Published in final edited form as:
Eur J Neurosci. 2011 March ; 33(6): 1123–1132. doi:10.1111/j.1460-9568.2011.07611.x.

Neurotransmitters couple brain activity to subventricular zone neurogenesis

Stephanie Z. Young, **M. Morgan Taylor**, and **Angélique Bordey**
Departments of Neurosurgery, and Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, CT 06520-8082.

Abstract

Adult neurogenesis occurs in two privileged microenvironments, the hippocampal subgranular zone of the dentate gyrus and the subventricular zone (SVZ) along the lateral ventricle. This review focuses on accumulating evidence suggesting that the activity of specific brain regions or bodily states influences SVZ cell proliferation and neurogenesis. Neuromodulators such as dopamine and serotonin have been shown to have long-range effects through neuronal projections into the SVZ. Local GABA and glutamate signaling have demonstrated effects on SVZ proliferation and neurogenesis, but an extra-niche source of these neurotransmitters remains to be explored and options will be discussed. There is also accumulating evidence that diseases and bodily states such as Alzheimer's disease, seizures, sleep, and pregnancy influence SVZ cell proliferation. With such complex behavior and environmentally-driven factors that control subregion-specific activity, it will become necessary to account for overlapping roles of multiple neurotransmitter systems on neurogenesis when developing cell therapies or drug treatments.

Introduction

Neurogenesis exists in two regions of the adult brain: the hippocampal subgranular zone of the dentate gyrus and the subventricular zone (SVZ) along the lateral ventricle. Neural stem cells are found in all mammalian species examined including humans, but the presence of neurogenesis in humans remains controversial (Curtis *et al*, 2007; Sanai *et al*, 2004). This review focuses on the SVZ, where neuroblasts are generated and are fate-committed to becoming granule or periglomerular interneurons in the olfactory bulb (OB).

Neurogenesis occurs in a privileged microenvironment called the neurogenic niche. In this niche, neurogenesis has long been thought to be protected from brain activities or states. However, accumulating evidence suggests that the activity of specific brain regions or bodily states can influence neurogenesis. For example, dopamine originating from neurons in the substantia nigra affects SVZ-OB neurogenesis (see references in the dopamine section). Environmental enrichment, which presumably activates several brain regions, also augments SVZ-OB neurogenesis (Rochefort *et al*, 2002). Environmental enrichment likely targets neurotransmitter systems and other signaling molecules including hormones and growth factors that have been shown to influence SVZ neurogenesis (for reviews see (Grote and Hannan, 2007; Hagg, 2005; Pathania *et al*, 2010)). In this review, we examine the action of neurotransmitters on neurogenesis and their effects on proliferation, migration, and survival of SVZ cells. We describe their local versus long-range signaling and how their signaling is affected by brain states. For each neurotransmitter system, we discuss evidence

Address for correspondence: Angélique Bordey, Ph.D. Department of Neurosurgery Yale University School of Medicine 333 Cedar Street, FMB 422 New Haven, CT 06520-8082 Phone: 203-737-2515 Fax: 203-737-2159 angelique.bordey@yale.edu.

and hypotheses that pathological states such as seizures and Parkinson's disease modulate neurogenesis, perhaps through alterations in specific neurotransmitter signaling.

We propose that understanding how the SVZ responds to the discussed signals will help uncover the impact of diseases, treatments, and brain states on cell recruitment and regulation of SVZ cell neurogenic potential. We apologize to the authors of papers that could not be cited here due to space constraints.

Structural organization of the SVZ

The SVZ is made up of three main cell types: neuroblasts, astrocyte-like cells (also called SVZ astrocytes), and intermediate progenitor cells called transit amplifying cells (TACs). Some of the astrocyte-like cells are neural progenitor cells (also called stem cells). They are capable of self-renewal and generate TACs that in turn generate neuroblasts. Neuroblasts are immature neurons that are fate-committed to becoming GABAergic granule or periglomerular interneurons in the OB. The tight association and organization allows for rapid paracrine communication between cells that are within the niche (for review see (Bordey, 2006; Pathania *et al*, 2010)). Its position near the ventricle and spanning a large portion of the brain allows for the possibility of extra-niche paracrine neurotransmission from nearby neurons and their collaterals. Paracrine neurotransmission has also been referred to as volume or non-synaptic transmission. In addition, the presence of an extensive blood vessel network suggests that hormones could impact neurogenesis in the SVZ (Mirzadeh *et al*, 2008; Shen *et al*, 2008; Snapyan *et al*, 2009; Tavazoie *et al*, 2008). Such a hormonal control of neurogenesis is not discussed in this review, which instead focuses on neurotransmitter systems.

Neurotransmitter systems directly affecting SVZ neurogenesis

The neurotransmitter systems covered here encompass the ‘traditional’ neurotransmitters, gamma-aminobutyric acid (GABA) and glutamate, normally considered as primarily confined to the synapse and responsible for fast synaptic transmission, and neuromodulatory transmitters or neuromodulators such as dopamine, serotonin, and acetylcholine that are secreted by a small group of neurons and can affect neuronal activity through large brain areas. We first discuss neuromodulators because there are clear examples of long-range paracrine or non-synaptic signaling through neuronal projections into the SVZ. The extra-niche signal from GABA and glutamate is more hypothetical, as discussed below. Figure 1 provides a diagram illustrating the presented findings that are also summarized in Table 1.

