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Neurotransmitter-mediated control of neurogenesis in the adult vertebrate brain

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Summary

It was long thought that no new neurons are added to the adult brain. Similarly, neurotransmitter signaling was primarily associated with communication between differentiated neurons. Both of these ideas have been challenged, and a crosstalk between neurogenesis and neurotransmitter signaling is beginning to emerge. In this Review, we discuss neurotransmitter signaling as it functions at the intersection of stem cell research and regenerative medicine, exploring how it may regulate the formation of new functional neurons and outlining interactions with other signaling pathways. We consider evolutionary and cross-species comparative aspects, and integrate available results in the context of normal physiological versus pathological conditions. We also discuss the potential role of neurotransmitters in brain size regulation and implications for cell replacement therapies.

Key words: Adult neurogenesis, Homeostasis, Neural stem cell, Neurotransmitter, Regeneration

Introduction

In the brain, signaling via neurotransmitters, small molecules released by neurons to communicate with other cells, has primarily been associated with the function rather than with the formation of neurons. However, several reports have identified roles for neurotransmitters in cell fate determination in a wide range of species both within and outside the central nervous system (CNS). A thorough discussion on the evolutionary origin of neurotransmitter signaling is outside the scope of this Review, but it is important to note that both neurotransmitters and their receptors (see Table 1) are present and functionally important in organisms without a nervous system. For example, γ-aminobutyric acid (GABA), glutamate and nitric oxide (NO) have all been detected in sponges and shown to regulate cell behavior (Ellwanger et al., 2007; Elliott and Leys, 2010). A recent transcriptome profiling of the sponge *A. queenslandica* revealed the expression of wide repertoire of components active in synapses found in the vertebrate nervous systems (Conaco et al., 2012). In the social amoeba *Dictysotelium*, disruption of a glutamate receptor by homologous recombination reveals a role for glutamate signaling in the suppression of cell division (Taniura et al., 2006), while GABA induces terminal differentiation of spores through a $GABA_B$ receptor (Anjard and Loomis, 2006). GABA and glutamate appear to play opposing roles in spore induction (Fountain, 2010) in *Dictyostelium*, indicating that the apparent antagonistic relationship between glutamate and GABA signaling was established prior to the evolution of synaptic communication in the CNS.

Furthermore, neurotransmitters control cell proliferation during development long before the onset of neurogenesis in mammals, as exemplified by GABA signaling in the early embryo (Andäng et al., 2008). Once developmental neurogenesis is initiated, neurotransmitter signaling has an impact on several aspects of neurogenesis, including proliferation, migration and differentiation in various locations in the CNS, such as the telencephalon, ventral midbrain and retina (Kim et al., 2006; Schlett, 2006; Heng et al., 2007; Martins and Pearson, 2008). In the lateral ganglionic eminence, for example, dopamine-mediated signaling influences proliferation of the dopamine receptor-expressing progenitor cells (Diaz et al., 1997; Ohtani et al., 2003).

All these observations suggest that regulation of the cell cycle and cell differentiation is an ancient function of neurotransmitters and that they may have been secondarily recruited to inter-neuronal communication during evolution. Thus, the control of neurogenesis – i.e. the progression of neural stem cells into functionally integrated mature neurons – may be a function of neurotransmitters that is as significant as, but evolutionarily primordial to, their role in synaptic transmission.

In this Review, we make an effort to integrate available data on neurotransmitter-mediated control of adult neurogenesis in comparative settings: both across species and in normal physiological versus pathological conditions, such as after injury and during neurodegeneration.

Cellular targets for neurotransmitter signaling in the brain

New neurons are continuously created and functionally integrated into existing neuronal networks in the adult brain. In almost all mammals, active adult neurogenesis is confined to two distinct locations: the subventricular zone (SVZ) of the lateral ventricles in the forebrain; and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus (Ming and Song, 2011). In the SGZ, quiescent radial glial-like cells (RGLs) exhibit neural stem cell (NSC) properties and give rise to proliferating neural progenitor cells of transit amplifying characters, which eventually become neuroblasts and subsequently differentiate into mature neurons (Malatesta et al., 2000; Noctor et al., 2001; Seri et al., 2004; Encinas et al., 2011; Bonaguidi et al., 2012). In this Review, we use the somewhat sweeping term RGLs [cells with a radial glia morphology that express both nestin and glial fibrillary acidic protein (GFAP)] for both SGZ and SVZ precursor cells, even though these cells have rather different features in the SVZ versus the SGZ (for a recent review, see Morrens et al., 2012).

As in mammals, the brain of adult non-mammalian vertebrates, such as fishes and amphibians, also harbors RGLs. Compared with mammals, the distribution of proliferating RGLs is more widespread (Chernoff et al., 2003; Grandel et al., 2006; Berg et al.,

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Table 1. Classification of neurotransmitters

Neurotransmitter		Receptor	Type of receptor	Cellular pathways	References
Acetylcholine		Nicotinic receptor	Selective cation channel composed of five protein subunits α, β, γ, δ and ε		(Itier and Bertrand, 2001
		Muscarinic M1, M3 and M5 receptors	G protein-coupled receptor	Gαq→PLC→↑IP_3+DAG	(Eglen et al., 2006)
		Muscarinic M2 and M4 receptors	G protein-coupled receptor	Gαi⊣AC→↓cAMP Gβγ→K^+ channel opening	
Amino acids	Glutamate	AMPA receptor	Cation channel, composed of a heterotetramer of GluA1, GluA2, GluA3 and GluA4 subunits		(Gasic and Heinemann 1991)
		NMDA receptor	High Ca^{2+} permeability, voltage-dependant Mg^{2+} block channel, composed of a heterotetramer of NR1, NR2 and NR3 subunits		(Mc Bain et al., 1994)
		Kainate receptor	Cation channel, composed of a heterotetramer of GluK1, GluK2, GluK3 and Gluk4		(Hollmann and Heinemann, 1994)
		Group I: mGluR1 and mGluR5 receptors	G protein-coupled receptor	Gαq→PLC→↑IP_3+DAG	(Benarroch et al., 2008)
		Group II: mGluR2 and mGluR3 receptors	G protein-coupled receptor	Gαi⊣AC→↓cAMP Gβγ→K^+ channel opening and Ca^{2+} channel closing	
		Group III: mGluR4, mGluR6, mGluR7 and mGluR8 receptors			
	GABA	$GABA_A$ receptor	Selective chloric channel, composed of five subunits (from up to 17 different subunits)		(Sieghart and Sperk, 2002; Benarroch et al., 2007)
		$GABA_C$ receptor			
		$GABA_B$ receptor	G protein-coupled receptor	Gαi⊣AC→↓cAMP Gβγ→K^+ channel opening	(Benarroch et al., 2012)
Monoamines	Serotonin (5-HT)	5-HT3 receptor	Cation channel		(Benarroch et al., 2009b)
		5-HT1 receptor	G protein-coupled receptor	Gαi⊣AC→↓cAMP Gβγ→K^+ channel opening	
		5-HT2 receptor	G protein-coupled receptor	Gαq→PLC→↑IP_3+DAG	
		5-HT5 receptor	G protein-coupled receptor	Gαi⊣AC→↓cAMP	
		5-HT4, 5-HT6 and 5-HT7 receptors	G protein-coupled receptor	Gαi→AC→↑cAMP	
	Dopamine	D1-like receptor: D1 and D5 receptors	G protein-coupled receptor	Gαi→AC→↑cAMP	(Neve et al., 2004)
		D2-like receptor: D2, D3 and D4 receptors	G protein-coupled receptor	Gαi⊣AC→↓cAMP Gβγ→K^+ channel opening and Ca^{2+} channel closing	
	Noradrenaline	α1-adrenoreceptors: $α1_A$, $α1_B$ and $α1_C$ receptors	G protein-coupled receptor	Gαq→PLC→↑IP_3+DAG	(Hieble et al., 2007)
		α2-adrenoreceptors: $α2_A$, $α2_B$ and $α2_C$ receptors	G protein-coupled receptor	Gαi⊣AC→↓cAMP	
		β1-adrenoreceptors: β1 and β2 receptors	G protein-coupled receptor	Gαi→AC→↑cAMP	
Neuroactive peptides	Neuropeptide Y	Y1, Y2, Y4, Y5 receptor	G protein-coupled receptor	Gαi⊣AC→↓cAMP Gβγ→K^+ channel opening and Ca^{2+} channel closing Gβγ→PIP_3→↑ERK Gβγ→PLC→↑ERK	(Benarroch et al., 2009a; Sah and Geracioti, 2012)
Soluble gases	Nitric oxide	Liposoluble		Gβγ→GC→↑cGMP	(Ignarro et al., 1989; Guix et al., 2005)

