levels of extracellular glutamate.

Seizures have a profound effect on dentate gyrus neurogenesis. Status epilepticus induced by pilocarpine injection, results in a dramatic increase in proliferation 3 days after treatment and a transient increase in new neurons 28 days after seizures [20]. The majority of these new neurons are found in the GCL, their normal location. However, a significant number of the new neurons formed following pilocarpine-induced seizures are found in ectopic locations. It is not clear how seizure activity alters the proliferation rates in the SGL or whether astrocytes are involved in this response. If astrocytes increase their proliferation

after seizures, it will be interesting to determine how long it takes for these cells to respond. If the high level of activity in the GCL during seizures is what causes the increase in proliferation, then a mechanism must exist for SGL progenitors to detect activity changes in the GCL. Perhaps SGL astrocytes sense either in activity or changes in extracellular glutamate levels as a consequence of convulsions.

Ischemia also has a marked effect on hippocampal neurogenesis. Transient global ischemia increases proliferation in the SGL by 12-fold between 6 and 11 days after surgery. There is a threefold increase in the number of new neurons 28 days after the last BrdU injection [18]. Interestingly, it has been shown that some of the effects of ischemia on the brain may be mediated by NMDA and AMPA receptors [40,41]. Moreover, 1 week after ischemia the binding of glutamate to NMDA and AMPA receptors is decreased by 20 and 40%, respectively [41]. It is not clear from the previous report if the decrease in binding is due to down-regulation of receptor numbers or a decrease in ligand-binding affinity. However, when NMDA receptor blockers were administered before causing global ischemia, the previously seen increase on proliferation was eliminated and proliferation rates remained similar to those of controls [40,42]. These reports are consistent with the idea that extracellular levels of glutamate in the GCL may regulate proliferation rates in the SGL.

Proliferation in the SGL is also increased during the afternoon of proestrus in the rat, when estrogens levels are at their highest [19]. Accordingly, ovariectomy decreases proliferation, and estrogens increase neurogenesis in the dentate gyrus [19]. In the afternoon of the proestrus there is an increase of GFAP immunoreactivity specifically in dentate gyrus astrocytes but not in the number of astrocytes [43]. Whether the effects of estrogens on proliferation are exerted directly on the progenitors via the estrogen receptors or indirectly through other receptor systems is unclear. However, it is known that estrogen treatment causes an increase in NMDA receptor density in granule neurons of the dentate gyrus [44,45]. Interestingly, NMDA receptor antagonists block estrogen-mediated increases on synaptogenesis [46,47]. It would be important to test if the increase in NMDA receptor density caused by estrogen is mediating the effects on neurogenesis. Also, it will be interesting to determine if estrogens have an effect on the firing rate of GCL neurons and on the extracellular levels of glutamate. As with other manipulations described above, changes in activity and extracellular glutamate levels in the GCL could be correlated with changes in the proliferation rate of SGL progenitors.

Interestingly, the effects of estrogens on SGL cell proliferation are modulated by serotonin (5-HT) [23] and serotonin regulates the release of glutamate via NMDA receptors [35]. Depleting 5-HT increases the extracellular levels of glutamate [35]. Thus, changes in glutamate released from granule neurons may signal astrocytes to proliferate. Alternatively, SGL astrocytes may directly sense serotonin levels since they express the 1A and 2A receptors [48,49].

Other treatments that affect proliferation of SGL cells include chronic morphine administration or lithium administration. Chronic morphine administration reduces the rates of proliferation by 28% [24] and reduces, at longer survivals, the total number of new neurons by approximately the same proportion. It has been shown that chronic morphine

administration inhibits DNA synthesis in astrocytes through a Ca^{2+} -dependent mechanism [50]. Therefore, chronic morphine administration may directly act on SGL astrocytes and inhibit their proliferation. Alternatively, morphine may alter the levels of granule cells firing and indirectly affect proliferation of SGL progenitors.

Lithium administration increases SGL proliferation by 25% but does not change the total number of new neurons [25]. Again the effects of lithium on proliferation could be mediated by glutamate, as lithium has been shown to modulate glutamate release through an NMDA-mediated calcium release mechanism [51].

It is not known how the different SGL cell types are affected by the different experimental paradigms described above. They may affect the proliferation of SGL astrocytes, D cells or both. Alternatively, the effects may not be on proliferation per se, but on the survival of the progenitors that have divided. We assume that many if not all the proliferative responses described above involve SGL astrocytes, as these cells seem to play a primordial role in SGL neurogenesis (see Section 2). It is therefore likely that a common mechanism exists to regulate the initiation of neurogenic events in the SGL. More research is required to identify the common factors that mediate changes in proliferation of SGL precursors. As stated above, changes in activity and/or in glutamate levels in the GCL are part of many, if not all, the experimental interventions considered. Perhaps astrocytes, in addition to their function as progenitors (described in Section 2) also play an important role as sensors of activity or of glutamate levels. In the next section we propose a model of radial regulation of neurogenesis in the GCL mediated by SGL astrocytes.

4. Radial regulation of adult neurogenesis; a hypothesis

As reviewed above, proliferation and neuronal recruitment in the adult dentate gyrus can be altered by adrenal steroids [15,28], the blockade of NMDA receptors [33], estrogen [19], seizures [17,20], ischemia [18], serotonin [23], opiate [24] and lithium administration [25]. Although all these treatments probably have different modes of action, they may all result in changes in granule neuron activity and/or their extracellular microenvironment within the GCL, which in turn may alter the proliferation of neuronal precursors in the SGL. Thus, we propose that changes in the activity of granule neurons may result in changing levels of extracellular glutamate and/or concentrations of ions that in turn stimulate germinal astrocytes to proliferate and concomitantly produce more neurons. The anatomy of SGL astrocytes is well suited for this role. SGL astrocytes have a long radial process with multiple branches that contact granule neurons within a radial array. The proliferative activity of individual SGL astrocytes may be regulated by the levels of activity within a column of granule neurons near their radial process.