Dopamine—Dopamine is a catecholamine that is synthesized by neurons mainly in the substantia nigra, ventral tegmental area, and hypothalamus, with neurological functions including roles in punishment and reward, mood, sleep, attention, and learning (Lima *et al*, 2009). Dopamine receptors are G protein-coupled receptors classified into two groups, D1-like (D1 and D5) and D2-like (D2, D3, and D4). The two groups are distinguished based on structure and interactions with different G proteins. D1-like receptors activate adenylyl cyclase, whereas D2-like receptors inhibit adenylyl cyclase activity (Callier *et al*, 2003).

Receptors and dopaminergic inputs in the SVZ: Both D1-like and D2-like receptors have been identified in rodent SVZ-derived neurospheres (Coronas *et al*, 2004; Hoglinger *et al*, 2004; Winner *et al*, 2009), and mRNA expression and *in vivo* studies have implicated the D3 receptor (D2-like) in embryonic and adult SVZ neurogenesis (Diaz *et al*, 1997; Kim *et al*, 2010; Van Kampen *et al*, 2004). D1-like receptors were found in the cytoplasm but not the cell membrane of TACs and in the cell membrane of neuroblasts, whereas D2-like receptors were most abundantly expressed in TAC cell membranes and sparsely in SVZ astrocyte cell

membranes (Hoglinger *et al*, 2004). TACs expressed D3 receptors while neuroblasts and SVZ astrocytes did not (Kim *et al*, 2010).

Dopaminergic projections to the SVZ from the substantia nigra have been demonstrated in rats (Hoglinger *et al*, 2004; Winner *et al*, 2006), mice (Baker *et al*, 2004) and primates (Freundlieb *et al*, 2006). In addition, postmortem studies in humans have identified dopaminergic fibers in contact with epidermal growth factor receptor (EGFR)-positive cells in the SVZ, which are presumably TACs (Hoglinger *et al*, 2004).

Influence of dopaminergic signaling and circuitry on SVZ neurogenesis: Convincing evidence suggests that dopamine has an impact on neurogenesis at several developmental stages and in regions including the adult SVZ. However, some controversy remains regarding the actual effect of dopamine on SVZ cell proliferation and neurogenesis as summarized below (for reviews see (Borta and Hoglinger, 2007; O'Keeffe *et al*, 2009a)). Two types of manipulations of dopaminergic signaling have been performed to test their effects on SVZ neurogenesis: pharmacological and genetic manipulations targeted to dopamine receptors and ablation of dopaminergic inputs projecting to the striatum and the SVZ. *In vivo* pharmacological manipulations using agonists or antagonists of selective dopamine receptors led to significant increases or decreases in SVZ neurogenesis in rodents as measured using injections of the S-phase marker bromodeoxyuridine (BrdU) (Kim *et al*, 2010; Kippin *et al*, 2005; Van Kampen *et al*, 2004). However, one study using D3 receptor ligand reported no effect (Baker *et al*, 2005). Discrepancies have been noted between studies that may be due to the age of the animals, the species, and perhaps the selectivity of the agonists or antagonists. The clinically relevant dopamine precursor, levodopa (L-DOPA), had surprisingly no significant effect on baseline SVZ cell proliferation in rats (O'Keeffe *et al*, 2009b). Studies using genetic manipulations have been limited. Only one study used transgenic knock-out mice for D2 receptors, but there was no effect on SVZ cell proliferation presumably due to compensatory mechanisms (Kippin *et al*, 2005). A better approach would be to use the floxed strategy to remove one receptor sub-type at a given time.

Ablation of dopaminergic inputs resulted in decreased proliferation in the SVZ, suggesting that substantia nigra neuron activity controls SVZ cell proliferation and neurogenesis (Baker *et al*, 2004; Cova *et al*, 2010; Freundlieb *et al*, 2006; Hoglinger *et al*, 2004; O'Keeffe *et al*, 2009a; 2009b). These studies ablated dopaminergic neurons in the substantia nigra through 6-OHDA or MPTP injection. The lesions resulted in loss of tyrosine hydroxylase (TH, the enzyme responsible from converting amino acid into DOPA, a dopamine precursor) immunoreactivity in the SVZ and a decrease in SVZ proliferation (Baker *et al*, 2004; Hoglinger *et al*, 2004; Winner *et al*, 2006). One study suggested that fiber-released dopamine acted through decreased local EGF production (O'Keeffe *et al*, 2009b). In addition, L-DOPA injection restored EGF levels to baseline and rescued ablation-induced SVZ cell proliferation (O'Keeffe *et al*, 2009b). Considering the function of the substantia nigra in reward, addiction, and movement, it is tempting to speculate that SVZ cell proliferation and perhaps neurogenesis are regulated by addictive behaviors and new movement-based learning paradigms.