Neurotransmitters can be subdivided into five main categories: cations, amino acids, monoamines, neuroactive peptides and soluble gases. The table summarizes different neurotransmitters, their receptors and the pathways implicated in their signaling transduction. This list is not exhaustive, we present only neurotransmitters implicated in modulating adult neurogenesis. Neurotransmitters can bind to ionotropic or metabotropic receptors. Ionotropic receptors regulate ion channels; metabotropic receptors are G-protein coupled.

5-HT, 5-hydroxytryptamine (serotonin); AC, adenylate cyclase; AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid; DAG, diacylglycerol; ERK, extracellular-signal-regulated kinase; GABA, γ-aminobutyric acid; GC, guanylate cyclase; IP_3, inositol triphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate [PtdIns(3,4,5)P_3]; PLC, phospholipase C; NMDA, *N*-methyl-D-aspartate.

2010) and a number of fish and amphibian species are able to regenerate substantial parts of the brain after injury or loss of neurons.

A central question in adult neurogenesis is how is the fate of these RGLs and their progeny regulated? Insights into this may provide clues as to how neurogenesis could be engineered in various pathological conditions. Whether the stem cells of the adult brain have restricted potential for a particular neural subtype, or whether they retain multi-lineage potential, with fate being defined by extrinsic influences, is still a matter of debate. Evidence suggests that, in the SVZ, there are subtype-specific pools of stem cells that retain their identity after transplantation to ectopic sites (Merkle et al., 2007). However, stem cells taken from the hippocampus and spinal cord lose their identity after being transplanted into ectopic sites (Suhonen et al., 1996; Shihabuddin et al., 2000). Thus, further studies are needed to examine the intrinsic lineage potential *in vivo* of different stem cell subtypes.

Stem cells reside in specific microenvironments in the body called the stem cell niche (Hsu and Fuchs, 2012). In the brain, this niche provides the appropriate environment for stem and progenitor cells, including RGLs, and niche signals are crucial in adult neurogenesis (Ming and Song, 2011). Work from several laboratories during the past decade has revealed that neurotransmitters provide important components of the niche signals and influence several aspects of neurogenesis, both during normal physiological conditions and in disease models (discussed further below) (Höglinger et al., 2004; Liu et al., 2005; Berg et al., 2011; Fernando et al., 2011; Alfonso et al., 2012).

Although neurotransmitter signaling is best understood in terms of signal release directly at the synapse (termed phasic activation), target cells can also be activated by neurotransmitters that diffuse away from the synapse or by non-synaptic secretion (tonic activation). In the adult mammalian hippocampus, for example, both GABA and glutamate are released from extrasynaptic areas (Rusakov and Kullmann, 1998; Brickley and Mody, 2012), and dopamine is released by dendrites in the substantia nigra of the midbrain (Björklund and Lindvall, 1975; Geffen et al., 1976; Beckstead et al., 2004). In addition, neurotransmitters are present in the cerebrospinal fluid and their concentrations change under various neurological conditions (Kuroda et al., 1982; Molina et al., 2005).

Moreover, neurotransmitter-responsive cells are not confined to neurons. Neurotransmitter receptors are expressed on different cell types in the adult brain. Glial cells, such as astrocytes, oligodendrocytes, oligodendrocyte precursor cells and microglia, all express various subtypes of neurotransmitter receptor (Porter and McCarthy, 1997; Bongarzone et al., 1998; Li and Stys, 2000; Pocock and Kettenmann, 2007). Other supporting cells in the brain, such as vasculature-associated pericytes and endothelial cells, express neurotransmitter receptors and are known to be regulated by neurotransmitters (Harik et al., 1981; Krimer et al., 1998).

Elucidating neurotransmitter action at the cellular level is particularly interesting in the context of cell lineage regulation during neurogenesis. Several models can be envisaged (Fig. 1), but one possibility is that each neurotransmitter regulates the production of neurons of its cognate subtype (Fig. 1A). Work on