Astrocytes have been considered subordinates in the brain hierarchy, supporting neurons physically and metabolically. But, increasing evidence indicates that astrocytes play an active role in the regulation and modulation of synaptic transmission ([52]; [53] and references therein). The traditional view is that astrocytes have essential roles in the creation of the local microenvironment to support neuronal function. It is well established that Astrocytes reuptake and inactivate neurotransmitters from the synaptic cleft and maintain

the ionic (i.e. Na^+ , Ca^{2+} , K^+ , Cl^- , HCO_3^-) homeostasis of extracellular spaces [54]. Ionic environment or extracellular neurotransmitters levels change as a consequence of local neuronal activation. Neuronal activity may modulate SGL neurogenesis by essentially similar processes. We propose that the ability of astrocytes to sense and modulate environments around neurons, may also serve to regulate their proliferation and the levels of neurogenesis in the SGL.

These support functions are likely linked to the origin of astrocytes and their functional homology to the primitive neuroepithelial cell [55]. Neuroepithelial cells transform during development into radial glia. Later in development, the radial glia transform into astrocytes [56]. The link between radial glia and astrocytes has also been established for the hippocampus; SGL astrocytes, the cells that function as the stem cells in the adult hippocampus (see Section 2), correspond to transformed and displaced radial glia [57,58]. Traditionally, radial glia and astrocytes have been thought of as members of a glial lineage [59]. However, other work suggests that neural stem cells may be contained within the neuroepithelium-radial glia-astrocytes lineage [60]. In birds, where neurogenesis continues in the telencephalon throughout life [3], radial glia are retained in the adult germinal centers and appear to function as the primary precursors [4]. In mammals, it was recently shown that radial glia give rise to neurons during cortical development [61,62]. Thus, radial glia, a complex cell with a prominent process, seem to have the ability to generate new neurons.

We propose here that the elaborate radial process of radial SGL astrocytes in the adult hippocampus may signal the cell body to generate progeny according to signals emerging in the GCL. The nature of these signals may be related to the normal function of astrocytes as scavengers of extracellular metabolites excreted by neurons. This same idea may apply to radial glia during development. Their radial processes frequently traverses territories where new neurons will ultimately reside. Radial cell processes may sense this microenvironment and adjust their proliferation accordingly. It is remarkable how elaborate the structure of radial glial cells and astrocytes in the SGL is. This is likely a reflection of the complex set of structural and metabolic duties they carry. This is not what would be expected for primary undifferentiated progenitor cells. How these cells combined their structural and metabolic support functions and at the same time serve as neural stem cells remains an interesting and important question for future research. Equally important is to determine how germinal astrocytes may differ from other astrocytes in the adult brain. Hippocampal dysfunction has been linked to depression, schizophrenia, intractable temporal lobe seizures and other disorders. Some of the experimental paradigms discussed above (Table 1) have been used to treat such disorders. It is interesting that these same manipulations alter the rate of proliferation in the SGL. Knowing the identity of the GCL stem cells and their mode of interaction with mature granule cells will be essential to understand how neurogenesis is regulated in the adult hippocampus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Astrocytes as stem cells in the adult hippocampus. (A) Cross section of the adult mouse brain at the level of the hippocampus (upper left), schematic illustration of the composition and architecture of the SGL and granule cell layer (expanded inset). SGL astrocytes (B cells) have long radial processes that penetrate the granule cell layer and short tangential ones that run parallel to the blades of the dentate gyrus. (A (inset), B) Proposed lineage in the adult dentate gyrus. Dividing B cells generate immature, dark cells (D cells) that divide and become granule neurons (G) [14]. D cells develop a branched apical process that becomes the dendritic arbor of a new granule neuron (G). SGL astrocytes: B cells (gray cytoplasm, black nucleus); D cells (black cytoplasm, gray nucleus). G: mature granule neuron (dotted, not filled). (C) Granule neurons labeled with alkaline phosphatase 30 days after infecting Gtva mice with RCAS-AP. Scale bar: 10 μ m.

Table 1

Experimental paradigms that affect neurogenesis in the adult hippocampus

Treatment	Effect of treatment	Proliferation (short survival)	Survival/ recruitment of new neurons (long survival)	Refs.
NMDA receptor antagonists	Decreases extracellular glutamate	Increase	Increase	[33–36,38]
NMDA administration	Increases extracellular glutamate	Decrease	Not determined	[33]
Adrenal hormones	Increases extracellular glutamate	Decrease	Decrease	[19,28–31]
Estrogen	Decreases extracellular glutamate via increase in NMDA receptors number	Increase (transient) in females in proestrus	No change	[19,23,43–47]
Seizures	NMDA receptor hyperactivation	Increase	Transient increase within 28d	[20]
Ischemia	NMDA receptor hyperactivation	Increase	Increase	[40–42,18]
Serotonin depletion	Increases extracellular glutamate	Decrease	Not determined	[23,35,48,49]
Opioids (morphine)	Anti-mitogenic to astrocytes	Decrease	Decrease	[24,50]
Lithium	NMDA receptor-mediated Ca^{2+} release	Increase	Not determined	[25,51]