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ERRATUM

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ORIGINAL PAPER

GABA and glutamate signaling: homeostatic control of adult forebrain neurogenesis

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Abstract The neurotransmitter GABA exerts a strong negative influence on the production of adult-born olfactory bulb interneurons via tightly regulated, non-synaptic GABAergic signaling. After discussing some findings on GABAergic signaling in the neurogenic subventricular zone (SVZ), we provide data suggesting ambient GABA clearance via two GABA transporter subtypes and further support for a non-vesicular mechanism of GABA release from neuroblasts. While GABA works in cooperation with the neurotransmitter glutamate during embryonic cortical development, the role of glutamate in adult forebrain neurogenesis remains obscure. Only one of the eight metabotropic glutamate receptors (mGluRs), mGluR5, has been reported to tonically increase the number of proliferative SVZ cells in vivo, suggesting a local source of glutamate in the SVZ. We show here that glutamate antibodies strongly label subventricular zone (SVZ) astrocytes, some of which are stem cells. We also show that some SVZ neuroblasts express one of the ionotropic glutamate receptors, AMPA/kainate receptors, earlier than previously thought. Collectively, these findings suggest that neuroblast-to-astrocyte GABAergic signaling may cooperate with astrocyte-to-neuroblast glutamatergic signaling to provide strong homeostatic control on the production of adult-born olfactory bulb interneurons.

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Introduction

The production of adult born neurons persists in two brain regions, the subventricular zone (SVZ, also called subependymal layer (Boulder Committee 1970)) and the dentate gyrus subgranular zone (SGZ) in the hippocampus. The SVZ contains the largest pool of dividing neural stem cells (NSCs) in the adult mammalian brain, including in humans (Sanai et al. 2004; Curtis et al. 2007). Division of NSCs generate transit amplifying cells, which in turn divide to give rise to neuroblasts (Doetsch et al. 1999a). These latter cells migrate along the rostral migratory stream (RMS) to the olfactory bulb where they differentiate into interneurons (Bryans 1959; Altman 1969; Luskin 1993; Swarzenski et al. 1996). Adult-born neuron production is an ongoing process. Estimates suggest that 10,000–30,000 neurons migrate to the olfactory bulb every day (Lledo et al. 2006). This high turnover rate necessitates profound homeostatic control mechanisms at the level of NSCs, and their proliferative and migrating neuroblasts. Homeostatic mechanisms provide a balance between proliferation, migration and survival of stem cells and neuroblasts in the adult neurogenic microenvironment (also called niche) to achieve adequate adult born neuron production. Improving our understanding of these control mechanisms will move us one step closer to promoting self-repair in the adult-injured brain.

The adult neurogenic niche contains many factors that control neural stem cell (NSCs) and neuroblast prolifera-

tion and migration (Hagg 2005). One of these factors, the neurotransmitter GABA, plays critical roles on the different steps of adult neurogenesis. GABA decreases the proliferation of NSCs and neuroblasts (Nguyen et al. 2003; Liu et al. 2005) while also reducing neuroblast migration rate (Bolteus and Bordey 2004). GABA thus exerts a negative influence on neuroblast production. During embryonic neurogenesis another neurotransmitter glutamate works in cooperation with GABA to control cortical development (for review see Owens and Kriegstein 2002; Schlett 2006). However, the role of glutamate in adult forebrain neurogenesis remains obscure. It is also unknown whether glutamate could cooperate with GABA to provide homeostatic control on adult-born neuron production.

Here we review the recent findings that GABAergic signaling in the SVZ and RMS plays an important role during adult neurogenesis. We also highlight questions that remain to be addressed. We then discuss published data suggesting the existence of glutamatergic signaling in the SVZ and present new data on the presence of AMPA/kainate-type glutamate receptors in neuroblasts. Finally, we discuss possible interactions between GABA and glutamate signaling that provide homeostatic control of adult neurogenesis.

Materials and methods

Immunohistochemistry

50–100 μm-thick slices were obtained from CD1 or C57Bl6 mice that were 24–30 days old. Free-floating sections were blocked (PBS + 0.3% Triton X100 + 2% BSA + /– 0.3% Tween-20) and incubated in the following primary antibodies for 2 h at RT or overnight at 4°C: goat anti-doublecortin (1:100, Santa Cruz, USA), guinea pig anti-glutamate-aspartate transporter (GLAST, 1:500, Chemicon, USA), mouse anti-glutamate (1:2000, Sigma, USA) (Platel et al. 2005), rabbit anti-GABA (1:500, Sigma, USA), rabbit anti-GAT1 (1:100, Chemicon, USA), and mouse anti-VGAT (1:1000, Synaptic Systems, Germany). After several washes, slices were incubated with the appropriate secondary antibody (Alexa Fluor series at 1:1000, Invitrogen, USA; or Cyanine series at 1:500, Jackson Labs) for 1 h at room temperature. Images were acquired on an Olympus FluoView 300 confocal microscope.

