From progenitors to integrated neurons: Role of neurotransmitters in adult olfactory neurogenesis.

From progenitors to integrated neurons: Role of neurotransmitters in adult olfactory neurogenesis

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ABSTRACT
Adult neurogenesis is due to the persistence of pools of constitutive stem cells able to give rise to a progeny of proliferating progenitors. In rodents, adult neurogenic niches have been found in the subventricular zone (SVZ) along the lateral ventricles and in the subgranular zone of the dentate gyrus in the hippocampus. SVZ progenitors undergo a unique process of tangential migration from the lateral ventricle to the olfactory bulb (OB) where they differentiate mainly into GABAergic interneurons in the granule and glomerular layers. SVZ progenitor proliferation, migration and differentiation into fully integrated neurons, are strictly related processes regulated by complex interactions between cell intrinsic and extrinsic influences. Numerous observations demonstrate that neurotrasmitters are involved in all steps of the adult neurogenic process, but the understanding of their role is hampered by their intricate mechanism of action and by the highly complex network in which neurotransmitters work. By considering the three main steps of olfactory adult neurogenesis (proliferation, migration and integration), this review will discuss recent advances in the study of neurotransmitters, highlighting the regulatory mechanisms upstream and downstream their action.

Keywords: Adult neurogenesis; Neurotransmitters; Interneuron

1. Introduction
Besides their classical role in chemical communication, neurotransmitters are reported to act very early during neurogenesis playing important functions on cell development (Behar et al., 1994, 1999; LoTurco et al., 1995).
Neurogenic processes, classically thought to occur only during brain development, persist in selected regions of the adult mammalian brain. During adulthood, the production of new functional neurons takes place in the hippocampal dentate gyrus and in the subventricular zone-olfactory bulb (SVZ-OB) system (Ming and Song, 2005). In the adult hippocampus, neurogenesis generates additional excitatory granule cells, whereas in the SVZ of the lateral ventricle neurogenesis gives rise mainly to inhibitory interneurons destined for the OB (Fig. 1). Several studies suggest that neurogenesis in these regions is modulated by experience and correlated to learning and memory functions (Zhao et al., 2008a). However, the role of neurogenic processes in the context of the mature brain is still elusive. Both forms of adult neurogenesis progress via division of radial glia-like stem cells into rapidly dividing intermediate progenitor cells and production of post-mitotic cells. In the SVZ-OB system a prominent migratory process takes place: neuronal progenitors travel along the rostral migratory stream (RMS) from the SVZ to the OB and accessory OB (AOB), where they differentiate and integrate functionally into local networks (Luskin, 1993; Oboti et al., 2009; Peretto et al., 2001).
Adult neurogenesis is a complex process that must be regulated at different stages of cell development including proliferation, migration and integration, in order to generate and functionally incorporate the new neurons. The final success of this event, which may sustain both physiological adaptation and repair processes (Lledo et al., 2006; Taupin, 2006; Vandenbosch et al., 2009), results from the interaction between intrinsic neuronal growth properties and regulatory molecules in the microenvironment. Moreover, external conditions including sensory, motor or

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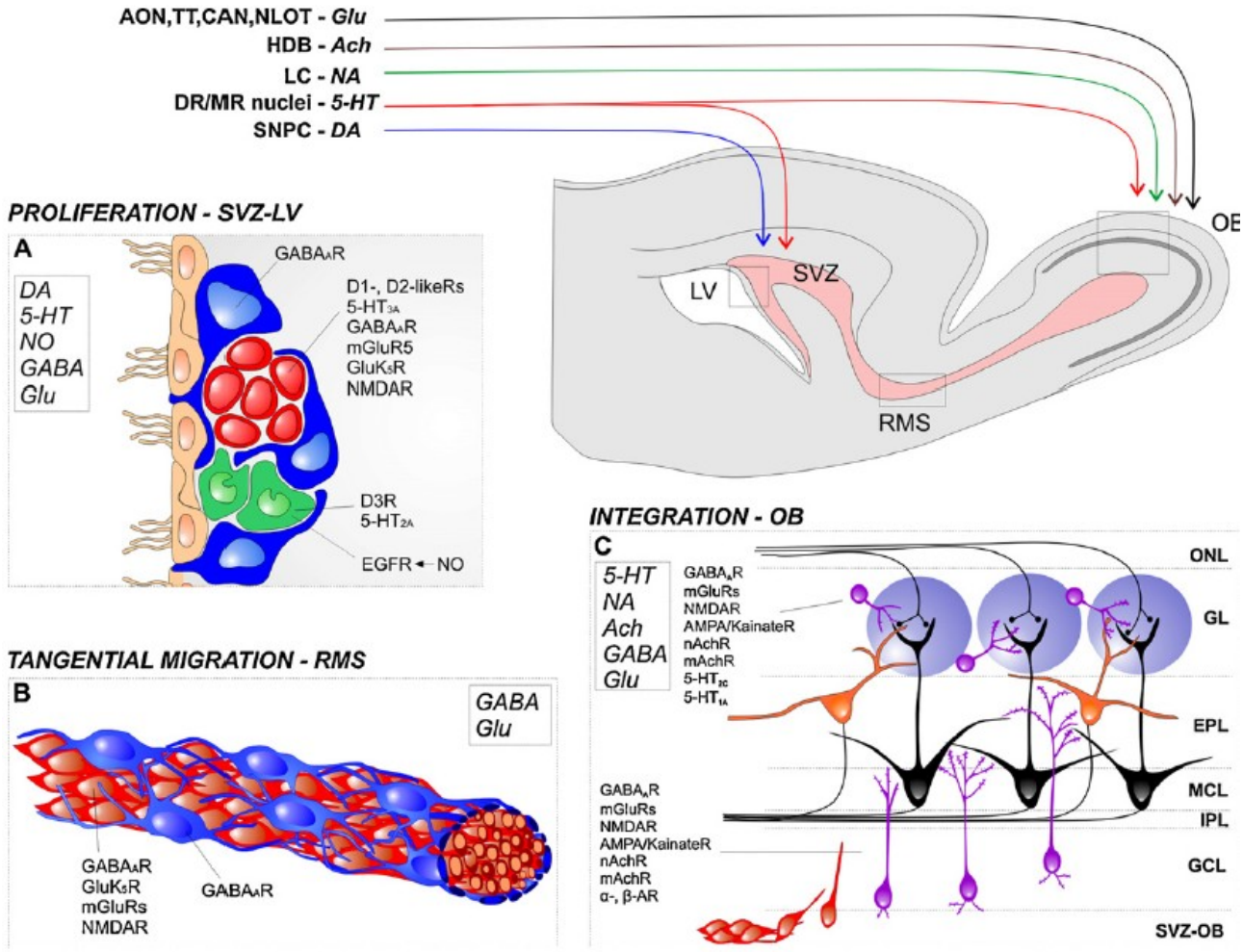

Fig. 1. Schematic representation of neurotransmitters controlling adult neurogenesis in the SVZ-OB system. A large number of neurotransmitters locally synthesized or released by afferents from different brain regions act at different steps of adult neurogenesis, regulating proliferation (A), migration (B) and integration (C) of newly generated cells. (A) Proliferation takes place in the SVZ lining the lateral ventricle, where astrocytes-like cells (type-B cells, blue) slowly divide to give rise to transiently amplifying progenitor cells (C-type cells, green) that in turn generate migrating neuroblasts (A-type cells, red). (B) Neuroblasts originated in the SVZ migrate tangentially along the RMS to reach the OB. In the adult, a characteristic ‘‘chain’’ migration involving bulks of cells sliding into the longitudinally oriented glial tubes has been described. (C) Once in the OB, newborn cells differentiate into PGCs in the Gl, and in GCs in the Gcl. 5-HT, 5-hydroxytryptamine, serotonin; ACh, acetylcholine; DA, dopamine; GABA, γ -aminobutyric acid; Glu, Glutamate; NA, Noradrenaline; NO, nitric oxide; AON, anterior olfactory nucleus; CAN, cortical amygdaloid nucleus; DR/MR, dorsal and medial raphe nuclei; HDB, horizontal limb of the diagonal band of Broca; LC, locus coeruleus; NLOT, nucleus of the lateral olfactory tract; PC, piriform cortex; SNPC, substantia nigra pars compacta; TT, tenia tecta; SVZ, sub-ventricular zone; RMS, rostral migratory stream; Onl, olfactory nerve layer; Gl, glomerular layer; Epl, external plexiform layer; Mcl, mitral cell layer; Gcl, granule cell layer. PGCs, periglomerular cells; GCs, granule cells.

social stimuli, as well as pathological conditions, may influence different steps of neurogenesis (Deng et al., 2010; Zhao et al., 2008b; Lazarini and Lledo, 2010;Whitman and Greer, 2009) and be mediated by context-dependent modulation of specific signals that include neurotrophins and neurotransmitters.