Pathological brain states: : Loss of dopaminergic neurons in the substantia nigra is the primary cause of Parkinson's disease (PD) and leads to decreased dopamine levels in the striatum (Kadir and Nordberg, 2010). Ablation of dopaminergic neurons in the substantia nigra is a classical method to model PD in animals. In these animal models of PD, SVZ proliferation was decreased suggesting that PD is associated with decreased neurogenesis (Baker *et al*, 2004; Cova *et al*, 2010; Hoglinger *et al*, 2004; O'Keeffe *et al*, 2009b; Winner *et*

al, 2009). Indeed, postmortem studies of PD patients have demonstrated a decreased number of proliferative cells in the SVZ (Hoglinger *et al*, 2004).

Serotonin—Serotonin (5-HT) is a monoamine that is synthesized by neurons in the raphe nuclei, which regulates many aspects of behavior including mood, sleep, appetite, reproductive activity, and cognition. Seven families of 5-HT receptors ($5\text{-HT}_{1\text{-}7}$) have been classified, and all except 5-HT_3 are G protein-coupled receptors. 5-HT_3 is a ligand-gated cation channel.

Receptors and serotonergic inputs in the SVZ: The exact expression pattern of 5-HT receptors in the SVZ remains controversial. RT-PCR from SVZ tissue suggests the expression of a wide array of 5-HT receptors: 1A, 1B, 1D, 2A, 2B, 2C, 3A, and 6 shown by Councill *et al*, 2006 but only 1A, 2A, and 2C reported by Hitoshi *et al*, 2007. Dissected SVZ tissue is often contaminated by striatal tissue which may explain some of the discrepancies. Pharmacological experiments implicate the presence and functionality of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors in the SVZ (Banasr *et al*, 2004; Soumier *et al*, 2010). Cell type-specific 5-HT receptor expression using immunohistochemistry remains to be determined. The SVZ in addition to the striatum receives serotonergic inputs from the raphe nuclei (Brezun and Daszuta, 1999; Lorez and Richards, 1982).

Influence of serotoninergic signaling and circuitry on SVZ neurogenesis: It is generally thought that serotonin has a positive effect on SVZ neurogenesis. Indeed, *in vivo* infusion of serotonin results in increased neurosphere production from the SVZ (Hitoshi *et al*, 2007). Agonists of 5-HT_{1A} and 5-HT_{2C} receptors increased SVZ proliferation (Banasr *et al*, 2004; Soumier *et al*, 2010) although 5-HT_{1B} receptor activation decreased SVZ proliferation *in vivo* (Banasr *et al*, 2004). It has not been determined, however, whether these effects are direct through activation of 5-HT receptors on SVZ cells or indirect through receptor activation on cells in other structures such as the choroid plexus, which is adjacent to the SVZ in the lateral ventricle (Soumier *et al*, 2010).

Ablation of raphe nuclei results in decreased SVZ proliferation (Banasr *et al*, 2004; Brezun and Daszuta, 1999). Pregnant female mice have higher levels of serotonergic innervation in the SVZ that has been suggested to be responsible for increased SVZ proliferation (Diaz *et al*, 2009). Considering that serotonin is well-known for its role in mood regulation, it is possible that mood disorders associated with altered serotonin levels have altered SVZ cell proliferation.

GABA—GABA is the main inhibitory neurotransmitter in the adult brain and an excitatory neurotransmitter in the developing brain. It acts through activation of ionotropic ligand-gated GABA_A or GABA_C receptors and G-protein coupled GABA_B receptors.

Receptors and GABAergic inputs in the SVZ: Functional GABA_A receptors have been identified in the SVZ/RMS on SVZ astrocytes and neuroblasts (Gascon *et al*, 2006; Nguyen *et al*, 2003; Stewart *et al*, 2002; Wang *et al*, 2003b). The presence of such receptors on TACs remains unexplored. The exact subunit composition in the SVZ and in the different cell types remains to be examined. RT-PCR from neurospheres or neonatal cultured neuroblasts has yielded the expression of α2, 3, 4, β1 and 2, and γ2 in neuroblasts (Nguyen *et al*, 2003; Stewart *et al*, 2002). The expression of GABA_B receptors has not been explored.

The SVZ is located along the striatum, which is predominately composed of GABAergic neurons. In addition, nitric oxide-containing GABAergic striatal neurons project into the SVZ (Moreno-Lopez *et al*, 2000). These neurons may thus provide an activity-dependent GABAergic control of SVZ neurogenesis. In addition, vesicular GABA transporter

expression (VGAT, using immunostaining) has been reported in the SVZ in agreement with the presence of GABAergic inputs from the striatum (Platel *et al*, 2007).

Influence of GABAergic signaling and circuitry on SVZ neurogenesis: The function of GABAergic signaling on SVZ neurogenesis has been previously reviewed (Bordey, 2006; 2007; Platel *et al*, 2008a). To be brief, GABA has significant impact on several phases of SVZ/OB neurogenesis: proliferation of the astrocyte-like stem cells and neuroblasts (in cultured slices) (Liu *et al*, 2005; Nguyen *et al*, 2003), neuroblast migration and differentiation in acute slices (Bolteus and Bordey, 2004a; Gascon *et al*, 2006). Some of these effects may involve the canonical CREB pathway activation as shown in the SVZ and hippocampal neurogenic zone (Giachino *et al*, 2005; Herold *et al*, 2010; Jagasia *et al*, 2009). Importantly, there are no *in vivo* data on the function of GABA and its receptors on SVZ neurogenesis.