Calcium imaging

Acute slices were loaded (45 min at 37°C) with the Ca^{2+}-sensitive dyes Fluo 4 AM or Oregon Green BAPTA 1-AM (4–5 μM in 0.1% DMSO with 0.02% Pluronic acid F-127), then washed for at least 30 min before imaging. Acute brain slices containing the SVZ or RMS were prepared as previously described (Wang et al. 2003). Ca^{2+} imaging experiments were performed on an Olympus Fluoview 300 confocal microscope equipped with a 60× objective. The frequency of cytosolic Ca^{2+} increases was calculated using Calsignal written by JCP (Platel et al. 2007). Images were acquired every 1.16–6 s. F_0 (i.e. baseline) is the mean fluorescence intensity of all of the regions of interest, and F is the mean fluorescence intensity in a single cell. A change in fluorescence was considered to be a Ca^{2+} increase if it was superior to 15% F/F_0 increase. Kainate was applied by pressure (Picospritzer II, General Valves) while DNQX was bath applied. Data are expressed as mean ± standard error. Statistical analysis used a two-tailed *t*-test except where noted.

Cell organization and identity in the neurogenic forebrain

The SVZ-ependymal region contains at least four different cell types defined by their morphology, ultrastructure, and molecular markers (Smart 1961; Altman 1963, 1969; Blakemore 1969; Privat and Leblond 1972; Kishi 1987; Sucher and Deitcher 1995; Lois et al. 1996; Jankovski and Sotelo 1996; Doetsch et al. 1997; Peretto et al. 1997; Mercier et al. 2002). Neuroblasts (also called type A cells (Lois et al. 1996)) migrate in chains to the olfactory bulb along the rostral migratory stream (RMS). Cells that express glial fibrillary acidic protein (GFAP, also called type B cells (Lois et al. 1996) or SVZ astrocytes (Doetsch et al. 1999a)) ensheath the chains of migrating neuroblasts and display several features of mature astrocytes (Liu et al. 2006b). Scattered, highly proliferative progenitors (transit amplifying cells or type C cells) form clusters next to the neuroblasts. The SVZ is separated from the ventricular cavity by a layer of ependymal cells. Immunohistochemical studies have revealed that a cluster of 3–5 neuroblasts is tightly encapsulated by one or two astrocytes in a coronal plane (Lois et al. 1996; Peretto et al. 1997; Bolteus and Bordey 2004) (Fig. 1A–C). Based on electron microscopy data, the extracellular space between neuroblasts or between neuroblasts and astrocytes is ~20–50 nm (Doetsch et al. 1997; Peretto et al. 1999). Although this distance is on the same order as that of the synaptic cleft, synapses are absent between SVZ cells (Doetsch et al. 1997; Liu et al. 2005). This arrangement and cell:cell proximity lend itself to a nonsynaptic signaling between neuroblast:neuroblast and neuroblast:astrocyte.

SVZ astrocytes have stem cell attributes, including self-renewal and multipotency (Chiasson et al. 1999; Doetsch et al. 1999a; Laywell et al. 2000; Capela and Temple 2002;