In this context, this review will cover recent progress on the impact of the major classes of neurotransmitters on adult neurogenesis, focusing on the SVZ-OB system. We will cover the role of neurotransmitters in regulating the different stages of adult OB interneuron development, from proliferation to migration and integration.

2. Cell proliferation

Within the adult SVZ, GFAP-expressing astrocyte-like cells, also called B-type cells, act as neural stem cells (Doetsch et al., 1999). These cells are slowly dividing progenitors which give rise to transiently amplifying progenitor cells, or C-type cells, expressing the epidermal growth factor receptor (EGFR). In turn, C-type cells generate neuroblasts, neural progenitor cells also called A-type cells, which express doublecortin (DCX) and PSA-NCAM. It is these neuroblasts that travel along the RMS to the OB (Lois and Alvarez-Buylla, 1994) (Fig. 1A).
A plethora of molecular factors have been implicated in the control of proliferation in the SVZ, including neurotransmitters, neurotrophic/growth factors and their reciprocal interactions (Table 1). Neurotransmitter inputs to cells in the SVZ could derive from resident cells, as well as from afferents projecting to the SVZ from different brain regions. In particular, the SVZ receives rich dopaminergic and serotonergic afferents while no cholinergic terminals are present (Azmitia and Segal, 1978; Freundlieb et al., 2006; Kaneko et al., 2006).

2.1. Monoamines: dopamine and serotonin

Dopamine is one of the most effective neurotransmitter governing proliferation of SVZ cells and the sole source of dopamine in the adult SVZ derives from afferents originating in the pars compacta of the substantia nigra (Freundlieb et al., 2006). Supporting a primary role for extrinsic dopaminergic innervation, dopamine transporters have been found in the afferent dopaminergic fibres but not on SVZ cells (Shibui et al., 2009), and tyrosine hydroxylase (TH), the enzyme involved in the synthesis of dopamine, is absent in all cell types of the SVZ suggesting local synthesis of dopamine is not taking place. Ablation of the SVZ dopaminergic innervation in mice, rats and non-human primates using the neurotoxins MPTP and 6-hydroxydopamine, results in a reduced cell proliferation in the SVZ (Baker et al., 2004; Freundlieb et al., 2006; Hoglinger et al., 2004; Winner et al., 2006). Reduced proliferation following degeneration of dopaminergic innervation, has been attributed to action on C-type cells (Borta and Hoglinger, 2007; Hoglinger et al., 2004); indeed, dopaminergic fibres reaching the SVZ preferentially contact C-type EGFR+ cells in both rodents and primates. Interestingly, a decreased rate of cell proliferation has been reported in the SVZ of post-mortem brain tissues from Parkinson's patients, a condition characterized by forebrain dopamine depletion secondary to degeneration of dopaminergic neurons in the substantia nigra pars compacta (Hoglinger et al., 2004). In these brains, the number of C-type cells is reduced compared to age-matched controls (Hoglinger et al., 2004; O'Keeffe et al., 2009).
Although numerous in vitro and in vivo observations have established the involvement of dopamine in SVZ proliferation, the mechanisms mediating this effect remain controversial (Borta and Hoglinger, 2007). Dopamine receptors are classified as either D1-like (D1 and D5) or D2-like (D2, D3 and D4) and both families appear early during embryonic development in the proliferative germinal areas of the brain. Among them, D3R retains the highest level of expression in the adult SVZ (Araki et al., 2007; Diaz et al., 1997; Kim et al., 2010) and is specifically expressed in the murine C-type cells and niche astrocytes (non-astrocytes-like stem cell; Kim et al., 2010). However, reports show that both D1- and D2-like receptors are expressed on migrating neuroblasts (Hoglinger et al., 2004; Kim et al., 2010).
In vitro assays using neurosphere cultures obtained from the SVZ of adult mice treated with the D2-like agonists bromocriptine and apomorphine, show significant increase in cell proliferation, while no effect is observed with the D1-like agonist SKF38393 (Coronas et al., 2004; Hoglinger et al., 2004). Recently, Merlo et al. (2011) showed that treatment of secondary neurospheres obtained from adult SVZ with the dopamine agonist pramipexole (PPX), causes a marked induction of cell proliferation that is sensitive to the selective D3 receptor antagonist U99194A as well as to sulpiride (D 2/3 R antagonist) (Merlo et al., 2011). PPX treatment significantly increases the percentage of

Table 1
Summary of known neurotransmitter role on adult neurogenesis in the SVZ-OB system.

	Proliferation	Migration	Integration	References
Acethylcholine				
Effects	nd	nd	Controversial (survival)[46–49]	1. Baker et al. (2004) 2. Hoglinger et al. (2004)
Target receptors	nd	nd	nAchRs, mAchRs[46,50] [neuroblasts]	3. Winner et al. (2006) 4. Freundlieb et al. (2006) 5. Borta and Hoglinger (2007)
Source	nd	nd	HDB[51]	6. O'Keeffe et al. (2009) 7. Coronas et al. (2004)
Putative interacting factors	nd	nd	nd	8. Merlo et al. (2011)
Dopamine				
Effects	+[1–11]	nd	nd	9. Van Kampen et al. (2004) 10. Winner et al. (2009) 11. Kim et al. (2010) 12. Yang et al. (2008)
Target receptors	D3R [C-type cells, niche astrocytes][8,11]; D1-, D2-likeRs [A-type cells][2,7,11]	nd	nd	13. Brezun and Daszuta (1999) 14. Banasr et al. (2004) 15. Keilhoff et al. (2006) 16. Hitoshi et al. (2007)
Source	SNPC[4]	nd	nd	17. Inta et al. (2008)
Putative interacting factors	EGF[6]; BDNF[5,8]; CNTF[12]	nd	nd	18. Azmitia and Segal (1978)
Serotonin				
Effects	+[13–15]	nd	=14 apex	19. Duan et al. (2008) 20. Thakker-Varia et al. (2007) 21. Nguyen et al. (2003) 22. Liu et al. (2005) 23. Stewart et al. (2002)
Target receptors	5-HT_{2A} [C-type cells][16]; 5-HT_{3A} [A-type cells][17]; 5-HT_{1A}, 5-$HT_{2A/2C}$[14]	nd	5-HT_{1A}[52]; 5-HT_{2C}[52,53]	24. Wang et al. (2003a, 2003b) 25. De Marchis et al. (2004) 26. Bolteus and Bordey (2004)
Source	DR-, MR-nuclei[18]	nd	DR-, MR-nuclei[54]	27. Di Giorgi Gerevini et al. (2004)
Putative interacting factors	BDNF, VGF[19,20]	nd	nd	28. Brazel et al. (2005)
Noradrenaline				
Effects	nd	nd	+(survival)[55–57]	29. Platel et al. (2008a) 30. Platel et al. (2008b)
Target receptors	nd	nd	α-, β-ARs[55,57]	31. Platel et al. (2010) 32. Platel et al. (2007)
Source	nd	nd	LC[58–62]	33. Cheng et al. (2003) 34. Packer et al. (2003)
Putative interacting factors	nd	nd	nd	35. Moreno-Lopez et al. (2004) 36. Romero-Grimaldi et al. (2006)
GABA				
Effects	−[21,22]	−[30,41–43]	+[63–65] (postnatal maturation)	37. Romero-Grimaldi et al. (2008) 38. Sun et al. (2005) 39. Matarredona et al. (2004)
Target receptors	$GABA_AR$ [B-, A-type cells][21–24]	$GABA_AR$ [astrocytes, A-type cells][41,42]	$GABA_AR$[64]	40. Moreno-Lopez et al. (2000) 41. Bolteus and Bordey (2004) 42. Mejia-Gervacio et al. (2011) 43. Present work
Source	A-type cells[23,25,26]	A-type cells[41]	nd	44. Gutierrez-Mecinas et al. (2007)
Putative interacting factors	nd	nd	CREB[66,67]	45. Chen et al. (2005) 46. Kaneko et al. (2006)
Glutamate				
Effects	+[27,28]	−(through $Glu_{K5}R$)[30] =(through mGluRs, NMDARs)[30,31,43]	+(survival)[31,68] =(maturation)[68]	47. Mechawar et al. (2004) 48. Cooper-Kuhn et al. (2004)
Target receptors	mGluR5, $Glu_{K5}R$, NMDARs [A-type cells][27,29–31]	mGluR5, $Glu_{K5}R$, NMDARs [A-type cells][30,31]	mGluRs, NMDARs, AMAPA/KainateRs[31,68]	49. Le Jeune et al. (1996) 50. Castillo et al. (1999)
Source	B-type cells[31,32]	nd	astrocytes, AON, TT, CAN, NLOT[31,51]	51. Matsutani & Yamamoto (2008) 52. Wright et al. (1995) 53. Petzold et al. (2009) 54. McLean and Shipley (1987) 55. Bauer et al. (2003)
Putative interacting factors	nd	nd	nd	56. Veyrac et al. (2005)
Nitric oxide				
Effects	−[33–39] (adult neurogenesis)	=35	nd	57. Veyrac et al. (2009) 58. Shipley et al. (1985)
Target receptors	Through EGFR [C-type cells][35,36]	[on migrating neuroblasts][44]	nd	59. Nicholas et al. (1993) 60. Ennis et al. (2007) 61. McLean et al. (1989)
Source	Nitrergic neurons at the SVZ-striatum boundary[37,40]; A-type cells in postnatal SVZ[37]	Nitrergic neurons surrounding the RMS[40]; RMS endothelial cells[45]	nd	62. Peretto et al. (1999) 63. Ge et al. (2007) 64. Gascon et al. (2006) 65. Akiba et al. (2009) 66. Saghatelyan et al. (2004) 67. Gascon et al. (2005)
Putative interacting factors	BDNF[33]	nd	nd	68. Lin et al. (2010)