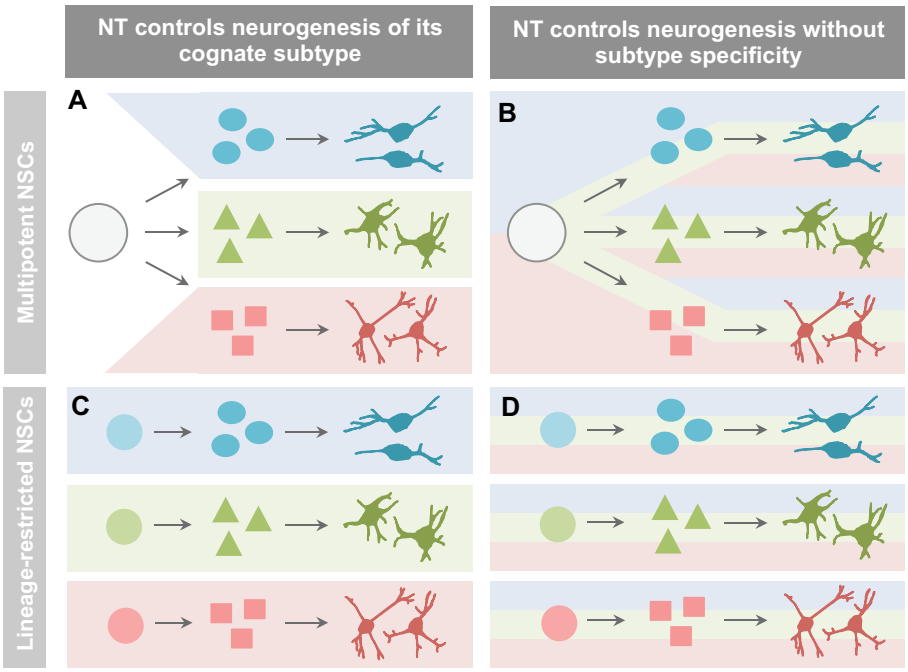

Fig. 1. Neurotransmitter signaling and lineage. Alternative mechanisms for neurotransmitter-mediated regulation of cell fate. (**A**) Each neurotransmitter (NT) controls neurogenesis of its cognate subtype. If neural stem cells (NSCs) are multipotent, transmitters should act on amplifying populations and not on the multipotent stem cell. (**B**) Neurotransmitters control neurogenesis without subtype specificity, regulating proliferation and differentiation of progenitors but with subtype choices being determined by other factors. If NSCs are multipotent, transmitters could act on both NSCs and/or amplifying populations. (**C**) Each neurotransmitter controls neurogenesis of its cognate subtype. If NSCs have restricted potential, transmitters could act on both NSCs and/or amplifying populations. (**D**) Neurotransmitters control neurogenesis without subtype specificity. If NSCs have restricted potential, transmitters could act on both NSCs and/or amplifying populations. The different colors indicate different types of neurotransmitters produced by the neurons. Empty large circles, multipotent NSCs; filled small circles, NSCs with restricted fate; ovals, rectangles and triangles indicate amplifying populations.

regeneration of dopamine neurons in a salamander model of Parkinson's disease provides evidence for such a mechanism (see Berg et al., 2011), but whether this is the case for each neurotransmitter and also under normal physiological conditions is unknown. It has now become feasible to combine manipulation of neurotransmitter signaling with appropriate lineage-tracing approaches, allowing detailed analysis of the potential mechanisms by which neurotransmitters regulate stem cell fate. This provides a tangible means with which to identify key molecular pathways that regulate adult neurogenesis and to define lineage relationships between precursor cells, and should also give insights into the roles of neurotransmitter signaling in brain disorders.

Neurotransmitter-mediated control of adult neurogenesis

In the following sections, we outline how neurotransmitters influence precursor cell fate in the two main neurogenic regions of the mammalian brain – the SVZ and the SGZ (summarized in Table 2). These studies do not always provide resolution in terms of the types of cells that are targeted, but show the significant consequence of altered neurotransmitter signaling on neurogenesis. These works also highlight potential future directions for better characterizing cellular dynamics during both normal and non-physiological neurogenesis by manipulation of neurotransmitter signaling.

Dopamine

Dopaminergic afferents originate from the substantia nigra pars compacta and project to the SVZ in rodents and primates (Höglinger et al., 2004; Freundlieb et al., 2006). As precursor cells in the SVZ, including transit amplifying cells and neuroblasts, express dopamine receptors, it is conceivable that dopamine released from these fibers controls aspects of neurogenesis in this region (Diaz et al., 1997; Höglinger et al., 2004). Ablation of midbrain dopamine neurons in rodents, by injection of selective neurotoxins, such as 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), results in reduced proliferation of progenitor cells in the SVZ and reduced neurogenesis (Baker et al., 2004; Höglinger et al., 2004; Winner et al., 2009; L'Episcopo et al., 2012). Reduced proliferation is partially rescued by increasing dopamine receptor signaling in the lesioned brain, and administration of dopamine receptor agonists is sufficient to increase proliferation of progenitor cells (Höglinger et al., 2004; Yang et al., 2008; Winner et al., 2009). Conversely, another study, in which the dopamine receptor antagonist haloperidol was administered for 14 days, showed an increase in proliferation and in the number of label-retaining cells (stem-like cells) in a dopamine D2 receptor-dependent manner (Kippin et al., 2005).

These seemingly contradictory results are not necessarily irreconcilable. The same neurotransmitter may exert opposing effects on NSCs and amplifying cells. Thus, dopamine signaling might inhibit stem cell proliferation while promoting proliferation of the transient amplifying cells. Given that stem cells are likely to divide less frequently than the amplifying populations, the effects on NSCs of manipulating neurotransmitter signaling will only be manifest after chronic treatment, as was the case in the study showing that dopamine signaling inhibits the production of new cells (Kippin et al., 2005). In other words, although dopamine could stimulate proliferation of amplifying populations, such cells are not produced if NSC division is inhibited – also by dopamine. In addition, experiments performed on 6-OHDA-lesioned animals may reflect the activation of other factors that could counteract, accentuate or mask the effect of dopamine signaling otherwise operating in the non-lesioned brain.

At present, it is not clear to what extent dopamine regulates proliferation of progenitor cells in the hippocampus. A decrease in proliferation has been reported after MPTP administration, but pharmacological manipulation of receptor signaling using several different administration protocols did not alter proliferation (Halim et al., 2004; Höglinger et al., 2004; Kippin et al., 2005).

Dopamine-mediated stimulation of proliferation is dependent on ciliary neurotrophic factor (CNTF), which is known to promote proliferation in the SVZ (Emsley and Hagg, 2003; Yang et al., 2008). A recent study has proposed that dopamine induces proliferation through Akt and extracellular signal-regulated kinase 1/2 signaling, whereas other studies suggest that dopamine stimulates the release of epidermal growth factor (EGF), which is known to promote proliferation of neural stem cells (Reynolds and Weiss, 1996; O'Keeffe et al., 2009; Lao et al., 2013).

GABA

GABA is the main inhibitory neurotransmitter in the adult vertebrate brain and is released primarily by interneurons but also by astrocytes. GABA is known to have a depolarizing effect on neural progenitor cells and immature neurons, both during developmental and adult neurogenesis (LoTurco et al., 1995; Dammerman et al., 2000; Ge et al., 2006). A subpopulation of nestin$^+$ precursor cells in the DG express functional $GABA_A$ receptors (Tozuka et al., 2005; Wang et al., 2005). Using a combination of optogenetic and clonal lineage-tracing techniques, Song et al. (Song et al., 2012) showed that GABA is released from parvalbumin-expressing interneurons in the adult dentate gyrus (DG) and inhibits the activation of quiescent RGLs through activation of the γ2-subunit-containing $GABA_A$ receptor.

In the SVZ, GABA also signals to and depolarizes neural progenitor cells, but the mechanism of release is different from that in the DG (Wang et al., 2003; Liu et al., 2005). Migrating neuroblasts release GABA in a non-synaptic, non-vesicular fashion, which tonically activates signaling in progenitor cells. $GABA_A$-receptor agonist administration limits proliferation in acute brain slices and *in vivo*, and leads to a decreased number of newborn NeuN$^+$ mature neurons cells *in vivo* (Nguyen et al., 2003; Liu et al., 2005; Fernando et al., 2011).