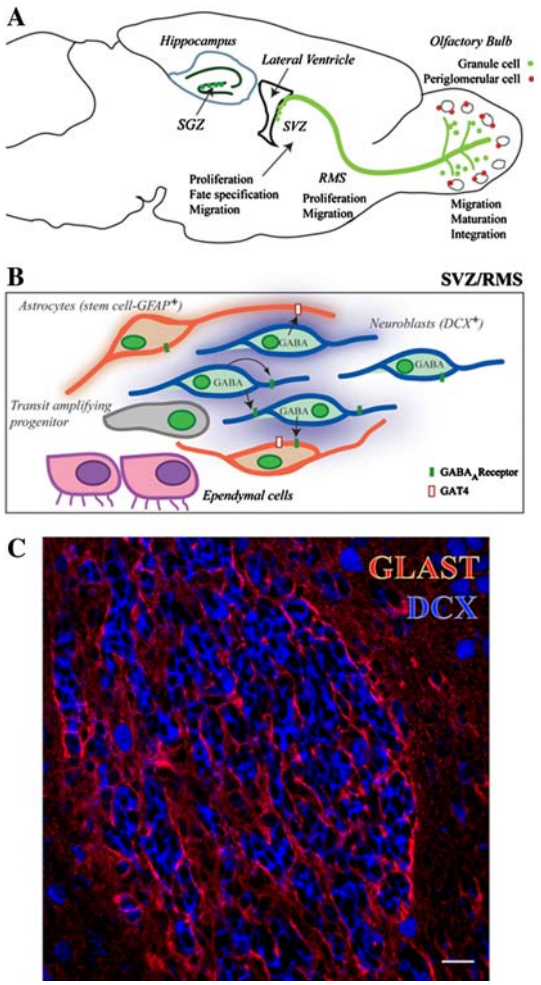

Fig. 1 Organizations of the adult subventricular zone. (**A**) Diagram of a sagittal rodent brain section illustrating the two neurogenic regions, the SVZ/olfactory system and the hippocampal subgranular zone (SGZ). In the SVZ, neuroblasts are continually generated and migrate as chains (not illustrated) throughout the SVZ, enter the RMS and differentiate into interneurons in the olfactory bulb (OB), including granule cells (green) and periglomerular cells (red). The different stages of neurogenesis are marked along the migratory path of the neuroblasts. The SGZ is located at the base of the granule cell layer in the hilus of the dentate gyrus (DG). (**B**) Diagram illustrating the cellular organization in the SVZ/RMS. SVZ/RMS neuroblasts (blue) that express doublecortin (DCX) and migrate to the olfactory bulb are ensheathed by astrocytes (red). Ependymal cells (purple) line the wall of the lateral ventricle in the SVZ. Scattered transit amplifying progenitors (grey) are present along the SVZ and RMS. Astrocytes express GFAP and constitute a pool of neural stem cells. GABA released from neuroblasts diffuses and activates $GABA_A$ receptors (green rectangles) in neuroblasts as well as astrocytes. GABA is also taken up by GABA transporters GAT4 (mouse) in astrocytes and GAT1 in neuroblasts if these latter are funcitonal. (**C**) Confocal microscopy photograph illustrating the cellular organization in the RMS: astrocytes labeled by GLAST antibodies (red) ensheath clusters of neuroblasts labeled by DCX antibodies (blue) in a coronal section. Scale bar: 20 μm

Doetsch et al. 2002; Garcia et al. 2004). It remains unclear whether every SVZ astrocyte can behave as a stem cell. Nevertheless, here we will refer to SVZ astrocytes as NSCs acknowledging that only a subpopulation of SVZ or RMS astrocytes may have stem cell features.

GABA signaling molecules in the SVZ and RMS

The SVZ represents a local GABAergic network where GABA, synthesized and released by neuroblasts, provides paracrine (i.e. nonsynaptic) signaling both between neuroblasts (Stewart et al. 2002; Wang et al. 2003; Nguyen et al. 2003; Bolteus and Bordey 2004) and from neuroblasts to NSCs (Liu et al. 2005) (see diagram in Fig. 1B and GABA immunostaining in Fig. 2A). Briefly, neuroblasts release GABA via an unknown Ca^{2+}-dependent mechanism (Liu et al. 2005). Liu et al. showed that GABA released from neuroblasts was independent of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, which is the minimum machinery required for exocytosis. $GABA_A$ receptors are expressed on both NSCs (Liu et al. 2005) and neuroblasts (Wang et al. 2003). GABA released either spontaneously or following electrical activation of SVZ cells activates GABA receptors in surrounding neuroblasts and NSCs (Bolteus and Bordey 2004; Liu et al. 2005). Once released GABA is taken up into astrocytes via high affinity GABA transporters, GAT4 (Bolteus and Bordey 2004). Thus, GABA signaling molecules are expressed in the SVZ and RMS, suggesting the presence of a tightly regulated GABAergic signaling in the SVZ and RMS. However, key pieces of the puzzle are missing, including GABA release mechanisms, the presence of signaling molecules in transit amplifying cells, and the presence of $GABA_B$ receptors in SVZ cells.