+: positive effect; −: negative effect; =: ineffective; nd: not determined. AON, anterior olfactory nucleus; CAN, cortical

amygdaloid nucleus; DR/MR, dorsal and medial raphe nuclei; HDB, horizontal limb of the diagonal band of Broca; LC, locus coeruleus; NLOT, nucleus of the lateral olfactory tract; SNPC, substantia nigra pars compacta; TT, tenia tecta.

both astroglial (GFAP-positive) and neuronal population (DCX-/MAP2-positive cells at early and late maturation stage respectively). However, while proliferation of astroglial cells is prevented by both U99194A and sulpiride, PPX neurogenic action is impaired only by sulpiride and mimicked by brain-derived neurotrophic factor (BDNF). Accordingly, PPX increases BDNF release with a mechanism involving D2 but not D3 receptors (Merlo et al., 2011). These results suggest that dopamine may have a dual action primary stimulating C-type cells proliferation through D3R activation and sequentially a neurogenic effect mediated by D2R and BDNF action (Borta and Hoglinger, 2007; Merlo et al., 2011).

Further evidences of dopamine involvement in SVZ proliferation derive from in vivo studies. Systemic treatment of either normal or dopamine-depleted rats with the agonist 7-OH-DPAT (7-hydroxy-N,N-di-n-propyl-2-aminotetralin, a putative D3 receptor agonist), levodopa or through oral administration of PPX, significantly increases progenitor cell proliferation in the SVZ in line with in vitro reports (Hoglinger et al., 2004; O'Keeffe et al., 2009; Van Kampen et al., 2004; Winner et al., 2009). Interestingly, oral PPX treatment selectively increases adult neurogenesis only in the SVZ-OB system and is accompanied by improved motor activity even after long-term PPX withdrawal (Winner et al., 2009). In addition, administration of the D3R preferential antagonist U99194A decreases SVZ neurogenesis in vivo by acting selectively on C-type cells (Kim et al., 2010). Although most evidences indicate a positive effect of dopamine in SVZ proliferation, opposite in vivo and in vitro results have been obtained by Kippin et al. (2005). Accordingly, chronic treatment of adult rats or mice with the dopamine antagonist haloperidol (high binding affinity for D2-like receptors) results in an increase in the number of primary neurospheres that can be isolated from adult SVZ and improves the number of BrdU-positive cells in both SVZ and OB (Kippin et al., 2005). Moreover, dopamine or its agonist quinpirole (a selective D 2/3 R agonist) but not SKF38393 (D1-like agonist) administration produces a dose-dependent inhibition of neurosphere formation (Kippin et al., 2005) in vitro. Several factors can be taken into account for this discrepancy. Among these, differences in the drug administration protocol (e.g. oral versus intraventricular administration), method to assess cell proliferation (SVZ-derived neurosphere versus in vivo evaluation) and dose-dependent affinity of dopamine agonists/antagonists to different receptor subtypes. Moreover, dopamine can act directly on progenitor cells or indirectly inducing growth factor release, and drug treatment alone or coupled to specific surgical or pharmacological denervation could influence release of growth factors and in turn control cell proliferation. Indeed, besides the previously cited BDNF, dopamine-mediated effects on adult neurogenesis have been shown to involve ciliary neurotrophic factor (CNTF) (Yang et al., 2008). Dopaminergic denervation in adult mice reduces CNTF mRNA levels whereas systemic D2-like receptors agonist administration increases proliferation of neuronal progenitors in the SVZ of wild-type but not CNTF knock-out mice (Yang et al., 2008). CNTF knock-out mice show reduced neurogenesis and nigro-striatal denervation does not affect SVZ proliferation (Yang et al., 2008), suggesting that the dopaminergic innervation may regulate neurogenesis through CNTF. Moreover, additional factors are likely to be involved; indeed, epidermal growth factor (EGF) has been recently shown to promote SVZ proliferation in response to dopamine stimulation both in vitro and in vivo (O'Keeffe et al., 2009).

In addition to dopamine, serotonin (5-HT) is also implicated as a regulator of neurogenesis. The notion that depression can arise from impaired hippocampal neurogenesis (Kempermann, 2002; Kempermann et al., 2008) and that an array of antidepressants work by stimulating neurogenesis, has led to the ''neurogenesis hypothesis of depression'' (Duman, 2004). However, while many studies address the involvement of serotonin in hippocampal neurogenesis and major depression/mood disorders, less is known about 5-HT role on the SVZ neurogenic niche. Serotonergic terminals, originating from the dorsal and medial raphe nuclei, innervate most of the forebrain structures (Azmitia and Segal, 1978) and dense 5-HT immunoreactive fibres are observed

in the walls of the lateral ventricles intermingled with newborn BrdU-labeled cells (Banasr et al., 2004). With the exception of the 5-HT_3 receptor, a ligand-gated ion channel, all other serotonin receptors are G protein-coupled (Pauwels, 2000). Although pharmacological in vivo and in vitro studies demonstrate that different families of 5-HT receptors (5-HT_{1A} , 5-HT_{1B} , 5-HT_{2A} , 5-HT_{2C}) are involved in the regulation of adult neurogenesis, their cellular localization in the SVZ is largely unknown. In vitro neurosphere cultures mainly composed of C-type cells, express only the 5-HT_{2A} receptor (Hitoshi et al., 2007). Transgenic mice expressing green fluorescent protein (GFP) under the promoter of 5-HT_{3A} receptor, as well as in situ hybridization data, show high expression of 5-HT_{3A} receptor on SVZ neuroblasts (Inta et al., 2008). Moreover, serotonin transporters have been found on both neuroblasts and 5-HT-projections to the SVZ (Diaz et al., 2009; Shibui et al., 2009). Acute 5-HT depletion via injection of the 5-HT neurotoxin 5,7-DHT (5,7-dihydroxytryptamine) in the raphe nuclei of adult rats, as well as chronic administration of 5-HT synthesis-inhibitor parachlorophenylalanine, result in significant reduction of cell proliferation in the SVZ (Brezun and Daszuta, 1999). Correspondingly, acute administration of serotonin receptor 5-HT_{1A} specific agonist 8-OH-DPAT (8-hydroxy-2-(di-N-prpylamino) tetralin) or the 5-$HT_{2A/2C}$ agonist DOI (2,5-dimethoxy-4-iodophenyl-2-aminopropane), lead to a net increase of cell proliferation in the SVZ (Banasr et al., 2004). It is proposed that failure of hippocampal neurogenesis could help to explain the cognitive deficits of depression (Kempermann, 2002; Kempermann et al., 2008) and that these effects can be at least in part recovered by antidepressant drugs of the serotonin reuptake inhibitor class. Changes in proliferation have also been observed in the SVZ following olfactory bulbectomy, an animal model for depression leading to depression-like behavioural deficits, such as reduced learning performance and altered aggression (Keilhoff et al., 2006). Decreased cell proliferation in the SVZ of bulbectomized rats is restored by imipramine, an inhibitor of 5-HT reuptake (Keilhoff et al., 2006). Similarly, antidepressant drugs have been also reported to reverse the loss of adult neural stem cells in the SVZ following chronic stress both in vitro and in vivo (Hitoshi et al., 2007) supporting that various components of the limbic system may exhibit alterations that can be reversed by monoaminergic antidepressants. Although progresses have been made in understanding serotonin role and regulation in SVZ adult neurogenesis, many questions remain still unsolved; i.e. the cellular targets of serotonin-mediated effects have not been described yet. Moreover, ‘‘indirect’’ serotonin effect on SVZ through its interaction with neurotrophic factors or other neurotransmitters like dopamine is also plausible. Indeed, in the hippocampus inhibition of serotonin reuptake increases BDNF and neurogenesis and both 5-HT and BDNF can regulate VGF that has both neurogenic and anti-depressant effects in mice (Duan et al., 2008; Thakker-Varia et al., 2007).