The proposed source of GABA is intrinsic to the SVZ, i.e. from neuroblasts. Indeed neuroblasts have been shown to synthesize and release GABA in a calcium-dependent but nonvesicular manner (De Marchis *et al*, 2004; Gascon *et al*, 2006; Liu *et al*, 2005; Nguyen *et al*, 2003; Wang *et al*, 2003b). However, it remains unclear whether some of the effects on the behavior of SVZ cells could be attributed to an external source, *i.e.* from striatal GABAergic neurons that are adjacent to SVZ cells.

Pathological brain states: Huntington's Disease (HD) is a neurodegenerative disorder that primarily “attacks” the striatum. HD is generally an inherited neurodegenerative disease caused by the accumulation of CAG-repeats in the huntingtin gene. Disruption of this gene leads to the degeneration and death of medium spiny neurons in the striatum. In human patients, markers of proliferation in the SVZ are increased compared to controls (Curtis *et al*, 2003; 2005). Similarly, quinolinic acid (QA)-induced models of HD show an increase in both SVZ proliferation and migration to the injury site (Tattersfield *et al*, 2004). QA is an excitatory amino acid that induces cell death, and injection into the striatum leads to destruction of medium spinal GABAergic neurons while cholinergic neurons remain intact (Beal *et al*, 1986; Brickell *et al*, 1999; Nicholson *et al*, 1995). Interestingly, this increase in SVZ neurogenesis persisted only 14 days post-QA injection perhaps due to repair over time and thus normalization of the injury. Such finding was not observed in a genetic mouse model of HD, the R6/2 mouse line (Phillips *et al*, 2006; 2005). Nevertheless, there was a decrease in adult born granule cells in these mice perhaps due to the observed re-routing of neuroblasts into the striatum (Kohl *et al*, 2010). It is important to examine whether GABAergic neurons projecting into the SVZ are spared in the R6/2 mice compared to the QA model. Although these data could be explained by the loss of GABAergic inputs in the SVZ and thus changes in SVZ cell proliferation, factors released due to neuronal cell death could contribute to the changes in SVZ cell proliferation independent of GABA. A more direct genetic manipulation of GABAergic inputs in the SVZ is required to address their function on SVZ proliferation and ultimately neurogenesis.

Glutamate—GABA's counterpart, glutamate, is also known to affect SVZ neurogenesis (for reviews see (Platel *et al*, 2008a; 2010b)). Glutamate signals through ionotropic AMPA/kainate and NMDA receptors as well as metabotropic mGluR1-8 receptors.

Receptors and glutamatergic inputs in the SVZ: *In vitro*, Brazel et al. (2005) showed that rat neural progenitor cells express AMPA, kainate, NMDA and group 2 mGluR receptors using calcium imaging and pharmacology (Brazel *et al*, 2005). In neurospheres, neural progenitor cells were also found to express mGluR1 (Castiglione *et al*, 2008). We provided evidence that in acute slices SVZ neuroblasts express a mosaic of glutamate receptors including AMPA and kainate (GluK5) receptors (Platel *et al*, 2007; 2008b), NMDA

receptors (Platel *et al*, 2010a), and mGluR5 (Platel *et al*, 2008b) based on calcium responses, electrophysiological recordings, and immunohistochemistry. mGluR5 were also shown to be expressed in SVZ cells *in vivo* (Di Giorgi Gerevini *et al*, 2004; Gandhi *et al*, 2008). Astrocyte-like cells do not express functional NMDA or AMPA/kainate receptors (Liu *et al*, 2005). There are no data on glutamate receptors in TACs. One recently identified source of glutamate is astrocyte-like cells in the SVZ. These cells express vesicular glutamate transporter 1 and release glutamate upon intracellular calcium increases (Platel *et al*, 2010a). It is unknown whether cortical axons projecting onto striatal neurons invade the SVZ.

Influence of glutamatergic signaling on SVZ neurogenesis: In cultures from SVZ neurospheres glutamate agonists decreased markers of cell death, and more specifically kainate and group 2 mGluR agonists increased proliferation according to ^{3}H-thymidine incorporation and cell counts (Brazel et al., 2005). There is also evidence that mGluR5 exerts a positive effect on SVZ cell proliferation *in vivo* and promoted neuroblast survival in cultures (Castiglione *et al*, 2008; Di Giorgi Gerevini *et al*, 2004; Gandhi *et al*, 2008). Antagonists of kainate receptors, but not those of mGluR5, decreased neuroblast migration in whole mount preparations of the SVZ (Platel *et al*, 2008b). Finally, genetic knockout of NMDA receptors using a floxed strategy *in vivo* led to neuroblast apoptosis suggesting that NMDA receptors are important for neuroblast survival (Platel *et al*, 2010a).