Our new data suggest that vesicular GABA transporters, VGATs, are absent from RMS and SVZ cells (Fig. 2B). This finding is consistent with the lack of the SNARE complex and synapsin 1 in neuroblasts (Liu et al. 2005). Here we show using immunostaining that another high affinity GABA transporter, GAT1, is also expressed in the SVZ and RMS in GLAST-negative cells, which are likely neuroblasts (Fig. 2C). It is, however, unknown whether these transporters are functional and work in reverse, thus contributing to GABA release as previously reported for other cell types (Cammack and Schwartz 1993; Cammack et al. 1994). One way to address this question is to acutely isolate neuroblasts and use a ''sniffer'' patch, which consists of an outside-out patch from a $GABA_A$ receptor-expressing cell, to examine whether spontaneous GABA release can be detected from neuroblasts. Liu et al. (2005) used a variation of this method. First, they lifted a neuroblast from an acute slice after obtaining a cell-attached recording. They then moved a ''sniffer'' patch obtained from either a nearby astrocyte or a striatal neuron to detect GABA release from the neuroblast. If spontaneous release

Fig. 2 Expression of GABA signaling molecules in the SVZ. (**A**) GABA immunostaining (green) in the SVZ shows the presence of GABA in some SVZ cells, but not in GLAST-positive cells (red, i.e. astrocytes). (**B**) Immunolabeling for vesicular GABA transporters, VGATs (green), is sparse or non-existent in SVZ cells. Prominent punctate labeling, by contrast, is observed in the striatum in the left of the panel. (**C**) Positive labeling for the GABA transporter GAT1 (green) in the SVZ is observed mainly in cells that do not stain positive for GLAST (red). Scale bars: 10 μm

was not detected, they electrically depolarized the cell-attached neuroblast to induce GABA release. Although this method is efficient at monitoring GABA release, it is technically more challenging than acutely dissociating neuroblasts. The presence of $GABA_B$ receptors in SVZ cells also remains unclear and need to be examined using immunostaining and functional assays such as perforated patch clamp recordings or calcium imaging.

Is GABA release from neuroblasts dynamic and regulated by other microenvionmental signals? GABA release is Ca^{2+}-dependent and may thus be regulated by factors increasing intracellular Ca^{2+} in migrating neuroblasts. Migrating neuroblasts display spontaneous high frequency Ca^{2+} transients (Fig. 3). In acute slices loaded with the calcium indicator Oregon Green BAPTA 1-AM, 61% of the cells in the RMS displayed spontaneous Ca^{2+} transients at a mean frequency of 15.5 peaks per hour. It is, however, unknown whether these Ca^{2+} transients are intrinsic, regulated or induced by microenvironmental factors. The neurotransmitter glutamate is a good candidate for regulating Ca^{2+} activity (see below). It is also possible that the cerebrospinal fluid gradient of Slit (Sawamoto et al. 2006) contributes to regulation of Ca^{2+} dynamics in migrating SVZ neuroblasts, as shown in migrating cerebellar granule cell precursor (Xu et al. 2004). Intracellular Ca^{2+} activity determines the state of excitability of migrating neuroblasts that are not able to generate action potentials while migrating in the SVZ and RMS. The properties of the Ca^{2+} activity in migrating neuroblasts have not yet been reported in the neurogenic forebrain, however, we are presently exploring this issue.

GABA: a negative regulator of neuroblast production in the SVZ

Functionally, $GABA_A$ receptor activation in neuroblasts results in a reduction of their speed of migration in the proximal RMS (Bolteus and Bordey 2004) and also the number of proliferative SVZ neuroblasts (Nguyen et al. 2003). It was at first surprising to find that ambient GABA decreased the speed of neuroblast migration in acute sagittal slices. However, two recent studies provide some additional support for this finding. Heck et al. (2007) found that application of the $GABA_A$ receptor antagonist, bicuculline, induced an increase in the migration speed of cortical neurons in organotypic neocortical slices from embryonic day 18–19. This increase in speed resulted in aberrant accumulation of neurons in the upper cortical layers. In the second study, Gascon et al. (2006) showed that GABA regulates dendritic growth in cultured neuroblasts from the SVZ or in acute slices. In particular, bicuculline promoted the rapid stabilization of new dendritic segments. The inhibitory effect of GABA on the speed of neuroblast migration may thus be due to a stabilization of their processes resulting in a loss of motility. GABA does not only alter the behavior of neuroblasts, but it was also shown to reduce the number of proliferative NSCs via tonic $GABA_A$ receptor activation (Liu et al. 2005). GABA's effect on NSC proliferation is reminiscent of the studies showing that tonic $GABA_A$ receptor activation limits the proliferation of cortical radial glia (LoTurco et al. 1995; Haydar et al. 2000). In addition, the functions of GABA on adult neurogenesis integrate well with the tight correlation between the behavior of NSCs and neuroblasts; local GABA signaling provides information to NSCs about the size of the neuroblast pool. As more neuroblasts are generated, more GABA is expected to be released into the extracellular space, resulting in increased $GABA_A$ receptor activation in NSCs. Since astrocytes generate neuroblasts (Doetsch et al. 1999a), an increase in the number of neuroblasts seems to serve as a negative feedback control of astrocyte proliferation and therefore neuroblast production. This negative feedback reconciles well with the constant migration of neuroblasts to the olfactory bulb, which would