2.2. Amino acids: GABA and glutamate

Many molecular components of the GABAergic signalling cascade have been identified in the SVZ. Electrophysiological evidence as well as immunohistochemical analysis for glutamic acid decarboxylase (GAD, the enzyme that catalyzes GABA synthesis) and GABA indicate functional GABA release from SVZ neuroblasts (Stewart et al., 2002; Bolteus and Bordey, 2004; De Marchis et al., 2004; Liu et al., 2005). GABA action is mediated by both ionotropic ($GABA_A$ and $GABA_C$) and metabotropic ($GABA_B$) receptors. Astrocyte–like stem cells and neuroblasts express GABA A receptors that can be activated by GABA released from neuroblasts spontaneously and upon depolarization (Liu et al., 2005; Nguyen et al., 2003; Stewart et al., 2002; Wang et al., 2003b), while it is still unknown whether $GABA_B$ and $GABA_C$ receptors are expressed in the SVZ. Moreover, astrocytes in the SVZ express the GABA transporter GAT4 that may control ambient GABA levels and limit transmitter diffusion (Bolteus and Bordey, 2004; Liu et al., 2005; Pathania et al., 2010). Functional properties of ionotropic $GABA_A$ receptors depend upon subunit composition. Molecular cloning studies have identified multiple $GABA_A$ receptor subunits in mammals: α1–6, β1–3, γ1–3, δε , π and θ (Hevers and Luddens, 1998; Bonnert et al., 1999; Whiting et al., 1999; Sinkkonen et al., 2000), whose diversity is further increased by alternative splicing (D’Hulst et al., 2009).

Immunocytochemistry on SVZ precursor cells in culture show the expression of α2, 3, 4, 5, b 1, 2–3, and γ2 subunits (Stewart et al., 2002) while neonatal PSA-NCAM-positive progenitors from neurospheres express α2, 4, 5, β1, 3,γ1, 2, 3, and δ subunit mRNA (Nguyen et al., 2003). The subunit combination of the $GABA_AR$ influences the efficacy of drugs on receptor modulation allowing to speculate on the types of subunits present in neuronal progenitors. In this context, the presence of γ2 subunit in SVZ progenitors has been further demonstrated by the low sensitivity to Zn^{2+} of $GABA_AR$-mediated currents and by the changes in GABA responses observed in the presence of the benzodiazepine agonist flunitrazepam or inverse benzodiazepine agonist DMCM (methyl 6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate) (Wang et al., 2003a, 2003b). Moreover, the benzodiazepine selective agonist zolpidem, with high affinity to α1 subunit, has low efficacy in the potentation of GABA response, supporting the absence of a 1 subunit in cultured SVZ neuronal progenitors previously described by RT-PCR and immunocytochemistry (Nguyen et al., 2003; Stewart et al., 2002; Wang et al., 2003b).

Pharmacological inhibition of GABA A receptors with SR95531 antagonist in organotypic slice culture from postnatal rat SVZ, provokes proliferation of PSA-NCAM-positive neuroblasts (Nguyen et al., 2003). Consistently, inhibition of $GABA_A$ receptors with bicuculline in SVZ cultures from young adult transgenic GFAP-GFP mice, induces increased proliferation of GFP-positive cells while broad inhibition of GAT3/GAT4 transporters induces an opposite effect (Liu et al., 2005). Based on these findings, the interaction between neuroblasts (A-type cells) and astrocyte-like stem cells (B-type cells) through a feedback involving GABA, has been proposed as a mechanism to maintain a balance between amplification and mobilization of progenitors in the SVZ. Accordingly, the release of GABA by SVZ neuroblasts would control astrocyte-like stem cell proliferation through $GABA_AR$ activation (Liu et al., 2005).

In developing neurons, the chloride equilibrium potential results in GABA exerting a depolarizing action leading to activation of voltage-gated calcium channels (VGCCs) (Owens and Kriegstein, 2002). Adult progenitor cells in the SVZ maintain many characteristics of embryonic development and GABA action on these neuroblasts results in activation L-type VGCCs and calcium increase similar to other developing neuronal systems (Nguyen et al., 2003; Wang et al., 2003b). This mechanism appears to occur not only in neuroblasts but also in SVZ astrocyte-like cells (Young et al., 2010). Indeed, using a transgenic mouse line in which GFP is expressed selectively in astrocytes cell membrane (hGFAP-MrgA1:GFP), Young and co-workers show that $GABA_A$ –induced calcium responses in astrocyte-like cells of the SVZ are predominately mediated by calcium influx through L- and T-type VGCCs (Young et al., 2010).

GABA effect on the SVZ may be antagonized by an opposite action of glutamate. The main glutamatergic source in the SVZ appears to be astrocyte-like cells (Platel et al., 2007, 2010). Indeed, SVZ and RMS astrocytes, marked by glutamate-aspartate transporter (GLAST), display intense glutamate staining, while neuroblasts (DCX+) are only weakly labeled for glutamate (Platel et al., 2007). Accordingly, a recent study showed that L-glutamate is concentrated in GLAST+ cells, which also express the vesicular glutamate transporter 1 (VGLUT1) (Platel et al., 2010). These data further support SVZ/RMS astrocytes as the source of glutamate, likely releasing in a vesicular mechanism.

Glutamate receptors are divided into different subtypes: ionotropic receptors (including NMDA and AMPA/kainate receptors), and metabotropic receptors (mGluRs, group I-III). Functional expression of AMPA or NMDA receptors has not been detected in astrocyte-like cells (Liu et al., 2005; Platel et al., 2010), while their expression on C-type cells still needs to be investigated. Neuroblasts have been shown to express functional mGluR5 and Glu K5 -containing kainate receptors, whose activation mediates increase in intracellular calcium transients (Di Giorgi Gerevini et al., 2004; Platel et al., 2008a, 2008b). Moreover, expression of functional NMDA receptors has been recently recorded in neuroblasts from the rostral part of the SVZ while no detectable currents have been identified in the more posterior SVZ along the lateral wall of the lateral ventricle nor in astrocyte-like cells (Platel et al., 2010). The percentage of NMDA responding neuroblasts increases along the

caudal to rostral SVZ-RMS axis to the OB, suggesting a continuum in maturation of newborn cells (Platel et al., 2010).
Despite the extensive characterization of glutamate and its receptors in the adult SVZ neurogenic niche, its role remains elusive. Adult mice lacking mGluR5 or treated with mGluR5 antagonists, show a reduction in the number of proliferating cells in the SVZ (Di Giorgi Gerevini et al., 2004) and activation of kainate or group II mGluRs on neurosphere cultures from postnatal rat SVZ, prevents apoptosis but only when the NMDA receptor is antagonized (Brazel et al., 2005). Thus, the complex role of glutamate depends on the receptor expression complement of the individual cells, that, in turn, may relay upon cell maturation state. Indeed, a mosaic expression of mGluR5, Glu_K5 and $GABA_A$ receptors resides in the SVZ, where $GABA_A$ expressing cells locate caudally in the SVZ and, as cells move rostrally, they begin to express a combination of multiple glutamate receptors (Pathania et al., 2010). Further studies are needed to gain a more comprehensive view of glutamate role in adult SVZ, however, it is possible that glutamate and GABA work in concert in the SVZ and that GABA anti-mitotic activity is balanced by positive regulation of glutamate on cell proliferation/survival.