Pathological brain states: Signals that increase calcium in astrocyte-like cells through Gq-coupled receptor activation lead to glutamate release and receptor activation in adjacent neuroblasts (Platel *et al*, 2010a). One remaining question relates to the identity of the signals controlling calcium activity in astrocyte-like cells. One pathological and perhaps physiological signal is prostaglandin E2 (PGE2). Prostaglandins, including PGE2, are potent mediators of inflammation and are produced from arachidonic acid via the action of cyclooxygenases (COX, also known as PGH synthase). PGE2 is synthesized from PGH2 via PGE synthase. Two isoforms of cyclooxygenase, COX-1 (constitutive) and COX-2 (low constitutive and inflammatory induced), have been cloned. COX-2 is expressed in SVZ microglial cells under normal conditions (Goncalves *et al*, 2010) and the choroid plexus releases significantly more PGE2 than acute SVZ explants (Dave *et al*, 2010), as shown using immunohistochemistry and ELISA measurements, respectively. As reported in mature astrocytes (Bezzi *et al*, 1998; Sanzgiri *et al*, 1999; Zanotti and Charles, 1997), we found that PGE2 induces calcium increase in SVZ astrocytes resulting in glutamate release and NMDA receptor activation in adjacent neuroblasts in acute slices (Dave *et al*, 2010).

A major pathological condition affecting glutamate levels is ischemia associated with stroke. However, because ischemia also affects other neurotransmitter systems, including GABA, aspartate, and ATP (Andine *et al*, 1991; Franke *et al*, 2006b; Vannucci *et al*, 1999), the role of ischemia on neurogenesis is discussed below.

Adenosine 5′-triphosphate (ATP)—ATP plays an important role in CNS development through activation of selective purinergic receptors such as the P2X family of ligand-gated ion channels (P2X1-7) and the P2Y families of G-protein-coupled receptors (P21-4, 6, 11-14) (for review see (Abbracchio *et al*, 2009; Zimmermann, 2006)).

Receptors and ATP sources in the SVZ: Astrocyte-like cells of the SVZ express functional ATP hydrolyzing ectonucleotidase in particular NTPDase2 suggesting the presence of ATP signaling in the SVZ (Braun *et al*, 2003; Lin *et al*, 2007). Indeed, cultured neurospheres constitutively released episodic bursts of ATP as shown using real-time bioluminescence imaging (Lin *et al*, 2007). Released ATP activates P2Y1 and P2Y2 receptor in cultured SVZ cells as shown using calcium imaging *in vitro* and

immunohistochemistry in tissue (Lin *et al*, 2007; Mishra *et al*, 2006). The identity of the SVZ cell types expressing these receptor remains to be examined.

Regarding P2X receptors, ependymal cells that line the lateral ventricle have been shown to express P2X receptors, in particular P2X7 and adenosine A2B receptors (Genzen *et al*, 2009a; 2009b). There are no data regarding other P2X receptors in the SVZ. However, immunostaining data in the OB show that granule cells express high levels of P2X2 and P2X4 receptors (Kanjhan *et al*, 1999; Le *et al*, 1998; Vulchanova *et al*, 1996), suggesting that neuroblasts acquire P2X receptors along the SVZ-RMS-OB axis. Here, we present data suggesting that neuroblasts acquire functional P2X receptors in the RMS (published with permission from Dr. Anna Bolteus). We used whole-cell patch clamp recording in acute sagittal slices from postnatal day 20-32 mice at room temperature. Experiments were performed in accordance with the Yale Animal Care and Use Committee guidelines. Slice preparation and recording equipment were as previously reported (Bolteus and Bordey, 2004b; Wang *et al*, 2003a). Recorded cells were identified as neuroblasts as previously reported based on their ionic signature (outwardly rectifying current profile) and biophysical properties (high input resistance) (Bolteus and Bordey, 2004b; Wang *et al*, 2003a) (see Figure 1A, inset). Pressure application of 100 μM or 1 mM ATPγS did not induce currents in SVZ neuroblasts, but only increased the baseline noise in 1/10 neuroblasts suggesting that SVZ neuroblasts do not express functional P2X receptors. In the RMS-OB, pressure application of 100 μM NaATP or ATPγS and 1 mM ATPγS induced inward currents of -7.9 ± 1.8 pA in 57% (n=12/21) and -13.4 ± 1.6 pA in 84% (n=67/80) neuroblasts of the RMS-OB, respectively (Figure 2A for 1 mM ATP-γS, mean ± SEM). ATPγS-induced currents inwardly rectified and reached a zero-current near +10 mM (n=5, 1 mM, Figure 2B), which is expected for non-selective cationic currents mediated by P2X receptors (North, 2002; Ralevic and Burnstock, 1998). ATPγS-induced currents were not blocked by 100 μM suramin or TNT-ATP (n=3 each, data not shown) suggesting the involvement of P2X4 receptors (Bo *et al*, 1995; North, 2002; Ralevic and Burnstock, 1998). In addition, ATPγS-induced currents were enhanced by 10 μM zinc (Zn^{2+}) application (n=3, Figure 2C). Collectively, these data suggest that neuroblasts acquire P2X receptors prior to entering the OB synaptic network.