In the adult SVZ, activation of the $GABA_A$ receptor induces phosphorylation of the histone variant H2AX, which in turn mediates the inhibitory effect of GABA on the cell cycle in this region (Fernando et al., 2011). The same mechanism has been observed in the GABA-mediated control of embryonic stem cell proliferation (Andäng et al., 2008). Interestingly, progenitor cells in the SVZ express the diazepam-binding inhibitor, which can bind to a subunit of the $GABA_A$ receptor and counteract the effect of tonic GABA release on neurogenesis (Alfonso et al., 2012).

Glutamate

The function of glutamate in adult neurogenesis has mostly been studied in the hippocampus. Glutamatergic input into the DG comes from three main sources: (1) dentate granule cells; (2) neurons in layer II of the entorhinal cortex that project to the middle and outer molecular layer of the DG through the perforant pathway; and (3) contralateral hilar mossy cells that project to the inner molecular layer (Witter, 2007; Kumamoto et al., 2012). Expression of ionotropic AMPA [2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid] or NMDA (*N*-methyl-D-aspartate)

Table 2. Neurotransmitters and cell fate in the adult vertebrate brain

Neurotransmitter	Regions studied	Observations	Possible downstream mechanism	References
Acetylcholine	SVZ and SGZ (rat)	Ablation of cholinergic neurons inhibits proliferation in the SGZ. Cholinergic drugs differentially regulate proliferation in the SGZ and SVZ.	N/A	(Abrous et al., 2002; Jang et al., 2002; Mohapel et al., 2005; Van Kampen et al., 2010; Rennie et al., 2011)
Dopamine	SVZ (rodents)	Ablation of dopaminergic input inhibits proliferation. Short-term receptor agonist treatment promotes proliferation. Haloperidol treatment leads to an increased number of label-retaining cells.	D2L-receptor activation stimulates EGF release. D2L receptor-mediated regulation of proliferation is CNTF dependent.	(Diaz et al., 1997; Baker et al., 2004; Baker et al., 2005; Höglinger et al., 2004; Kippin et al., 2005; Yang et al., 2008; O'Keeffe et al., 2009; L'Episcopo et al., 2012)
Dopamine	SGZ (rodents)	Ablation of midbrain dopamine neurons inhibits proliferation in mice. D2L receptor antagonist treatment does not affect proliferation in mice or rats but promotes proliferation in gerbils.	N/A	(Dawirs et al., 1998; Wakade et al., 2002; Höglinger et al., 2004; Halim, 2004; Kippin et al., 2005)
Dopamine	Midbrain (amphibia)	Ablating midbrain dopamine neurons or haloperidol treatment activates quiescent progenitor cells	N/A	(Parish et al., 2007; Berg et al., 2010; Berg et al., 2011)
GABA	SGZ (mouse)	GABA released by PV interneurons depolarizes progenitor cells and inhibits proliferation via $GABA_A$-receptor activation	N/A	(Song et al., 2012)
GABA	SVZ (mouse)	GABA released by neuroblasts depolarizes progenitor cells and inhibits proliferation via $GABA_A$-receptor activation	GABA inhibits DNA synthesis mediated by the histone γH2AX	(Wang et al., 2003; Liu et al., 2005; Fernando et al., 2011)
Glutamate	SVZ (rodents)	Progenitor cells express glutamate receptors; glutamate promotes proliferation of SVZ-derived progenitor cells *in vitro*	Possible downstream mediators include BDNF, bFGF and CDK2	(Brazel et al., 2005; Di Giorgi-Gerevini et al., 2005; Schlett, 2006; Platel et al., 2007; Platel et al., 2008)
Glutamate	SGZ (rodents)	Under physiological conditions, NMDA-receptor agonist treatment inhibits proliferation of mGLUR5-expressing RGLs. In injured brain, NMDA-receptor agonists induce proliferation.	N/A	(Cameron et al., 1995; Kitayama et al., 2003; Nochi et al., 2012)
Nitric oxide	SVZ and SGZ (rodents)	Under physiological conditions, NO inhibits proliferation in neurogenic niches. Upon injury, NO increases proliferation.	Under physiological conditions, NO inhibits EGFR signaling. Injury-induced activation is EGFR independent.	(Packer et al., 2003; Moreno-Lopez et al., 2004; Villalobo, 2006; Torroglosa et al., 2007; Carreira et al., 2010)
Neuropeptide Y	SVZ and SGZ (rodents)	NPY has a pro-proliferative effect in neurogenic niches	Y1-receptor activation induces proliferation through the MAPK/ERK pathway, and this process is mediated by intracellular NOS	(Hansel et al., 2001; Howell et al., 2005; Agasse et al., 2008; Decressac et al., 2009; Thiriet et al., 2011; Cheung et al., 2012)
Noradrenaline	SGZ (rodents)	Ablation of noradrenergic projections inhibits proliferation in the SGZ, while pharmacological activation of the β3-adrenergic receptors promotes proliferation	Possible downstream mechanisms involve increased levels of intracellular cAMP	(Kulkarni et al., 2002; Balu et al., 2009; Jhaveri et al., 2010)
Serotonin	SVZ and SGZ (rodents)	A 5-HT-receptor agonist promotes proliferation in both SGZ and SVZ. Antagonist treatment inhibits proliferation in SGZ.	N/A	(Brezun et al., 2000; Radley and Jacobs, 2002; Banasr et al., 2004; Arnold and Hagg, 2012)

5-HT, 5-hydroxytryptamine (serotonin); BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CDK2, cyclin-dependent kinase 2; CNTF, ciliary neurotrophic factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GABA, γ-aminobutyric acid; MAPK, mitogen-activated protein kinase; mGLUR5, metabotropic glutamate receptor 5; N/A, not applicable; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; NPY, neuropeptide Y; PV, parvalbumin; RGLs, radial glial-like cells; SGZ, subgranular zone; SVZ, subventricular zone.

receptors (ion channels – see Table 1) has not been reported in the nestin$^+$ RGLs in the hippocampus (Tozuka et al., 2005; Wang et al., 2005). However, both short-term and long-term *in vivo* administration of the glutamate-receptor agonist NMDA reduces proliferation, while NMDA-receptor antagonists increase proliferation of progenitor cells in the DG (Cameron et al., 1995; Kitayama et al., 2003; Halim et al., 2004). Ablation of cells in the entorhinal cortex leads to increased proliferation, suggesting that

some of the glutamatergic input comes from this source (Cameron et al., 1995). Among the metabotropic glutamate receptors (G protein-coupled receptors), mGluR3, mGluR4 and mGluR5 have been detected on progenitor cells in the adult hippocampus (Di Giorgi Gerevini et al., 2004; Di Giorgi-Gerevini et al., 2005), and mGluR5 has been observed on a subset of RGLs (Nochi et al., 2012). Long-term treatment with a mGluR2/3 antagonist leads to increased proliferation (Yoshimizu and Chaki, 2004), whereas 7-day treatment with mGlu3R and mGlu5R antagonists reduces proliferation *in vivo* (Di Giorgi-Gerevini et al., 2005).