2.3. Others: nitric oxide

Nitric oxide (NO) is a short-life diffusible gas synthesized by nitrergic neurons that express the neuron specific form of nitric oxide synthase (nNOS). Although NO cannot be strictly categorized as a classical neurotransmitter, it is considered in this review based on release by presynaptic terminals in an activity-dependent manner. Close proximity between nitrergic neurons and neuronal progenitors has been described in the SVZ of both postnatal (P7) and adult mice (Moreno-Lopez et al., 2000; Romero-Grimaldi et al., 2008) suggesting an action of NO on SVZ niche. Interestingly, expression of nNOS differs in postnatal development and adult age (Romero-Grimaldi et al., 2008). Neuroblasts, identified by PSA-NCAM immunolabeling, never express nNOS in the adult SVZ whereas PSA-NCAM partially overlaps with nNOS in postnatal SVZ (Romero-Grimaldi et al., 2008). In the OB, where new neurons finally integrate, colocalization of nNOS and PSA-NCAM is found in both postnatal and adult mice (Romero-Grimaldi et al., 2008), suggesting that while NO could have a paracrine effect in the adult SVZ, it may work in an autocrine manner in the OB.
NO action in the SVZ is also developmentally regulated. While prevention of NO synthesis does not affect postnatal SVZ cell proliferation, adult neuronal precursors in the SVZ are highly sensitive to nNOS inhibition (Romero-Grimaldi et al., 2008). In physiological conditions, endogenous NO negatively regulates adult SVZ cell proliferation and pharmacological inhibition of nNOS synthesis by L-NAME, 7-NI (7-nitroindazole) or its genetic inactivation, results in increased proliferation in the SVZ and consequently higher newborn cell density in the OB (Cheng et al., 2003; Moreno-Lopez et al., 2004; Packer et al., 2003; Romero-Grimaldi et al., 2006). Interestingly, enhanced neurogenesis induced by chronic nNOS inhibition impacts olfactory performance improving mice olfactory learning in an odour memory task (Romero-Grimaldi et al., 2006). Additional evidences for a direct effect of NO on SVZ neurogenesis has been obtained in nNOS knockout mice (Packer et al., 2003; Sun et al., 2005) as well as using in vitro primary cultures that show increased cell proliferation following L-NAME administration during culture period (Matarredona et al., 2004).
Due to the rapid diffusion of NO, the paracrine anti-proliferative action could be exerted on any cell types in the SVZ. However, co-labeling analysis of BrdU and specific markers for SVZ population in control condition or following L-NAME administration, show preferential action of NO on EGFR+ (Romero-Grimaldi et al., 2006), nestin+ and βIII-tubulin-negative cells (Moreno-Lopez et al., 2004), which correspond to C-type cells. In contrast, it has also been described that absence of the endothelial isoform of NOS (eNOS) decreases neurogenesis in the SVZ (Chen et al., 2005). These data suggest an unusual mechanism whereby SVZ proliferation could be differently regulated depending on which isoform of NOS is the source of the gaseous messenger (Chen et al., 2005).
There are several clues that point to EGFR as a candidate molecular target for the anti-proliferative

effect of NO in the SVZ. C-type cells, the main target of NO action in the adult SVZ, express EGFR whose activation by specific ligands, such EGF-like growth factors, increases SVZ progenitors proliferation (Craig et al., 1996; Kuhn et al., 1997). Since NO reversibly inhibits the EGFR tyrosine kinase activation in neural cells (Murillo-Carretero et al., 2009), it is possible that this receptor is involved in mediating NO action on SVZ proliferation. Interaction between NO and neurotrophins has also been proposed to regulate SVZ proliferation. In particular, it has been shown that NO acts in a positive feedback loop with BDNF to regulate neuronal progenitor cell proliferation in an in vitro model of neuronal progenitor cells (NPCs) (Cheng et al., 2003). In this work, BDNF reduces NPC proliferation and increases the expression of nNOS in differentiating neurons. The stimulatory effect of BDNF on neuronal differentiation of NPCs is blocked by L-NAME administration, suggesting that interplay between the two molecules control the proliferation and differentiation of NPCs (Cheng et al., 2003).

3. Migration

Neuroblasts originated in the SVZ migrate tangentially along the rostral extension of the SVZ to reach the OB. In the adult, a characteristic ‘‘chain’’ migration involving bulks of cells sliding into the longitudinally oriented glial tubes has been described (Lois et al., 1996; Peretto et al., 1997) (Fig. 1B). Although tangential migration begins at birth, the glial tubes do not form until the third postnatal week. In those first weeks the glial processes of astrocytes form a relative homogeneous network through which tangential migration occurs (Peretto et al., 1997, 1999, 2005). Once migrating cells reach the OB, they detach from chains and migrate radially along blood vessels (Bovetti et al., 2007b) to reach their final destination in the glomerular (Gl) and granule cell layer (Gcl) where most of them differentiate into interneurons (Luskin, 1993). Previous studies from our and other groups, reported that in rodents the average speed of adult tangential and radial neuroblast migration range from 20 to 40 μm/h and consists of cycles of higher speed advancement interspersed with stationary/slower periods (Bovetti et al., 2007a; Lois and Alvarez-Buylla, 1994; Luskin and Boone, 1994). Neuroblast migration is highly directional with the majority of cells polarized with their leading process orientated toward the OB (Bovetti et al., 2007a; Lois and Alvarez-Buylla, 1994; Luskin, 1993), although a small number of cells can migrate in opposite direction. Neuroblast migration is governed by numerous factors, including molecules mediating cell-to-cell and cell-to-substrate interactions, chemorepulsion mechanisms, extracellular matrix remodelling and neurneurotrasmitters (Pathania et al., 2010; Whitman and Greer, 2009).

3.1. Amino acids: GABA and glutamate

Among neurotransmitters, GABA and glutamate seem to be the major players in SVZ-derived neuroblast migration. Neuroblasts originating in the SVZ express both GABA and glutamate receptors in a mosaic, developmental-related combination along the caudal to rostral axis (Pathania et al., 2010). Bolteus and Bordey (2004) showed that ambient GABA reduces the speed of neuroblast migration in acute slices from young mice through activation of GABA A receptors. Activation of these receptors leads to interfere with calcium release from intracellular calcium stores and reduces migration. Furthermore, inhibition of GABA uptake by administration of the GATs blockers nipecotic acid or SNAP5114, results in elevated ambient GABA, significantly decreasing neuroblast migration speed. This highlights the role of astrocytes, that uniquely express the GABA transporter GAT4, in the homeostatic balance that regulates ambient GABA levels and consequently controls the migration rate of neuroblasts (Bolteus and Bordey, 2004).
$GABA_A$ receptor activity produces depolarizing or hyperpolarizing effects depending on Cl^- gradient across cell consequently affecting cell membrane potential (Mejia-Gervacio et al., 2011; Misgeld et al., 1986; Mueller et al., 1984). The intracellular Cl^- concentration is regulated by the activity of ionic transporters such as the $Na^+ –K^+ –2Cl^-$ (NKCCl) that increases intracellular Cl^-

concentration at rest (Yamada et al., 2004). Since the NKCCl transporter is express in migrating neuroblasts along the RMS and associated to depolarizing effect of GABA, it has been recently proposed to play a role in shaping the action of GABA in neuroblast migration (Mejia-Gervacio et al., 2011). However, although impairment of NKCC1 activity decreases cell migration along the RMS, this effect is independent of the modulation exerted by $GABA_A$ receptors (Mejia-Gervacio et al., 2011). Rather, decreased neuroblast migration could depend on the depolarization of the resting membrane potential in cells with impaired NKCC1 function (Mejia-Gervacio et al., 2011). Accordingly, depolarization induced by KCl treatment also decreases neuroblast migration (Bolteus and Bordey, 2004) suggesting that cell motility along the RMS could be regulated by manipulation of the resting membrane potential through different mechanisms independent by neurotransmission (Mejia-Gervacio et al., 2011).
Although the number of NMDA receptors expressed by neuroblasts increases progressively along the RMS, they do not appear to be involved in neuroblasts migration. Indeed, young adult single-cell NR1 knock-out mice, in which the NMDAR subunit NR1, that is essential for NMDAR functionality, has been deleted in individual neuroblasts through SVZ electroporation, do not show any difference in the speed of neuroblast migration (Platel et al., 2010). Conversely, antagonist-mediated inhibition of Glu_{K5} -containing kainate receptor but not of the metabotropic mGluR5 receptor, increases the speed of neuronal migration (Platel et al., 2008b). Using time-lapse confocal microscopy on fluorescently labeled neuroblasts in acute brain slices (Bovetti et al., 2007a; Bovetti et al., 2007b; De Marchis S. et al., 2001), we also analyzed the involvement of GABA and glutamate receptors in neuroblast tangential migration along the RMS, both in early postnatal period (P5, when chain migration does not occur yet) and in young-adult mice (P21) when glial tube are formed (Peretto et al., 2005). Application of the GABA A antagonist gabazine (10 μM) on acute brain slices, increases the migration rate by 50% and 45% in P5 and P21 mice respectively, while GABA A agonist muscimol (10 μM) decreases neuronal precursor speed by 30% (P5) and 40% (P21) (Fig. 2A and B). The percentage changes in neuroblast migration speed are a close match to those previously reported for GABA modulated RMS migration (Bolteus and Bordey, 2004) and similar between early postnatal and young adult mice. Thus, chain migration is not fundamental for GABA mediated action. We also tested the effect of AMPA/kainate and NMDA antagonists DNQX (10μM) and APV (50 μM) as well as the mGluR class I specific antagonist NPS2390 (10 μM) on P5 and P21 tangential migration. As shown in Fig. 2 we did not find any difference in neuroblast migration rate either with DNQX/APV nor NPS2390 antagonists. These results are in agreement with previous studies showing that NMDA and metabotropic glutamate receptors are not involved in RMS neuroblast migration (Platel et al., 2008b; Platel et al., 2010). However while Platel et al. (2008) show increase speed rate following inhibition of Glu_{K5} -containing kainate receptors we did not find any regulation on neuroblast migration by DNQX/APV antagonists. This discrepancy could be due to selective block of Glu_{K5} compared to the broad spectrum antagonists DNQX and APV.