Influence of ATP signaling on SVZ neurogenesis: Activation of the metabotropic $P2Y_1$ and $P2Y_2$ receptors in cultured adult SVZ cells augmented cell proliferation in the presence of mitogenic growth factors (Mishra *et al*, 2006). Consistent with this result, P2Y receptor antagonists suppressed proliferation and permitted differentiation into neurons and glia *in vitro* (Lin *et al*, 2007). The function of P2X7 receptors in ependymal cells and ultimately neurogenesis remains to be examined. Similarly the function of P2X in neuroblasts in the RMS-OB suggests a function on neuroblast differentiation that needs to be explored.

Pathological brain states: Extracellular levels of ATP and its metabolites increase under injurious conditions including hypoxia, ischemia, traumatic insults and epilepsy-associated seizures (for reviews, see (Abbracchio *et al*, 2009; Franke *et al*, 2006a; 2006b)). ATP thus plays an important role in the CNS response to inflammation, ischemia, mechanical insult, and seizures. ATP could thus be a signal released during these pathological conditions that will affect neurogenesis.

Indirect action of other neurotransmitter systems and brain states on SVZ neurogenesis

Acetylcholine—Acetylcholine (ACh) was the first neurotransmitter discovered. Although the number of cholinergic neurons in the brain is small, cholinergic afferents are spread throughout the brain. Cholinergic signaling is important in the modulation of various brain

states including learning, memory consolidation, attention, and sleep. Its receptors include the ionotropic nicotinic and metabotropic muscarinic ACh receptors.

There is evidence upstream of the SVZ that lesions of cholinergic inputs decrease the number of newly born neurons in the OB using BrdU (Cooper-Kuhn *et al*, 2004), though no direct cholinergic inputs have been identified in the SVZ. Similarly, enhancing cholinergic signaling with donepezil enhanced the survival of newly born OB neurons although no effect was seen in the proliferation of the SVZ (Kaneko *et al*, 2006). In contrast, nicotinic beta-2 knockout animals show increased survival of newly born neurons in the OB (Mechawar *et al*, 2004). ACh has thus a complex effect on neuronal survival in the OB that requires further investigation.

Pathological brain state: ACh is also known to regulate dopamine release in the striatum by regulating the firing of dopaminergic neurons in the substantia nigra (Aosaki *et al*, 2009; Lester *et al*, 2010). It is thus highly conceivable that ACh could indirectly regulate SVZ cell proliferation through modulation of dopamine release. ACh levels are altered in certain neurodegenerative disorders, in particular Alzheimer's disease (AD) (Schliebs and Arendt, 2006). Indeed, the severity of AD correlates with a decrease in choline acetyl transferase (ChAT), which is indicative of a decrease in overall cholinergic tone in the brain. Interestingly, in AD patients Ziabreva and colleagues (2006) correlated a decrease in ChAT to a nine-fold decrease in proliferating cells in the SVZ (Ziabreva *et al*, 2006). Although correlative, it is possible that changes in ACh levels directly or indirectly altered SVZ cell proliferation during the course of AD. This needs to be further investigated.

Ischemia—Even brief insults to blood flow in the brain can have profound effects on SVZ cell proliferation and migration. Middle cerebral artery occlusion increases migration of neuroblasts (*i.e*. doublecortin-positive cells) from the SVZ to peri-infarct regions (Kojima *et al*, 2010; Komitova *et al*, 2005; Ohab *et al*, 2006) (for review (Ohab and Carmichael, 2008; Zhang *et al*, 2005)). Stroke models in adult rodents show that ipsilateral to the injury, there is a long-lasting increase in proliferation of SVZ cells and migration toward the injury site (Arvidsson *et al*, 2002; Komitova *et al*, 2005; Parent *et al*, 2002; Zhang *et al*, 2001). Stroke was shown to increase neurogenesis in the SVZ and shortens the cell cycle of SVZ cells (Zhang *et al*, 2008b) (for reviews see (Kernie and Parent, 2010; Zhang *et al*, 2008a)).

In neonates, controversial findings on the effects of ischemia on SVZ neurogenesis have been reported. Using a hypoxia/ischemia model in postnatal day 7-10 rats, increased apoptosis of SVZ cells and more specifically oligodendrocyte progenitors was reported in the SVZ (Brazel *et al*, 2004; Levison *et al*, 2001). In contrast, Ong and colleagues (2005) provided evidence that a milder hypoxia/ischemia injury in postnatal day 7 rats increased the size of the SVZ and increased incorporation of BrdU in the SVZ ipsilateral to the injury site as previously reported in adult rats (see above) (Ong *et al*, 2005). Factors such as severity and site of injury, type of injury, and age or stage of SVZ cells can influence the detection of proliferating or apoptotic cells. In addition, cell type may matter as stem cells may react differently to ischemic conditions compared to neuronal or oligodendrocyte progenitors (Romanko *et al*, 2004).