The effect of glutamate receptor signaling on adult neurogenesis has also been studied in the injured brain. Acute administration of group II mGlu receptor agonist has been shown to reduce injury-induced proliferation in the DG (Feng et al., 2011). Chronic activation of the ionotropic glutamate receptors in ischemic brains leads to increased proliferation in the in the DG, whereas acute administration of antagonists in brains subjected to seizures has the reverse effect (Arvidsson et al., 2001; Jiang et al., 2004).

These results suggest that the effect on precursor cells in the hippocampus is different depending on whether the brain is injured and on which receptor subtypes are predominantly expressed by the target cells. A plausible explanation of these diverging observations could be that neurotransmitter signaling in these cases is not a crucial determinant of cell fate but rather acts as a modulator. Thus, the main cellular response is not determined by the neurotransmitter but rather by other factors whose identity varies in different experimental settings.

In the SVZ, glutamate receptors have not been reported on the RGLs or on the transient amplifying cells *in vivo*. mGluRs and kainate receptors have been observed on neuroblasts in the SVZ (Di Giorgi-Gerevini et al., 2005; Platel et al., 2008; Platel et al., 2010). The origin of glutamate appears to be the subventricular astrocytes, in which vesicular glutamate transporter 1 is expressed (Platel et al., 2010). Initial results suggest that blocking glutamate signaling in the brain results in decreased proliferation of neuroblasts, whereas treatment with a mGluR2/3 agonist did not affect proliferation (Di Giorgi-Gerevini et al., 2005).

The downstream mechanisms of glutamate-mediated regulation of progenitor cell proliferation in the adult brain has not been extensively studied. Glutamate signaling is known to induce expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor and fibroblast growth factor (FGF) (Zafra et al., 1991; Uchida et al., 1998; Mackowiak et al., 2002). Further studies using converging experimental settings are needed to clarify the role of glutamate on cell proliferation and subsequent neurogenesis.

Acetylcholine

Cholinergic input into the DG comes from the medial septum (Swanson and Cowan, 1979; Dougherty and Milner, 1999) and long-term treatment with the ionotropic acetylcholine-receptor agonist nicotine has been shown to decrease proliferation in the DG (Abrous et al., 2002; Jang et al., 2002). In the DG, fibers expressing choline acetyltransferase have been observed in close proximity to progenitors, although no such fibers have been observed in the SVZ (Kaneko et al., 2006). Muscarinic acetylcholine receptors have been identified on RGLs and polysialic acid-neural cell adhesion molecule-positive (PSA-NCAM$^+$) cells in the SGZ (Kaneko et al., 2006; Itou et al., 2011).

Ablation of cholinergic neurons in the adult brain leads to reduced proliferation in the SGZ and also to impaired spatial memory (Mohapel et al., 2005a; Van Kampen and Eckman, 2010). Studies in which acetylcholine-mediated signaling was pharmacologically manipulated for 10 days revealed that activation of muscarinic M1 receptors leads to increased proliferation in the SGZ, whereas activation of nicotinic receptors had the reverse effect (Van Kampen and Eckman, 2010). Acute administration of the acetylcholine-receptor agonist physostigmine inhibits cell proliferation in the DG, while long-term treatment with the acetylcholinesterase inhibitor donepezil or the muscarinic acetylcholine receptor antagonist scopolamine does not affect the number of cells expressing proliferating cell nuclear antigen (Mohapel et al., 2005b; Kotani et al., 2006).

Serotonin

Serotonergic projections originating from the raphe nucleus are found in the DG (Mongeau et al., 1997). Depletion of these neurons leads to decreased proliferation in the DG (Brezun and Daszuta, 1999). This effect is rescued by grafting of fetal raphe neurons, suggesting that serotonin (5-hydroxytryptamine, 5-HT) has a stimulating effect on neurogenesis in the DG (Brezun and Daszuta, 2000). Mice that lack the 5-HT transporter (5-HTT), which is required for 5-HT reuptake into the presynaptic cell, have higher 5-HT levels in the synaptic cleft and extra-synaptic area, and showed an increased number of proliferating cells in the DG at 14.5 months (Schmitt et al., 2007). Several experiments followed up these studies. First, chronic administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI) increased BrdU incorporation in the DG (Yoshimizu and Chaki, 2004; Encinas et al., 2006). Second, both acute and chronic pharmacological manipulations of 5-HT receptor signaling affect proliferation of adult neural progenitor cells in the SVZ and the SGZ (Banasr et al., 2004). For example, a single injection of 5-HT1A-receptor antagonists decreases BrdU incorporation in the DG, and activation of the same receptor leads to an increase in BrdU incorporation (Radley and Jacobs, 2002; Banasr et al., 2004; Huang and Herbert, 2005; Grabiec et al., 2009). Other 5-HT receptors have been implicated in neurogenesis, including 5-HT1B, 5-HT2A, 5-HT2C and 5-HT4 (Banasr et al., 2004; Lucas et al., 2007; Jha et al., 2008). Nevertheless, there remains some controversy surrounding the expression pattern of these receptors in the neurogenic zones (Councill et al., 2006; Hitoshi et al., 2007).

Noradrenaline

Noradrenergic projections originating from the locus coeruleus project to the DG (Loy et al., 1980; Mongeau et al., 1997). Administration of the noradrenaline reuptake inhibitor reboxetine leads to increased proliferation in the hippocampus (Malberg et al., 2000). Further studies have revealed that a single intrahippocampal injection of a β_3-adrenergic receptor (β_3-AR) agonist into the brain or systemic administration over 7 days of isoproterenol, a nonselective β-AR agonist, increases proliferation in the DG and leads to higher number of nestin$^+$ GFAP$^+$ cells (Jhaveri et al., 2010). Ablation of noradrenergic neurons leads to reduced proliferation of progenitor cells in the SGZ, although proliferation in the SVZ remains unchanged after such injury (Kulkarni et al., 2002; Balu et al., 2009). These studies indicate different responses of progenitor cells to noradrenaline signaling, depending on their location in the brain. The issue remains unresolved of whether these observations reflect inherent differences between progenitor cells in the SGZ versus SVZ, or whether the environment dictates responsiveness to noradrenaline signaling. Such a context-dependent effect could be explained, for example, by an indirect

non-cell autonomous action of neurotransmitters through other extrinsic factors.

The downstream mechanisms of noradrenergic control of progenitor cell proliferation in the adult brain have not been extensively examined. Nevertheless, activation of β_3-AR has been shown to induce increased levels of intracellular cAMP, which in turn is known to regulate proliferation of progenitor cells (Nakagawa et al., 2002; Jhaveri et al., 2010; Doze and Perez, 2012). Further studies are needed to examine this hypothesis.