3.2. Others: nitric oxide

Two main putative sources of NO can be identified along the RMS: the nitrergic neurons surrounding the RMS and extending processes parallel to neuroblast chain (Moreno-Lopez et al., 2000) and blood vessels endothelial cells that express eNOS (Chen et al.,2005) and directly contact migrating cells forming scaffold for their migration (Snapyan et al., 2009). The presence of the NO transduction machinery (Gutierrez-Mecinas et al., 2007) and of the NO synthesizing enzymes along RMS compartment (Moreno-Lopez et al., 2004), suggest a role for this diffusible gas in modulating neuroblast migration; however, controversial results have been obtained. Treatment with the nitric oxide donor DETA-NONOate [(Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl)aminio]-diazen-1-ium-1,2-diolate], promotes SVZ neuroblast migration in the ischemic brain by up-regulating the expression of the chemokine (CXC motif) receptor 4 (CXCR4) and the tyrosine kinase receptor Tie2 in the SVZ (Cui et al., 2009). Similarly, an impairment in SVZ progenitor cell migration has

been described in eNOS deficient mice both in vitro and in vivo following stroke (Chen et al., 2005). Although a role of NO in SVZ precursor migration toward the injured sites has been established in ischemic brain (Chen et al., 2005; Cui et al., 2009), chronic systemic administration of L-NAME, a broad spectrum NOS inhibitor, does not compromise constitutive neuroblast migration directed to the OB (Moreno-Lopez et al., 2004). However, global NO synthesis inhibition could hide specific effects induces by different NOS. Available genetic models or specific inhibitors for NOS isoforms will help to discriminate whether different source of NO may undergo to specific regulation and thus differently modulate SVZ neuroblast migration.

4. Integration

Once in the bulb, newborn cells differentiate mainly into olfactory interneurons. Most of the SVZ-derived cells (90%) contribute to granule cell (GC) population while a smaller part migrate further to differentiate in periglomerular cells (PGCs) in the glomerular layer (Fig. 1C). Not all the cells that reach the OB survive; about half of newborn GCs and PGCs are eliminated within a time window that extends from 15 to 45 days after they are born in the SVZ (Petreanu and Alvarez-Buylla, 2002; Bovetti et al., 2009; Whitman and Greer, 2007). Addition of new GABAergic interneurons could modulate the activity of mitral and tufted output neurons by mediating the spatial and temporal coding of olfactory inputs and outputs (Lledo et al., 2008). GCs and PGCs are represented by multiple subtypes of inhibitory interneurons, differing in their functions within the OB circuits. The best described are three major classes of PGCs characterized by expression of calbindin (CB), calretinin (CR) or only GABA (Parrish-Aungst et al., 2007). A subpopulation of GABAergic cells express TH, the rate limiting synthetic enzyme for dopamine, and have traditionally been considered PGCs. However their interglomerular connections argue that they are more appropriately classified as short axon (SA) cells (Kiyokage et al., 2010). New dopaminergic/GABAergic SA cells are also added to the OB circuit by adult neurogenesis (De Marchis et al., 2007; Kohwi et al., 2007). Among GCs, we recently characterized a subset of inhibitory interneurons defined by the expression of neurogranin, that localize in the deeper portion of the Gcl (Gribaudo et al., 2009).
The processes regulating newborn OB interneuron cell-fate, death or survival and synaptic maturation are poorly understood. Cell-autonomous mechanisms likely govern specification of OB interneurons early in their differentiation pathway through the expression of a combinatorial code of transcription factors (Bovetti et al., 2007c; De Marchis et al., 2007; Kohwi et al., 2007). Conversely activity plays an important role in SVZ-derived cell selection and synaptic integration. Higher survival rate occurs in presence of an olfactory enriched environment, or when animals are exposed to an olfactory learning experience (Rochefort et al., 2002; Alonso et al., 2006; Bovetti et al., 2009). Furthermore, odour deprivation decreases the survival rate of SVZ-derived cells as well as their dendritic length and spine density without affecting the pre-existing granule cells (Bovetti et al., 2009; Mandairon et al., 2006; Saghatelyan et al., 2005). Which factors mediate experience-dependent modulation of newborn cells survival and integration into the OB is unknown, but trophic factors and neurotransmitters are good candidates.

4.1. Acetylcholine

Cholinergic fibres from the horizontal limb of the diagonal band of Broca project to all bulbar layers, with the heaviest density occurring in the Gl and Epl, while the OB itself appears to be devoid of intrinsic cholinergic neurons (Matsutani and Yamamoto, 2008)
and no cholinergic innervation has been observed in the SVZ or RMS (Kaneko et al., 2006;

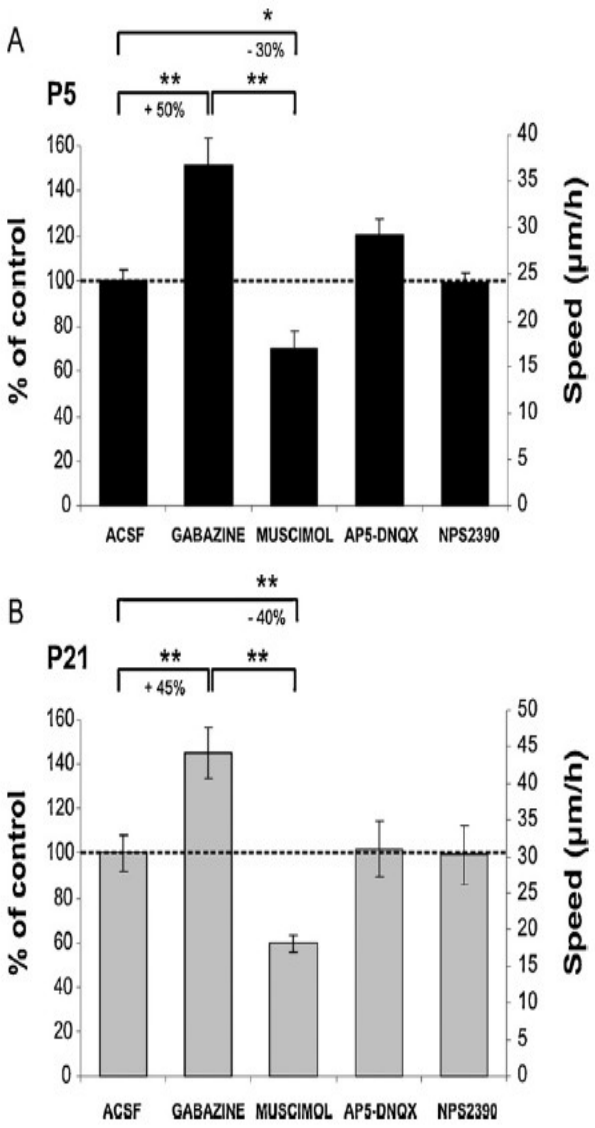

Fig. 2. Time-lapse confocal microscopy on fluorescently labeled neuroblasts in acute brain slices was used to analyze tangential neuroblast migration along the RMS in control condition and following incubation with GABA and glutamate receptor agonists and antagonists. Briefly, Cell Tracker Green (CTG) was injected into CD1 strain postnatal day 2 and postnatal day 18 mice; animals were sacrificed 2 days following CTG injection. Sagittal slices were prepared following the protocol previously described (De Marchis et al., 2001). For time lapse confocal microscopy slices were placed in a temperature-controlled chamber maintained at 34°C; through which oxygenated ACSF medium (120 mM NaCl, 3 mM KCl, 2 mM $CaCl_2$, 1.3 mM $MgSO_4$, 25 mM $NaHCO_3$, 10 mM Glucose, 5 mM BES) was flowing (2.5 ml/min). Images were taken with an Olympus confocal microscope every 10 min for 90–120 min. The speed of the migrating cells was calculated only for those cells that remained in focus for the entire duration of the imaging. The X and Y coordinates of the center of every moving cell was plotted in CorelDraw and the distance traveled calculated using the Pythagorean Theorem. The total migratory rate was calculated by summating the distances traveled between each frame divided by the total imaging time. Cells that moved less then one cell diameter were not included in the analysis as we considered these movements to be cell intrinsic. The effects of drugs on the migration rate were calculated by comparing the mean of cell velocity in control conditions (ACSF) with that in the drug-treated slices. (A and B) Average change in the speed of neuronal precursor migration along the RMS induced by applications of different drugs in P5 (A) and P21 (B) mice. GAB_AAR activation mediates neuroblast tangential migration at both ages. No influence on cell migration was detected inhibiting NMDA and AMPA or Group I metabotropic glutamate receptors. Values are expressed as percentages of control and average speed means ± SEM; one-way ANOVA followed by Bonferroni post-test was used to compare data. *$P \leq 0.05$; **$P \leq 0.01$.