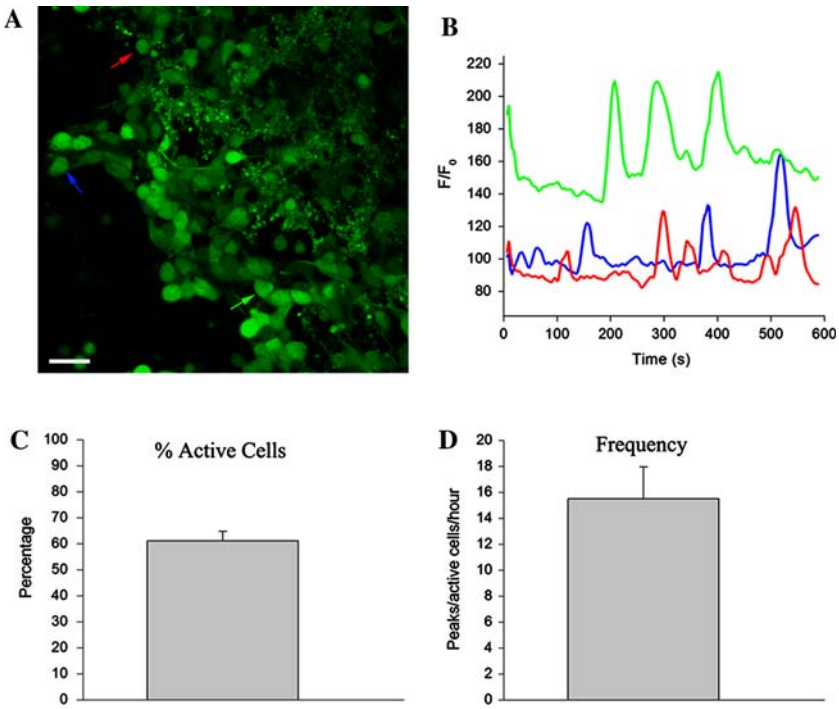

Fig. 3 Neuroblasts display spontaneous Ca^{2+} transients. (**A**) Image of a confocal section displaying Oregon Green loading in an acute coronal slice containing the RMS. Cells denoted by arrows (red, blue, and green) exhibit spontaneous Ca^{2+} activity as shown in (B). (**B**) Ca^{2+} activity graphs of cells shown in (A). (**C–D**) Bar graphs of the percentage of cells displaying spontaneous Ca^{2+} transients (C) and of the frequency of these transients (D) in 3 slices. 31 to 65 cells were analyzed per slice (mean of 51.3, $n = 3$)

limit ambient GABA accumulation in the SVZ, and with increased proliferation of astrocytes following elimination of neuroblasts (Doetsch et al. 1999b).

Local glutamatergic signaling in the neurogenic forebrain

One candidate molecule to counteract the inhibitory effect of GABA on progenitor proliferation and neuroblast migration is the neurotransmitter glutamate. Based on published data and new data presented here we propose that glutamatergic and GABAergic signaling maintains homeostasis of the production of adult born neurons. We will address this issue by discussing the two following questions. First, does glutamatergic signaling exist in the SVZ and RMS? Second, what are the functions of the different glutamate receptors on adult neurogenesis?