Nitric oxide

NO is an atypical neurotransmitter, in the sense that it is not stored in vesicles or released by exocytosis, but is rather synthesized at the location of release and diffuses through membranes into neighboring cells. In the brain, NO is synthesized by three different kinds of nitric oxide synthases (NOSs), neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS) (Jaffrey and Snyder, 1995; Prast and Philippu, 2001). nNOS is expressed by neurons in close proximity to the SVZ and the DG (Valtschanoff et al., 1993; Moreno-López et al., 2000; Islam et al., 2003). Under physiological conditions, NO inhibits neurogenesis (Packer et al., 2003; Moreno-Lopez et al., 2004; Villalobo, 2006). Although 2-month-old mice that lack functional nNOS have increased proliferation in both the SVZ and DG, in aged mice (18 months) the stem cell population in the DG appears to be smaller, and proliferation is significantly reduced compared with control littermates (Packer et al., 2003; Keilhoff, 2011). These observations indicate that NO keeps slowly proliferating stem cells quiescent, and lack of nNOS accelerates the depletion of stem cells. *In vitro* studies have suggested that NO inhibits proliferation partly by inhibiting the EGF receptor, whereas the stimulatory effect of NO after injury is independent of the EGF receptor (Torroglosa et al., 2007; Carreira et al., 2010).

Neuropeptide Y

The role of neuropeptide Y (NPY) in adult neurogenesis was first described in the olfactory epithelium, where NPY was found to increase proliferation of neural progenitor cells (Hansel et al., 2001). In the brain, NPY is widely expressed and has now been shown to control numerous aspects of neurogenesis. In the hippocampus, NPY is expressed by the GABAergic interneurons that are situated in the hilus and in the DG (Köhler et al., 1986; Freund and Buzsáki, 1996). *In vivo* and *in vitro* studies show that NPY has a pro-proliferative effect in both the SVZ and the SGZ (Howell et al., 2005; Agasse et al., 2008; Decressac et al., 2009; Thiriet et al., 2011).

Studies using knockout mice and receptor-specific modulators found that the Y1 receptor is essential for the NPY-mediated effect on progenitor proliferation (Hansel et al., 2001; Howell et al., 2005; Agasse et al., 2008; Decressac et al., 2009). A recent study points towards an epistatic relationship between NPY and NO signaling (Cheung et al., 2012). This work on cultured nestin$^+$ hippocampus-derived cells suggests that the pro-proliferative effect of NPY is dependent of endogenous NO signaling.

Interaction with other signaling systems

A crucial issue is whether cell fate decisions are directly or indirectly controlled by neurotransmitters. Signaling through neurotransmitter receptors may be relayed through other signaling systems (Fig. 2). Thus, cell proliferation and survival may be promoted by neurotransmitters indirectly: for example, through increasing release of either growth or neurotrophic factors that in turn function in paracrine and/or autocrine manners. Alternatively, neurotransmitters may upregulate tyrosine kinase receptors and hence downstream signaling without increasing ligand expression. Related to this, and touched on above, is the issue of the extent to which neurotransmitters are crucial determinants of cell fate or, conversely, tune cellular responses to other signals. It is possible that neurotransmitters only amplify or dampen other signals, for example growth factors, but they could also establish cellular responsiveness to other factors. However, other signaling pathways may act as modulators of neurotransmitter signaling. Neurotransmitters and cytokines may also control neurogenesis independently and by acting on different cell populations during different steps in the process. At present, the available literature on the mechanisms underlying such interactions is relatively sparse. Nevertheless, several reports suggest interactions between neurotransmitter, growth factor, neurotrophic factor and cytokine signaling pathways both in the SVZ and the hippocampus (Yang et al., 2008; Winner et al., 2009; Colditz et al., 2010; Merlo et al., 2011). Neurogenesis in the hippocampus is the most frequently examined process in the context of neurotransmitter signaling, not the least because stress and antidepressants, such as SSRIs, seem to have opposing effects on neurogenesis. Although stress leads to reduce hippocampal neurogenesis, chronic antidepressant treatment has the opposite effect (Duman and Li, 2012; Eisch and Petrik, 2012).

Interactions in hippocampal neurogenesis

Several reports link BDNF to neurotransmitter-mediated neurogenesis. Administration of antidepressants to *Bdnf*$^{+/-}$ animals or animals in which BDNF-receptor signaling is impaired showed that neurotransmitters and BDNF produce coordinated effects on net neurogenesis: whereas the antidepressant increases proliferation, BDNF is important for the long-term survival of newborn neurons (Sairanen et al., 2005). In accordance with these observations, administration of the SSRI fluoxetine to mice lacking the BDNF receptor p75 increased proliferation but did not change the number of newborn neurons in the DG (Colditz et al., 2010). However, simultaneous blocking of the BDNF receptor trkB indicated that the pro-proliferative effect of fluoxetine was mediated through trkB (Pinnock et al., 2010). The monoamine

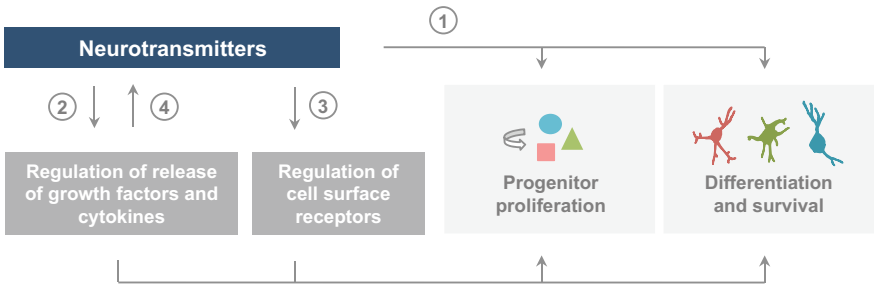

Fig. 2. Interactions between neurotransmitters and other signaling systems. Cell fate decisions during neurogenesis such as proliferation, differentiation and survival could be regulated by neurotransmitters directly (1) or indirectly through regulation of soluble factors (2) and their receptors (3). There are also data supporting the idea that growth factors regulate cell fate decisions through the release of neurotransmitters (4).

reuptake inhibitor tesofensine also increases BDNF mRNA levels (Larsen et al., 2007). Similarly, selective α2-AR antagonist treatment caused increased BDNF expression concomitant with improved survival of newborn neurons without any observed effect on progenitor cell proliferation (Rizk et al., 2006).

The interaction between neurotransmitters and neurotrophic factors is not necessarily unidirectional. A recent study indicated a reciprocal interaction, showing that BDNF promotes differentiation and maturation of progenitor cells by enhancing GABA release in the SGZ (Waterhouse et al., 2012). A potential interaction between the vasculature, hippocampal neurogenesis and neurotransmitters was suggested by the finding that the SSRI fluoxetine increased vascular endothelial growth factor (VEGF) expression and cell proliferation, while co-administration of an antagonist of the VEGF receptor Flk1 abolished the effect of the antidepressant on cell proliferation (Warner-Schmidt and Duman, 2007). The source of VEGF in the hippocampus is unclear, but it is noteworthy that blood vessels provide scaffolds for migrating neuroblasts in the olfactory bulb (Bovetti et al., 2007). In addition, several studies have identified a specialized vascular niche for NSCs (Palmer et al., 2000; Mirzadeh et al., 2008; Shen et al., 2008; Tavazoie et al., 2008) and the vasculature can provide guidance to migrating neuronal precursors through BDNF signaling (Snapyan et al., 2009).