As mentioned above, ischemic models lead to alterations in the levels of several neurotransmitters including glutamate, aspartate, GABA and ATP (Andine *et al*, 1991; Franke *et al*, 2006b; Vannucci *et al*, 1999). Previous studies reported glutamate's effects on SVZ cell proliferation and neuroblast survival *in vivo* through mGluR5 and NMDA receptors (Di Giorgi Gerevini *et al*, 2004; 2005; Gandhi *et al*, 2008; Platel *et al*, 2010a). GABA and ATP also affect neural progenitor cell proliferation and neurogenesis *in vitro* or in slices (Lin *et al*, 2007; Liu *et al*, 2005; Mishra *et al*, 2006). It is thus possible that part of

the ischemic effect on SVZ cell proliferation and survival involve a direct action of GABA, glutamate, and ATP on SVZ cells. The effect on neuroblast migration and attraction to the injury site involves chemokines and other attractant molecules, the synthesis of which may be regulated by neurotransmitters.

Seizures—Seizure activity, in particular pilocarpine-induced status epilepticus, has been shown to increase SVZ cell proliferation and ultimately OB neurogenesis (Kang *et al*, 2004). The mechanism for this increase remains unclear. Seizures are characterized by abnormal and large amplitude electrical activity. This activity involves an excessive release of glutamate and GABA, among other neurotransmitters, and can also involve hormones over a longer time scale. The neurotransmitter systems discussed above may contribute to the seizure-induced regulations of neurogenesis. In addition, electroconvulsive therapy (ECT) used to treat depression was reported to increase several growth factor genes' expression in the choroid plexus (Newton *et al*, 2003). These factors released from the choroid plexus could directly influence SVZ cell proliferation, but the mechanism of seizure-induced neurogenesis remains unknown.

Treatments for seizures often involve altering and enhancing GABAergic neurotransmission to counteract the excessive excitatory activity induced by a seizure. Such seizure treatment can potentially alter neurogenesis directly through $GABA_A$ receptors or indirectly by modulating other neurotransmitter systems. Supporting such an effect although it has not been examined in the SVZ, the seizure medication levetiracetam inhibits the ectopic neurogenesis in the hippocampus that occurs with kindled seizures (Sugaya *et al*, 2010).

Sleep—Almost all animals go through periods of rest that can be referred to as sleep. Sleep itself is a complex process controlled by various neurotransmitter systems and is modulated by circadian rhythms. There are also two main types of categorized sleep that have been studied in relation to neurogenesis: rapid eye movement (REM) and non-REM sleep. Changes in neurogenesis due to circadian rhythms have mostly been examined in the hippocampus, while literature surrounding sleep and SVZ neurogenesis appears to be more limited. In the rat SGZ of the hippocampus, prolonged, but not short-term, sleep deprivation appears to decrease neurogenesis (for reviews see (Guzman-Marin *et al*, 2007; Meerlo *et al*, 2009)). Sleep deprivation has been known to affect the function of various neurotransmitter systems including glutamatergic, GABAergic, cholinergic, and serotonergic systems, so it is surprising that there have not been reported effects of sleep deprivation on SVZ cell proliferation. Effects, however, may be missed if not assessed at the peak of proliferation during circadian rhythms, and changes can depend on the duration or type of sleep deprivation or species (for review see (Longordo *et al*, 2009)).

Melatonin, a hormone that is regulated by circadian rhythms involved in sleep, can also affect other neurotransmitter systems such as the production of serotonin (Sun *et al*, 2002). Cultured SVZ cells were shown to express melatonin receptors, the inhibition of which drove cells toward neuronal differentiation (Sotthibundhu *et al*, 2010). In addition, melatonin increased the proliferation of adult SVZ-derived cells in culture (Sotthibundhu *et al*, 2010). Given this recent evidence, it would be interesting to examine the effects of melatonin on SVZ cell proliferation and differentiation *in vivo*, and whether this action is direct or indirect through serotonin.

Pregnancy—Prolactin contributes to increases in SVZ neurogenesis during pregnancy (Shingo *et al*, 2003). Prolactin levels cycle and change during pregnancy, and the spikes in serum levels have an impact on maternal behavior post-partum. Larsen and Gratten (2010) show that blocking prolactin spikes during pregnancy not only decreases SVZ neurogenesis, but concurrently increases anxiety in new mothers and inhibits maternal behavior such as

pup retrieval (Larsen and Grattan, 2010). To show that the inhibition of post-partum maternal behavior is not just due to the lack of prolactin, but also due to the decrease in neurogenesis, Larsen and Grattan (2010) injected the mitotic inhibitor methylazoxymethanol treatment (MAM). MAM is a mitotic inhibitor and decreases SVZ neurogenesis. These authors also reported that MAM-treated mice exhibited similar post-partum behavioral deficits as those mice without prolactin surges during pregnancy. In this case, the observed behavior is presumably driven by SVZ neurogenic defects that in turn may be controlled by prolactin. More importantly, prolactin release appears to be under the control of both serotonin and dopamine (Clemens and Shaar, 1980).