The existence of glutamatergic signaling requires identification of source cells that release glutamate, target cells that express glutamate receptors, and removal mechanisms to limit extracellular glutamate accumulation and receptor desensitization. Among the possible sources of glutamate, we favor NSCs. NSCs display astrocytic properties (Liu et al. 2006b) and mature astrocytes release glutamate via several mechanisms (Evanko et al. 2004). Nevertheless, it is possible that ependymal cells, which in many ways resemble astrocytes (Liu et al. 2006b), release glutamate as well. It is unlikely that neuroblasts, which are GABAergic (Bolteus and Bordey 2004; Liu et al. 2005), release glutamate although immature cells may transiently release both glutamate and GABA (Gutierrez 2005). We thus performed immunostaining for glutamate as previously described (Platel et al. 2005). Figure 4A shows that glutamate antibodies strongly labeled SVZ astrocytes while weakly labeled neuroblasts. Astrocytes and neuroblasts were identified by GLAST and doublecortin (DCX) immunostaining, respectively (Braun et al. 2003a; Liu et al. 2006a). SVZ astrocytes may thus be a source of glutamate. Very little is known about glutamate receptor expression in the SVZ or RMS. Glutamatergic signals are conveyed by different glutamate (Glu) receptor subtypes, namely ionotropic NMDA and non-NMDA or AMPA/kainate subtypes (Sommer and Seeburg 1992; Hollmann and Heinemann 1994) and metabotropic (mGlu; group-I–III subtypes (Pin and Duvoisin 1995; Conn and Pin 1997; Cartmell and Schoepp 2000)). Regarding NSCs, our recent study suggests that they do not express functional AMPA or NMDA receptors as shown using patch clamp recordings of SVZ astrocytes (Liu et al. 2006b). It remains unclear whether NSCs express mGluRs. Regarding neuroblasts, it is thought that they do not express AMPA and NMDA receptors until they enter the granule cell layer of the olfactory bulb (Carleton et al. 2003). However, our recent data suggest that some neuroblasts begin expressing functional AMPA/kainate receptors in the SVZ (Fig. 4B–D). To optimize our detection of AMPA receptors, kainate was applied at 300 μM. At this concentration, kainate produces incompletely desensitizing activation of AMPA receptors (Huettner 1990; Lerma et al. 1993) but would lead to