Whitman and Greer, 2007). Centrifugal cholinergic fibres terminate primarily onto olfactory interneurons (Kasa et al., 1995; Nickell and Shipley, 1987) and are frequently observed to be in contact with PSA-NCAM neuroblasts in the OB (Kaneko et al., 2006) suggesting that the neuromodulatory effects of Ach in the bulb are preferentially mediated by interneurons. Ach action is mediated by two types of receptors: the nicotinic Ach receptors (nAchRs), composed by heteromeric (α4 and β2 subunits) or homomeric (α7 subunit) pentamers forming gated ion channels, and the muscarinic Ach receptors (mAchRs) a family of G-protein coupled receptors classified into 5 subtypes (m1-m5). Receptor subunit composition as well as cellular localization strongly influence Ach action. nAchR containing α7 subunits, for instance, has been shown to rapidly desensitize whereas α4- β2-containing nAchRs show slower desensitization rates (Changeux et al., 1998; Gerzanich et al., 1994; Zhang et al., 1994). Moreover, α7-containing receptors are found preferentially in synaptic location contrary to receptors composed of β2 subunits that have been localized perisynaptically (Clarke, 1993) suggesting that β2-containing receptors may be more suitable to activation through a paracrine Ach action.

Olfactory interneurons express both type of Ach receptors (Kaneko et al., 2006) whose distribution within the OB is segregated with a low degree of overlap (Castillo et al., 1999). Moreover, although both receptor families have been found in the Gl and Gcl, nAchRs are preferentially expressed by PGCs that show high expression of the α7 subunit (Le Jeune et al., 1996) whereas GCs seem be primarily, but not uniquely, modulated by mAchRs (Castillo et al., 1999). Finally, changes in subunit composition in immature versus mature cells has also been reported (Kaneko et al., 2006). Immature PSA-NCAM positive cells in the OB, for instance, rarely display α7 immunoreactivity that has been detected in mature NeuN expressing cells, suggesting that SVZ-derived interneurons do not express the a 7 subunit until they have differentiated (Kaneko et al., 2006).

The complexity of Ach action mediated by different receptor subtypes, subunit composition and cellular localization could help to explain the discrepancy reported on Ach role in adult neurogenesis. Indeed, although it is accepted that Ach does play a role in the control of SVZ-derived cell survival in the OB, there are conflicting results on its mode of action (Cooper-Kuhn et al., 2004; Kaneko et al., 2006; Mechawar et al., 2004). In β2 knock-out mice, survival of newborn cells is increased but only in the Gcl. Moreover, nicotine exposure in wild type-animals decreases BrdU-positive cell survival in the Gcl while no effect is detected in β2 knock-out suggesting that the β2–nAchRs mediate this effect (Mechawar et al., 2004). Specific effects on GCs may be explained by the higher proportion of non- β2 α7-containing nAchRs in the Gl (Le Jeune et al., 1996). Conversely, cholinergic forebrain lesion in adult rat through injection of the immunotoxin 192IgG-saporin, has opposite effect on newly generated GCs and PGCs decreasing or increasing their survival respectively (Cooper-Kuhn et al., 2004; Kaneko et al., 2006). Accordingly, treatment with donepezil a selective non-competitive inhibitor of acetylcholinesterase that increases extracellular Ach in the brain, enhances survival of newborn GCs in the OB (Kaneko et al., 2006).

Differences in PGCs and GCs Ach-mediated effects may reflect the involvement of the two populations at different levels of the olfactory processing. Indeed, PGCs in the glomeruli interact with olfactory nerve terminals and/or the primary dendrites of mitral/tufted cells and Ach could indirectly regulate olfactory nerve and mitral/tufted cell inhibition through activation of PGCs (Castillo et al., 1999). Conversely, GCs contribute to the network activity of the OB by inhibiting mitral/tufted cell dendrites and by facilitating both cell synchronization and network oscillations (Lazarini and Lledo, 2010). Ach has been shown to modulate the output of granule cells in opposite direction that depend on the subcellular localization of mAchRs (Castillo et al., 1999). Somatically localization of mAchRs reduces excitability of granule cells whereas presynaptically distribution of mAchRs enhances GABA release on mitral/tufted cells (Castillo et al., 1999). How these sites of cholinergic modulation influence olfactory processing, however, is still to be investigated.

4.2. Monoamines: noradrenaline, serotonin

The olfactory bulb receives a rich noradrenergic innervation which arises from the locus coeruleus (LC), mostly projecting to the deeper layers of the bulb, particularly the inner plexiform layer (Ipl) and Gcl where mRNA for α- and β-adrenergic receptors have been detected (Shipley et al., 1985; Nicholas et al., 1993). In addition, LC-noradrenergic terminals have been shown to contact SVZ-derived cells within the OB (McLean et al., 1989; Peretto et al., 1999), supporting a role of noradrenergic inputs in OB neurogenesis. Injection of the α2-adrenoreceptor antagonist dexefaroxan in adult rats, that increases NA availability by blocking inhibitory presynaptic α2-autoreceptor, reduces spontaneous bulbar neuronal death in the Gcl and SVZ of the OB (Bauer et al., 2003). Moreover, chronic treatment of adult mice with dexefaroxan following olfactory axotomy (surgical deafferentation of the OB) induces a neuroprotective effect reducing neuronal death, glial activation and cell proliferation that result following injury (Veyrac et al., 2005). Newborn GCs may represent one of the targets of LC noradrenergic innervation. Accordingly, exposure of adult mice to olfactory enriched environment, enhances NA release in the OB and increases survival of newborn GCs (Veyrac et al., 2009). Blocking α1- and β-adrenoceptor activity through administration of the antagonist labetalol, prevents the pro-survival effect of olfactory enrichment without affecting odour exploration, supporting a central role for NA in coupling activity to the modulation of adult neurogenesis (Veyrac et al., 2009). This hypothesis is sustained by studies showing that adult-generated GCs in the OB are required for olfactory fear conditioning, perceptual learning and long-term memory of associative olfactory learning (Lazarini and Lledo, 2010), cognitive functions regulated by NA release. Indeed, increased NA concentration has been found in the OB of animals exposed to different olfactory cues, preferentially novel or salient odours (Brennan et al., 1990; Rosser and Keverne, 1985; Veyrac et al., 2009) and NA release in the OB appears to be important for the acquisition and/or formation of conditioned odour preferences or specific odour memories and for spontaneous and rewarded-motivated discrimination (Harley et al., 2006; Mandairon et al., 2008; Sullivan et al., 1992; Veyrac et al., 2009).
While noradrenergic innervation targets mainly the Ipl and Gcl, serotonergic fibres originating in the dorsal and medial raphe nuclei, project primarily to the Gl, although lower density innervation exists in all OB layers (McLean and Shipley, 1987). Receptors for serotonin have been found in PGCs and mitral/tufted cells (Wright et al., 1995), but the exact role in odour processing is unknown. Injection of a specific serotonergic neurotoxin in adult rats results in reduced olfactory discrimination, and depletion of 5-HT fibres in rat pups causes a failure in the development of odour preference (Moriizumi et al., 1994; McLean et al., 1993). Petzold et al. (2009) suggested that the serotonergic system regulates odour input in the OB. Glomerular activation after odour stimulation is attenuated by 5-HT_{2C} receptor activation and amplified by 5-HT_{2C} receptor inhibition (Petzold et al., 2009), indicating a prominent role of serotonin in the initial steps of olfactory processing. Whether serotonin-mediated effects involve also regulation of newborn olfactory interneurons seems to be unlikely. Indeed, while 5-HT has a well-defined role in progenitor proliferation in neurogenic niches, no effects have been found on neuroblast survival following administration of serotonin reuptake inhibitors (Banasr et al., 2004; Malberg et al., 2000).