Interactions in SVZ neurogenesis

Dopamine-receptor agonists applied to SVZ-derived neurospheres stimulate BDNF release, increase cell proliferation and increase the number of differentiating cells (Merlo et al., 2011). The exact mechanism of the crosstalk between dopamine receptors and BDNF signaling remains unclear but the increased number of differentiated cells in the cultures is blocked by inhibition of Akt signaling both after administration of BDNF and a selective D3-receptor agonist (Merlo et al., 2011). Interestingly, neuronal maturation in neonatal striatum and adult rat nucleus accumbens is promoted by activation of dopamine receptor signaling, which is linked to BDNF production through Ca^{2+} signaling and Ca^{2+}/calmodulin-dependent protein kinase II activation (Hasbi et al., 2009).

In an analogous manner, dopamine signaling can modify EGF receptor expression. Treatment with the dopamine-receptor agonist pramipexole leads to increased EGF receptor expression in SVZ-derived neuronal progenitor cells *in vitro*. In accordance with this, pramipexole treatment increases olfactory bulb neuron number, seemingly as a consequence of enhanced proliferation in the SVZ (Winner et al., 2009). Further support for dopamine/EGF crosstalk was provided by experiments showing that dopamine receptor-mediated stimulation of cell proliferation was EGF receptor dependent. Moreover, EGF levels drop with reduced numbers of dopamine neurons, along with the number of newborn neurons. Consistently, individuals with Parkinson's disease have lower levels of EGF receptor in the SVZ compared with controls (O'Keeffe et al., 2009).

Dopamine signaling is also linked to CNTF. CNTF is known to increase survival of neurons, and intra-cortical injection of CNTF increases proliferation of SVZ cells (Arakawa et al., 1990; Emsley and Hagg, 2003). CNTF is expressed by astrocytes in the SVZ and the DG, which are in close proximity to dopaminergic nerve terminals. In contrast to controls, *Cntf*$^{-/-}$ mice do not show increased proliferation in the SVZ upon D2-receptor agonist treatment. Moreover, nigrostriatal denervation does not affect cell proliferation in *Cntf*$^{-/-}$animals (Yang et al., 2008).

Stimulation of nicotinic cholinergic receptors promotes cell proliferation in SVZ, concomitant with increased FGF2 mRNA levels. Antibodies against FGF2 and blockade of FGF receptor signaling abolished the increased cell proliferation resulting from acute nicotine-receptor agonist administration (Mudò et al., 2007). It is noteworthy that although FGF2 is expressed by GFAP^{+}/nestin^{-} cells, FGFR1 is expressed by nestin^{+} cells, indicating a paracrine action of FGF.

Although the above studies all indicated that neurotransmitters stimulate proliferation through growth factor or cytokine signaling, the reverse effect (inhibition of proliferation) was demonstrated in the case of NO. NO normally inhibits signaling through EGF receptors, and blocking NO synthesis therefore promotes neurosphere formation and growth (Torroglosa et al., 2007). Somewhat unexpectedly, NO seems to have the opposite effect in a model of cerebral ischemia, although the pro-mitotic effect of NO in that context might not be mediated through EGF signaling (Carreira et al., 2010).

Neurotransmitter-mediated control of brain size and regeneration

Control of NSC fate is crucial both for the maintenance of the homeostatic state and for its restoration following stress or trauma. This very broadly defined task has many facets and its regulatory needs are context dependent. For example, in brain regions with constitutive production of neurons, NSCs must be kept cycling in order to maintain homeostasis. Conversely, regions with no or very little cell turnover, NSCs or cells with stem cell potential should essentially be kept quiescent. Both of these archetypical steady states are amenable to adjustment in response to changes in the environment. The extent of flexibility varies among species, and hence various model organisms provide different tools with which to address these issues.

Neurotransmitter-mediated control of quiescence

As discussed above, substantial neurogenesis in mammals is restricted to the SVZ and SGZ, even though it is possible to evoke neurogenic responses to some extent in other regions (for a review, see Sohur et al., 2006). By contrast, some non-mammalian vertebrates, such as fish, newt and axolotl species, display more widespread constitutive neurogenesis (Zupanc et al., 2005; Adolf et al., 2006; Grandel et al., 2006; Berg et al., 2010; Maden et al., 2013). These animals also possess a marked regenerative capacity following chemical and physical injury (Zupanc and Ott, 1999; Parish et al., 2007; Kroehne et al., 2011), characterized by upregulation of neurogenesis. Newts provide an interesting model in this context, because there is no correlation between their neurogenic/regenerative response and the distribution of constitutively active neurogenic niches (Berg et al., 2010). For example, when midbrain dopamine neurons are chemically ablated using 6-OHDA, all lost neurons are replaced in the otherwise quiescent midbrain, leading to complete histological and functional recovery with no overproduction of dopamine neurons (Parish et al., 2007). Thus, the system is useful for addressing the mechanisms underlying the reversible suppression or induction of neurogenesis, and the appropriate restoration of quiescence.

Work on newts has shown that dopamine signaling controls the production of neurons both during quiescence and during regeneration following chemical ablation. First, systemic administration of dopamine-receptor antagonists undermines the normal quiescence of RGLs, leading to *de novo* neurogenesis from RGLs and to the appearance of excessive number of dopamine neurons (Berg et al., 2011). Second, administration of L-DOPA (L-3,4-dihydroxyphenylalanine), a substance widely

used to treat individuals with Parkinson's disease, efficiently blocked RGL proliferation, neurogenesis and regeneration after chemical ablation in a dopamine-receptor signaling manner (Berg et al., 2011). These results indicate a feedback-like mechanism in which the presence of sufficient number of dopamine neurons prevents formation of new neurons by keeping RGLs quiescent. Upon loss of dopamine neurons, the block is relieved, allowing cells to enter a neurogenic program, which will be an ongoing process until the block is restored by the reformation of sufficient number of neurons, and consequently homeostatic dopamine signaling.

In a conceptually similar manner, the activity of dentate granule cells, induced by social isolation of animals and relayed through GABA released by parvalbumin-expressing interneurons, was found to keep NSCs quiescent in the hippocampus (Song et al., 2012). Thus, the study establishes a communication between neurons and NSCs that is dependent on neuronal activity.

Feedback mechanisms are essential for keeping tissue size constant in many contexts (Bullough, 1965; Pellettieri and Sánchez Alvarado, 2007). Based on the above data, a tempting speculation is that neurotransmitters act as mediators between neurons and precursor cells to regulate neuron production (Fig. 3). A feedback mechanism of this kind would be a plausible means to allow compensatory changes in NSC activity in response to challenges, should these be social isolation [in the case of GABA signaling in the rodent hippocampus (Song et al., 2012)] or loss of neurons [e.g. the loss of midbrain dopamine neurons in the newt (Berg et al., 2011)]. Furthermore, in the constitutive neurogenic niche of the SVZ, the cell cycle of GFAP$^+$ cells is under tonic GABA control, which is released from the maturing neuroblasts (Liu et al., 2005; Fernando et al., 2011). Interestingly, work in the zebrafish telencephalon identified a self-limiting mechanism that controls continuous neurogenesis through inter-progenitor cell communication, in a process by which cycling progenitors inhibit the cell cycle progression of their neighbors (Chapouton et al., 2010). Although the regulation described in zebrafish relies on lateral inhibition mediated by Notch signaling rather than any neurotransmitter-mediated activity, these observations further indicate the existence of feedback loops during neurogenesis in several contexts and species.