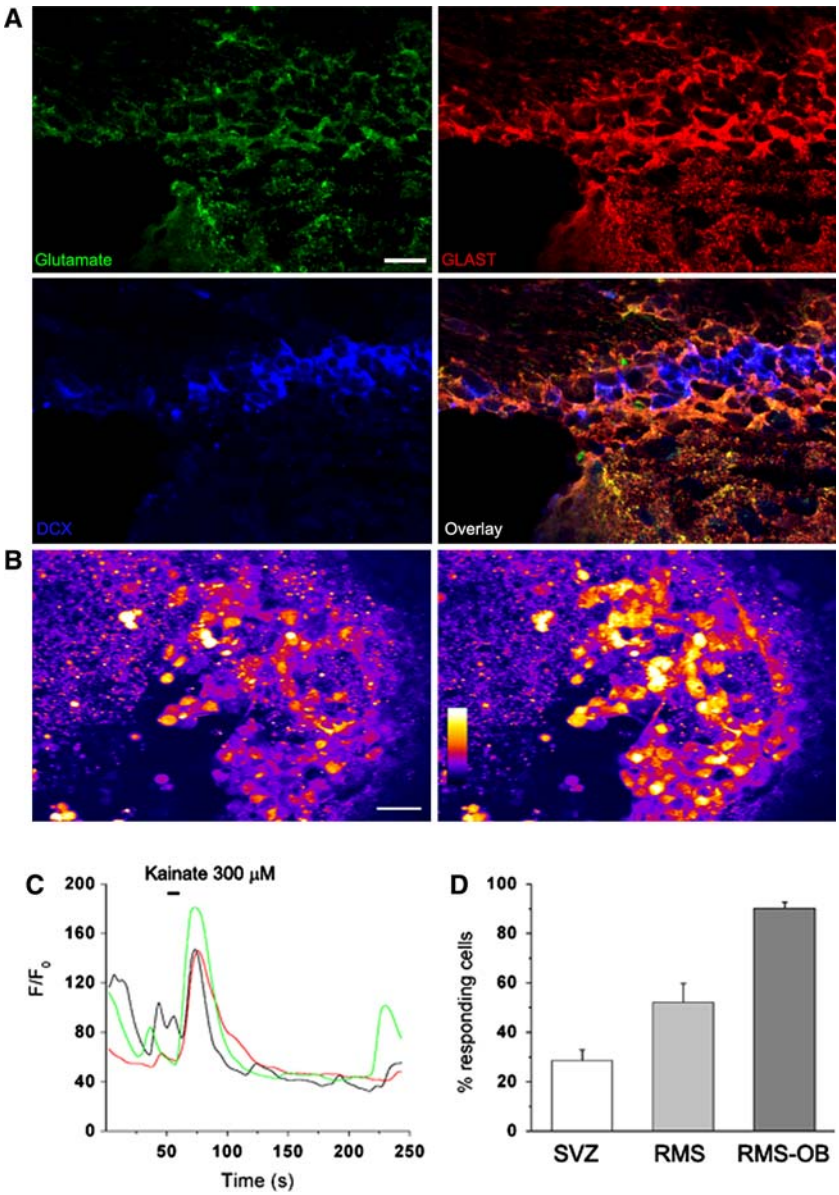

Fig. 4 Astrocytes contain glutamate while neuroblasts express AMPA-type glutamate receptors. (**A**) Image of a confocal section displaying co-immunostaining for glutamate (green), GLAST (red), and DCX (blue) in the SVZ. Scale bar: 10 µm. (**B**) Images of an acute slice containing the RMS-OB and loaded with Fluo 4-AM. Image before (left panel) and after (right panel) application of kainate (300 µM, 10 s). In this slice, 85% of the cells responded to kainate suggesting the functional expression of AMPA receptors in RMS cells. The slice was made from a postnatal day 25 mouse. (**C**) Ca^{2+} activity traces of three representative cells showing some spontaneous activity and Ca^{2+} increases in response to kainate application. (**D**) Bar graphs of the percentage of cells responding to kainate application as a function of their location along the rostro-caudal axis, i.e. SVZ, RMS, and RMS of the OB (RMS-OB). An increasing percentage of neuroblasts acquire functional AMPA receptors during migration to the OB

desensitization of kainate receptors. Kainate was pressure applied for 10 s onto SVZ and RMS cells in acute brain slices and intracellular Ca^{2+} concentration was monitored with Fluo 4 fluorescence. Kainate significantly increased intracellular Ca^{2+} in 29 ± 4% of the SVZ cells (Fig. 4C, $n = 6$ slices). About 90% of the kainate-induced Ca^{2+} increases in the SVZ was blocked by the competitive AMPA/kainate receptor antagonist DNQX (60 µM). The large percentage of cells responding to kainate and their morphology suggest that some of the responding cells are neuroblasts. We observed a progressive increase in the number of cells responding to kainate application along the rostral-caudal axis. In the RMS, 52 ± 10% of the cells ($n = 4$) responded to kainate while nearly all of the cells responded to kainate (90 ± 2%, $n = 3$) in the RMS of the olfactory bulb. A study also reported that 40–60% of progenitors examined 16 h after plating neurospheres from neonatal rat SVZ expressed functional AMPA, kainate and NMDA receptors (Brazel et al. 2005). It is, however, difficult to extrapolate data obtained from plated neurospheres because the culture medium contains growth factors, which may affect the differentiation of neuroblasts. Using immunostaining, it was reported that mGluR5 (group I subtype coupled to phospholipase C and IP3-regulated intracellular stores) are expressed in the postnatal SVZ (Di Giorgi Gerevini et al. 2004). However, it is not known which cell types express these receptors. In addition, the mGluR3 agonist, N-acetylaspartylglutamate, induced Ca^{2+} increases in 45% of cultured cells from SVZ neurospheres (Brazel et al. 2005). Finally, glutamate receptor expression

in transit amplifying cells has not been explored. Once released, glutamate is not degraded in the extracellular space but needs to be taken up into cells. Extracellular glutamate levels are regulated by high affinity transporters named EAAT1 (GLAST), EAAT2 (GLT-1), EAAT3-5 in human (rodent homologs, Palacin et al. 1998). NSCs in the SVZ express GLAST and GLT-1 (Braun et al. 2003b; Bolteus and Bordey 2004). It remains unknown whether neuroblasts and transit amplifying cells express some of the other glutamate transporters.

Glutamate: a positive regulator of adult neurogenesis

Only one study thus far has examined the effect of glutamate receptor inhibition on the number of dividing cells in the SVZ in vivo. Di Giorgi-Gerevini et al. (2005) reported that adult mice lacking mGluR5 or treated with mGluR5 antagonists showed a dramatic reduction in the number of proliferating cells in the SVZ (Giorgi-Gerevini et al. 2005). This in vivo study shows that mGluR5 are tonically activated by ambient glutamate suggesting a local source of glutamate in the SVZ consistent with our strong immunoreactivity in SVZ astrocytes (see Fig. 4). The authors also used neurospheres from the forebrain of embryonic day 20 mice making comparison with in vivo data difficult. Using cultured SVZ cells plated from perinatal SVZ neurospheres, Brazel et al. (2005) showed that group II mGluR stimulation for 24 h reduced basal level of apoptosis and increased the proliferation of presumably transit amplifying cells, but did not increase the NSC pool. They also showed that kainate and glutamate increased cell proliferation and reduced the level of apoptosis, but only when NMDA receptors were blocked. From these findings, glutamate may exert a positive influence on adult forebrain neurogenesis by increasing the number of SVZ cells via mGluR activation. The function of AMPA receptors in neuroblasts remains unclear. AMPA receptors reduce DNA synthesis of presumably radial glia in acute embryonic neocortical slices (LoTurco et al. 1995). In other systems, AMPA receptor activation was reported to exert a positive proliferative effect (for review see Schlett 2006). Collectively, it can be speculated that glutamate acting at both ionotropic and metabotropic receptors positively affects the production of adult-born neurons.