4.3. Amino acids: GABA and glutamate

During embryonic development GABA plays a key role in neurogenesis affecting proliferation, migration and neurite out-growth. Depolarizing GABA signalling modulates dendritic development of postnatally generated neurons in both hippocampus and olfactory bulb (Gascon et al., 2006; Ge et al., 2007). In the OB, incubation of SVZ-derived cell cultures from postnatal rat (at 1 day in vitro; 1 DIV) as well as OB slices, with the $GABA_A$ receptor antagonist bicuculline (but not $GABA_B$ and $GABA_C$ receptors antagonists), shows a reduction in dendritic complexity affecting primarily the number and length of primary dendrites. GABA application has an opposite effect stimulating

dendritic growth in new neurons (Gascon et al., 2006). This effect of GABA on dendrites development affects only immature neurons and is mediated by $GABA_A$ receptor depolarization and calcium influx through L-type voltage gated calcium channels. As the cell develops there is increased expression of the K^+/Cl^- cotransporter KCC2 and electrophysiological recordings as the mature chloride potentials establish, show a progressive shift toward a GABA-induced hyperpolarization of cultured SVZ-derived cells (Gascon et al., 2006). Accordingly, once the switch to hyperpolarizing GABA occurs, the action of bicuculline on dendritic development ceases (Gascon et al., 2006). During the integration of newborn Gcs, reduced dendritic length and spine density occurs following sensory deprivation (Saghatelyan et al., 2005). Potentially, neuroblast differentiation and dendritic initiation through GABA actions could be coupled to olfactory network activity. Supporting a network activity hypothesis, Akiba et al. (2009) showed that KCl-mediated depolarization, mimicking olfactory receptor neuron input in organotypic slice culture from TH-GFP mice, increases GFP expression in SA/PG cells. Addition of GABA to the depolarized slices further induces TH expression in additional SA/PG cells, a process requiring activation of L- and P/Q-type calcium channels (Akiba et al., 2009). Thus, the authors propose a model in which GABA promotes development of dendritic projections and synaptic connections in dopaminergic progenitors. Once GABA-mediated synaptic connections are formed and glutamatergic inputs received, TH expression is induced and maturation completed (Akiba et al., 2009). These results are consistent with previous works reporting that GABAergic signal precedes glutamatergic input in the maturation processes of newborn olfactory interneurons (Belluzzi et al., 2003; Akiba et al., 2009). GABA involvement in neuroblast differentiation may also occur indirectly by regulating transcription factors, such as the cAMP response element-binding protein (CREB). Numerous studies demonstrate that CREB activation through phosphorylation is influenced by neural activity (Lonze and Ginty, 2002; Giachino et al., 2005). A recent study showed that GABA-mediated excitation regulates CREB activation at early developmental stages of newborn hippocampal neurons (Jagasia et al., 2009). In the hippocampus, developmental defects following loss of GABA-mediated excitation can be compensated by enhanced CREB signalling suggesting that CREB signalling occurs downstream of GABA-mediated excitation (Jagasia et al., 2009). CREB may regulate the synthesis of neurotrophic factors such BDNF or tenascin-R whose activity-dependent expression has been reported to mediate SVZ-derived cells maturation (Saghatelyan et al., 2004; Gascon et al., 2005).

Less information is available about glutamatergic signalling during SVZ-derived cell differentiation. Neuroblasts do express functional ionotropic and metabotropic glutamate receptors that have been shown to regulate both proliferation and migration (see previous sections). Moreover, two recent studies described the involvement of NMDARs in survival of SVZ-derived olfactory interneurons (Lin et al., 2010; Platel et al., 2010). The expression of functional NMDARs in young-adult mice (P20-P30) increases along the SVZ-OB pathway and the percentage of neuroblasts responding to NMDA improves to 90% (starting from an initial 20% in the SVZ) in the OB (Platel et al., 2010). Most of the neuroblasts in the RMS and OB display spontaneous NMDAR activation but lack the machinery for vesicular glutamate release that has been detected in SVZ/RMS astrocytes, suggesting the presence of ambient glutamate along the pathway whose release is presumably mediated by astrocytes (Platel et al., 2010). Genetic removal of NR1 subunit with consequent loss of NMDAR function obtained through injection of retroviral vectors encoding the Cre recombinase enzyme in the SVZ of $NR1^{fl/fl}$ mice (Lin et al., 2010) or alternatively by in vivo postnatal electroporation of a Cre-containing plasmid into the SVZ of $NR1^{fl/fl}$ mice (Platel et al., 2010), induces a strong decrease of neuroblast survival in the OB. However, the two studies (Lin et al., 2010; Platel et al., 2010) propose divergent mechanisms to explain NMDARs involvement in olfactory interneuron precursor survival. In the study by Lin and colleagues, genetic loss of NR1 subunit causes a strong reduction of NMDAR-deficient cells in the Gcl starting 3 weeks after virus injection and reaching the complete elimination of NMDAR-deficient cells 28 dpi, a timing that coincides with a critical period for integration of newly generated GCs (Yamaguchi and Mori,

2005). Complete loss of NMDAR-deficient cells is rescued enhancing activity via expression of the bacterial voltage-gated sodium channel (NaChBac) together with the Cre recombinase in the SVZ of $NR1^{fl/fl}$ mice. Moreover, NaChBac-positive NMDAR-deficient cells show no morphological alterations and receive AMPA-mediated input supporting that they are integrated into OB circuits. These data indicate that the requirement for NMDARs in the integration of new GCs depends on the overall levels of neuronal activity in the neuron and is independent on how this depolarization is achieved (Lin et al., 2010).
A different mechanism in NMDA-mediated survival has been proposed by Platel et al. (2010), according to which NMDA receptors provide early survival cues to neuroblasts prior to entering the OB network. Indeed, injection of the NMDA blocker MK-801 in DCX-GFP mice, as well as genetic removal of NR1 subunit by in vivo postnatal electroporation of a Cre-containing plasmid into the SVZ of $NR1^{fl/fl}$ mice, results in increased numbers of apoptotic neuroblasts and decreased newborn cell incorporation in both the RMS and Gcl already 2 weeks after electroporation (Platel et al., 2010). Since NMDARs do not control migration along the SVZ-OB pathway, it is likely that the expression of functional NMDARs is critical for neuroblast survival during the migration from the SVZ to the OB before they assume their role in olfactory circuits (Platel et al., 2010).
It is possible that NMDAR-mediated regulation of neuroblasts survival involves both mechanisms but in different proportion according to the animal age. Indeed, the large majority of olfactory interneurons are generated in the first postnatal weeks and electroporation in the neonatal SVZ may induce diverse effects according to the different cellular organization of the SVZ (Peretto et al., 1997) and to specific properties of progenitors in neonates and adult mice (De Marchis et al., 2007; Merkle et al., 2007). It is also possible that the two methods used in Lin et al. and Platel et al. studies (retroviral versus electroporation injection) induce a slightly difference in the efficacy of NR1 loss, however this could explain the different proportion of NMDAR-deficient cells loss rather than be responsible of two different mechanisms involved in the regulation of neuroblast survival.
Other sources of glutamate in the OB are the afferents from higher order regions. Indeed, the OB contains large number of glutamate centrifugal fibres contacting olfactory interneurons. The origins of these fibres include the anterior olfactory nucleus (AON), the tenia tecta (TT), the piriform cortex (PC), the cortical amygdaloid nucleus (CAN) and the nucleus of the lateral olfactory tract (NLOT), and their projections to the OB are usually referred as ‘‘feedback’’. Indeed, neurons in these cortical areas receive inputs from the OB and, in turn, send axons back to the OB (Matsutani and Yamamoto, 2008). Cortical innervation to the bulb heavily innervates GCs. Potentially, glutamatergic input during the period of newborn cell integration could be a mechanism whereby cortical feedback directly controls the integration of new cells.

5. Concluding remarks

The literature addressed to the role of different types of neurotransmitters in the control of adult neurogenesis is growing rapidly. At present, the complexity of the process is clearly very high and our understanding incomplete (Table 1). The difficulty in approaching such issue, resides in the mode of action, that depend on neurotransmitter receptor composition, affinity, distribution, desensitization profiles, compensatory and reuptake mechanisms, and intracellular pathways. The same neurotransmitter can thus play opposing roles by acting at diverse time on different receptors or in different brain regions, according to a dynamic process that is temporally and spatially regulated. Upstream or downstream interaction between neurotransmitters, as well as with neurotrophic factors through both autocrine or paracrine mechanisms, further increases the complexity.
Improved knowledge of neurotransmitter function in neurogenesis, will potentially allow regulation of adult neurogenesis through pharmacologically targeting endogenous mechanisms. However, development of neurotransmitter drugs addressed to specific receptor sub-types or combination, will be necessary to provide a method to precise target cell type and specific regulatory step (i.e. cellular

proliferation, migration or integration). Indeed, many neurotransmitter drugs have a wide range of action that depends on receptor affinity and composition, and are usually administrated systemically, possibly inducing side-effects difficult to control, that in turn can affect neurogenesis. The neurogenic side effects of common system antipsychotics or other compounds are only now being considered. External conditions, including sensory stimuli, can modulate adult neurogenesis and this effect is partially mediated by neurotransmitter action. Thus, targeting network activity, through for instance specific protocols of sensory stimulation, or neurotrophic factors, could possibly be taken in consideration to regulate adult neurogenesis.

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