In the context of lineage (see Fig. 1), it is noteworthy that the GABA receptor agonist muscimol did not inhibit proliferation of RGLs during newt midbrain dopamine neuron regeneration (Berg et al., 2011). In addition, when cholinergic neurons in the newt midbrain were ablated, increased dopamine levels did not inhibit progenitor cell proliferation and regeneration of cholinergic neurons (Berg et al., 2011). Both of these observations provide evidence for the co-existence of lineage-restricted NSCs in distinct anatomical regions. Interestingly, optogenetic control of somatostatin or vasoactive intestinal polypeptide-expressing interneurons did not influence RGL proliferation in the adult mouse hippocampus, as was the case with parvalbumin-expressing interneurons (Song et al., 2012). However, the hippocampus is not suitable for addressing the potential heterogeneity of stem cells with respect to neuronal subtype commitment, as neurogenesis in this region is largely restricted to one subtype of glutamatergic neuron.

Implications for regenerative medicine

Replacing neurons that are lost as a consequence of neurodegenerative disease or trauma is a major goal of regenerative medicine. One way this could be achieved is the appropriate stimulation of neurogenesis *in situ*. The neurotransmitter mediated end-product inhibition of neurogenesis found in both regenerative and non-regenerative species may have significant implications for such strategies.

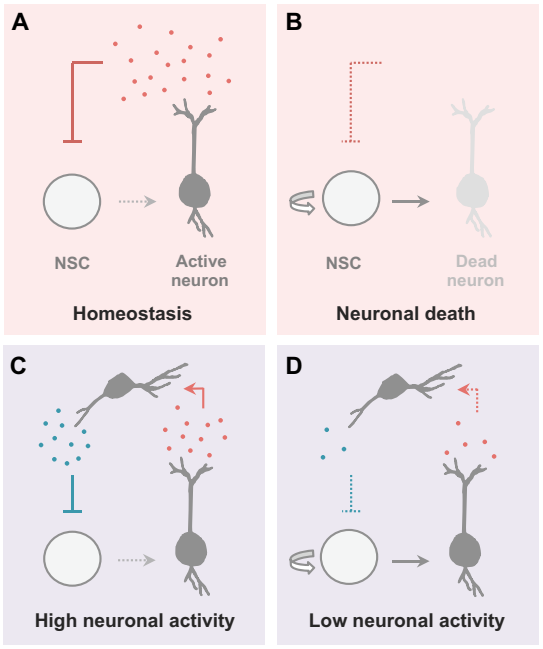

Fig. 3. Negative control of neurogenesis. (**A**,**B**) The neurotransmitter produced directly regulates neurogenesis in a feedback-like manner, as seen in newt midbrain (A). Loss of neurons and consequent drop in neurotransmitter release allows quiescent cells to re-enter the cell cycle (B). (**C**,**D**) Neurons regulate neurogenesis through an intermediate neuronal subtype, as seen in the mammalian DG, where GABAergic interneurons inhibit proliferation of stem cells, which give rise to glutamatergic granule neurons. The high activity of the network with high GABA levels counteracts proliferation (C), whereas low activity leads to increased proliferation (D). GABA, γ-aminobutyric acid; NSC, neural stem cell.

Although RGLs in mammals are mostly found in the SV and SG zones, cells with neurogenic potentials are also found in non-germinal regions, which could be targeted for cell replacement (Sohur et al., 2006; Robel et al., 2011). Supporting this possibility, results on newts (Berg et al., 2011) show that it is possible to evoke substantial neurogenesis leading to efficient regeneration in regions of the adult vertebrate brain where neurogenesis has ceased to occur after embryonic development.

Several other observations could be consistent with the idea that neurotransmitters suppress the proliferation of progenitors with stem cell properties and that interfering with this mechanism might promote regenerative neurogenesis in disease conditions. Rats injected with 6-OHDA, which recapitulates of the loss of midbrain dopamine neurons in individuals with Parkinson's disease, showed increased proliferation of nestin-expressing cells in normally non-neurogenic midbrain regions (Lie et al., 2002). This response may be a consequence of the loss of dopamine release, which normally occurs through dendrites of midbrain dopamine neurons (Geffen et al., 1976). Although activated cells did not give rise to neurons locally after the depletion of dopamine neurons, transplantation to the germinal hippocampus demonstrated their neurogenic potential (Lie et al., 2002). This suggests that, although the cellular potential is present, the local

environment is non-permissive. Generating a permissive environment in such brain regions would have clear implications for regenerative medicine. Given that a frequent treatment for the motor symptoms of individuals with Parkinson's disease is pharmacological compensation of dopamine loss by L-DOPA, it would be important to investigate whether cell cycle re-entry of neurogenic progenitors in the mammalian midbrain is also under the negative control of dopamine signaling.

A number of reports in animal models of Alzheimer's disease are also consistent with a compensatory proliferative response to loss of appropriate neuronal function. Mice carrying a mutation in the amyloid precursor protein showed increased hippocampal proliferation, which the authors suggest could be a consequence of impaired neurotransmission (Jin et al., 2004a). Several studies reported increased proliferation and a higher number of immature neurons in the hippocampus of a transgenic mouse model of Alzheimer's disease (Lopez-Toledano and Shelanski, 2007; Yu et al., 2009). In addition, another report showed an increased number of immature neurons in the brains of individuals with Alzheimer's disease (Jin et al., 2004b). However, no connection between a presumed loss in neurotransmitter signaling and enhanced neurogenesis has been firmly established.

Conclusions

Accumulating evidence demonstrates that alterations in neurotransmitter signaling impinge on adult neurogenesis. These effects are diverse and context dependent, and further work is required to clarify further how various neurotransmitter signaling pathways control neurogenesis. In particular, new knowledge regarding the downstream signaling pathways is warranted, which is important both for understanding the mechanisms of neurotransmitter signaling in the context of cell fate decisions and for pinpointing possible drug targets.

The substances used for analyzing these phenomena are often drugs administered to individuals with various neurological disorders, including depression and neurodegenerative diseases, such as Parkinson's disease. Thus, it is important to examine further how administration of these drugs affects neurogenesis. To make further progress in our understanding of how neurotransmitters mediate information exchange between neurons and their precursors it seems essential to refine and complement the currently dominating strategy of systemic drug administrations. Such refinement should ideally include fate-mapping approaches and targeted activation of neuron firing.

With these approaches to hand, considerable progress could be made in our understanding of the mechanisms and consequences of neurotransmitter-mediated regulation of neurogenesis. Combining cell-tracking studies with experimental manipulation of neurotransmitter release should help us to understand how stem and progenitor cells are organized, and to what extent neurotransmitters influence the production of neurons in a subtype selective manner in different brain regions during normal physiological conditions and in brain disorders.

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Competing interests statement

The authors declare no competing financial interests.

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