Concluding remarks

Data discussed and presented here support the emerging idea that a homeostatic balance between GABA and glutamate signaling may be present even before synaptic transmission is established (Fig. 5). It may underlie

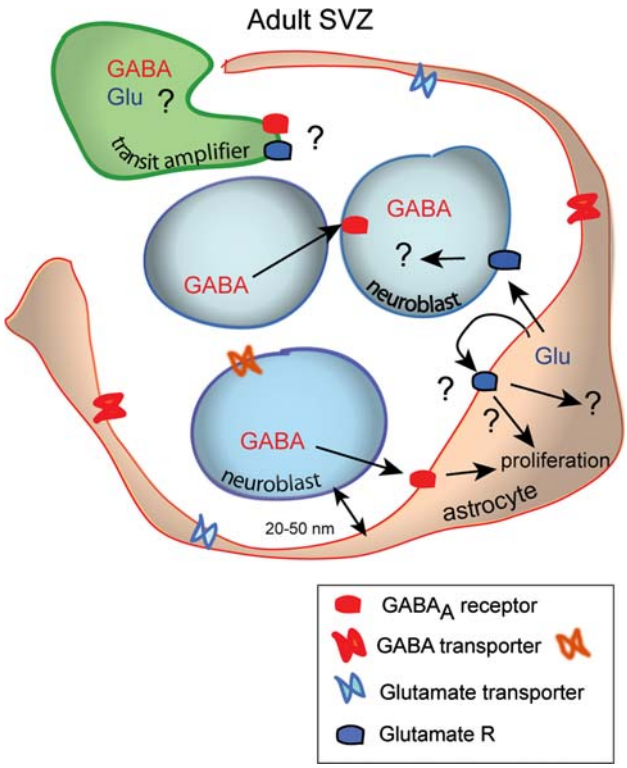

Fig. 5 Hypothetical model illustrating a homeostatic control of neuroblast production by GABA and glutamate. Neuroblasts express $GABA_A$ receptors and AMPA receptors in the SVZ and RMS. Neuroblasts release GABA that activates $GABA_A$ receptors on themselves and surrounding astrocytes. In turn, astrocytes surrounding neuroblasts release glutamate which may activate AMPA receptors on migrating neuroblasts. mGluRs are expressed in the SVZ but the identity of the cell bearing these receptors is unknown. $GABA_A$ receptor activation by ambient GABA leads to a decrease in the number of proliferative astrocytes and neuroblasts while mGluR activation by ambient glutamate induces an increase in the number of proliferative cells in the SVZ. The function of AMPA receptors in neuroblasts remains unknown

fundamental processes of adult neurogenesis, such as proliferation and survival of progenitor cells. Interactions between GABA and glutamate signaling likely occur on the different elements of signaling (i.e. release, receptor activation and uptake) leading to a homeostatic control of adult neurogenesis. For example, glutamate released from SVZ astrocytes may lead to Ca^{2+}-dependent GABA release from neuroblasts via AMPA receptor activation as previously reported in the embryonic intermediate zone (Poluch and Konig 2002). GABA is then expected to act as a negative feedback regulator of SVZ astrocyte proliferation. The diversity of glutamate receptors, as opposed to GABA receptors, allow for a fine control of the different steps of adult neurogenesis. Controls exerted on multiple stages of neuron production may limit an acute alteration of cell production (by e.g. gene mutations or damages) to significantly impair neurogenesis. Alternatively, a chronic

disruption of the homeostatic balance may profoundly affect neurogenesis and lead to NSC exhaustion or aberrant proliferation. Clinically, novel drugs affecting GABA and glutamate signaling molecules may prove to be relevant for therapeutic applications aimed at promoting cell replacement by endogenous progenitors during the course of neurodegenerative diseases.

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