Conclusion

It is evident that many neurotransmitter systems impinge on the SVZ, creating a complex picture of the various signals influencing the production of new neurons. These systems provide a link between our brain activity or emotional and bodily states and SVZ neurogenesis. As discussed, activity in the subtantia nigra (dopamine) or the raphe nucleus (serotonin) can directly influence SVZ cell proliferation. These findings emphasize or re-emphasize two important limitations in our studies of neurogenesis. First, captive mice reared in small cages may display lack of such system-based control of neurogenesis or altered control in a low stimuli environment. Second, enervation by neurotransmitter systems such as dopamine and serotonin as well as receptor expression may differ in the rostral/caudal and dorsal/ventral regions of the SVZ. It is well-known that the SVZ is not homogeneous in its architecture and fate of neural stem cells (Merkle *et al*, 2007). Preferential control by neurotransmitter systems of SVZ sub-regions is thus expected. This obviously can lead to significant errors in analyzing global proliferation all along the SVZ using the mitotic marker bromodeoxyuridine. Such a heterogeneity calls for a live imaging approach such as functional MRI to examine which subregions of the SVZ are activated by certain brain activity and neurotransmitter systems to spatially target cell proliferation analysis. Finally, attempts to use neurogenic regions to produce new neurons to regenerate lost nuclei in neurodegenerative disease will have to take into account the potentially overlapping role of multiple neurotransmitter systems on neurogenesis.

Acknowledgments

This work was supported by grants from the NIH R01 DC007681 and NS062731 (A.B.) and NRSA F31 NS063758 (S.Z.Y). We would like to thank Dr. Anna Bolteus for data included in this manuscript.

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Figure 1.

Neurotransmitters and related neuromodulators modify neurogenesis by relaying signals from other parts of the brain. **(A and B)** Tables summarizing brain activity (A) and disease or injury states (B) and the corresponding neurotransmitters involved with these states. * denotes postulated role. **(C)** Sagittal representation of relevant structures in the mouse brain and their associated neurotransmitters. Ctx, cortex; LV, lateral ventricle; OB, olfactory bulb; RMS-OB, rostral migratory stream of the olfactory bulb; RN, raphe nuclei; SN, substantia nigra; Str, striatum; SVZ, subventricular zone.

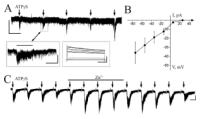

Figure 2. Neuroblasts in the RMS-OB express functional P2X receptors

(A) Pressure application of ATPγS (1 mM, 3 sec) induces reproducible inward currents in a neuroblast recorded at -70 mV in the RMS-OB. The left inset illustrates one of the inward currents at a higher time scale. The cells were identified as neuroblasts based on their outwardly rectifying current profiles (right inset, voltage steps shown in B). The liquid junction potential was corrected off-line. The recording solution contained (in mM): 140 KCl, 1 $CaCl_2$, 10 EGTA, 10 HEPES (pH 7.2). Scales: 10 pA/ 30 s, 5 pA/ 2 s (left inset), 200 pA/ 100 ms (right inset) **(B)** Current-voltage relationship illustrating that ATPγS-induced currents inwardly rectify (mean ± SEM, n=5). **(C)** Zn^{2+} enhanced 1 mM ATPγS-induced current amplitudes (n=3 cells). Scale: 10 pA/ 4 s.

Table 1

Summary of discussed findings.

Neurotransmitter	Receptors in the SVZ	Projections from NT releasing neurons	Effect on SVZ proliferation	Effect on migration	Effect on SVZ cell survival	Associated brain states or pathologies	Effect of pathology on NT signaling
Acetylcholine	none; nAChR α7/β2 in OB	?	?	?	Increased in (N) near OB	Alzheimer's Disease	Decreased
ATP	P2X2, P2X4 (N*); P2X7 (E*) P2Y (N)	SVZ or surrounding astrocyte-like cells?	Increased	?	?	Hypoxia/Ischemia Seizure Injury	Increased Increased Increased
Dopamine	D1-like (TAC cytoplasm) D2-like (TAC, A*) D3 (TACs, but not A or N)	Substantia nigra (rodents, primates, humans)	Increased	?	?	Parkinson's Disease	Decreased
GABA	α2, 3, 4, β1 and 2, and γ2 (N) $GABA_A$ subunits - unknown (A)	Striatal neurons (?)	Decreased	Decreased	?	Huntington's Disease Seizures	Decreased/altered ?
Glutamate	AMPA GluK5 (N) NMDA (N) (Group I) mGluR1 and 5 (N) Group 2 mGluRs	SVZ or surrounding astrocyte-like cells (rodent)	Increased (in neural progenitor culture)	None	Increased in (N)	Ischemia/Hypoxia Seizure	Increases in adult Increases
Serotonin	5-HT 1A, 2A, 2 C (may have others)	Raphe nucleus	Increased	?	?	Pregnancy Mood disorders Sleep	Increased- can regulate prolactin release Decreased/altered Melatonin (dependent on serotonin for synthesis)-increases SVZ proliferation

*A= astrocyte-like cells; N= neuroblast; E= ependymal cell; TAC= transit amplifying cells.