

The how and why of adult neurogenesis

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Received: 4 April 2007 / Accepted: 9 June 2007 / Published online: 29 June 2007
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Abstract Brain plasticity refers to the brain's ability to change structure and/or function during maturation, learning, environmental challenges, or disease. Multiple and dissociable plastic changes in the adult brain involve many different levels of organization, ranging from molecules to systems, with changes in neural elements occurring hand-in-hand with changes in supportive tissue elements, such as glia cells and blood vessels. There is now substantial evidence indicating that new functional neurons are constitutively generated from endogenous pools of neural stem cells in restricted areas of the mammalian brain, throughout life. So, in addition to all the other known structural changes, entire new neurons can be added to the existing network circuitry. This addition of newborn neurons provides the brain with another tool for tinkering with the morphology of its own functional circuitry. Although the ongoing neurogenesis and migration have been extensively documented in non-mammalian species, its characteristics in mammals have just been revealed and thus several questions remain yet unanswered. Is adult neurogenesis an atavism, an empty-running leftover from evolution? What is adult neurogenesis good for and how does the brain 'know' that more neurons are needed? How is this functional demand translated into signals a precursor cell can detect? Adult neurogenesis may represent an adaptive response to challenges imposed by an environment and/or internal state of the animal. To ensure this function, the production, migration, and survival of newborn neurons must be tightly controlled. We attempt to address some of

these questions here, using the olfactory bulb as a model system.

Keywords Neural stem cells, Adult neurogenesis, Stem cell niche, Olfactory bulb

Introduction

Embryonic stem cells are pluripotent early progenitors whose differentiation is arrested by the conditions in which they are cultured. In vivo, these cells give rise to germ cells and to a wide range of more specialized stem cells that help build and maintain diverse tissues within the adult organism. Here, we review the advances made over the past years in our knowledge primarily of adult stem cells (see Glossary), but also of the microenvironments (niches; see Glossary) that maintain them. Understanding the interactions among the stem cell, its niche and the tissue in which it resides might reveal ways to prolong tissue function and to effectively employ replacement cells derived from embryonic stem cells.

Neural stem cells are the self-renewing, multipotent cells that generate the main phenotypes present in the nervous system (Fig. 1). During development, neural stem cells participate in the formation of the nervous system. It was believed that the generation of neuronal cells in mammals was mostly limited to the pre-natal phase of development, and that the adult brain was devoid of stem cells, and thus of the ability to make new nerve cells and regenerate after injuries (Ramon y Cajal 1928). Seminal studies in the 60's, that were substantiated in the 70's and 80's, reported that neurogenesis might occur also in the adult brain of rodents (Altman 1962, 1969; Altman and Das 1965; Kaplan and Hinds 1977; Bayer et al. 1982). With the

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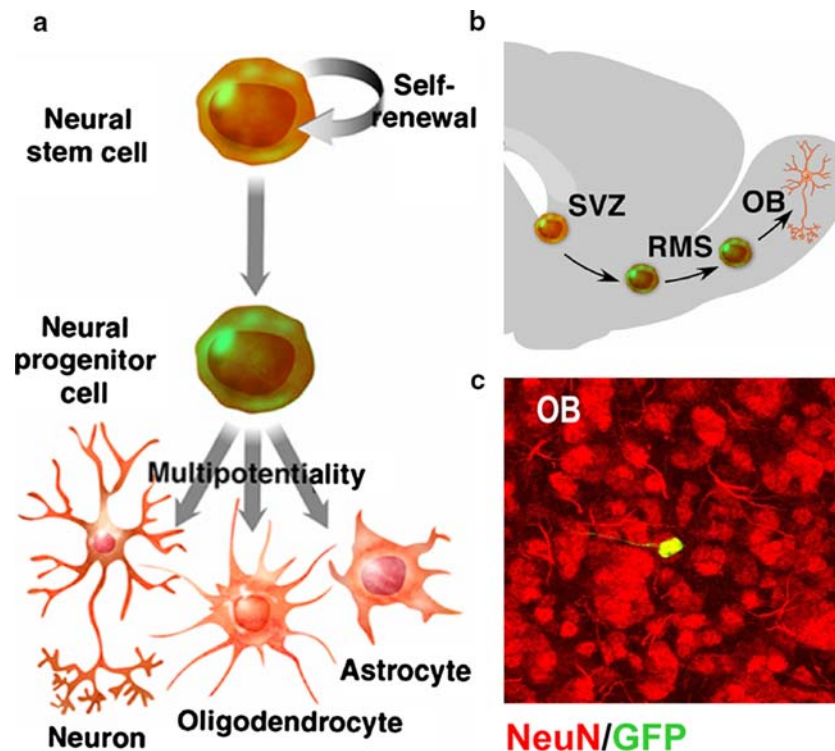


Fig. 1 Neural stem cells in the adults brain and its progeny (a) Neural stem cells (NSC) are multipotent cells that can undergo self-renewal, mature into adult stem cells or differentiate in response to many signals. Progressive differentiation of stem cells, involves the generation of precursors with a restricted set of fate choices, that will mature to generate fully differentiated astrocytes, oligodendrocytes or neurons. (b) In the SVZ, newly generated neuronal cells migrate

through the rostral migratory stream (RMS) to the olfactory bulb (OB), where they differentiate into interneurons. (c) Neural stem cells were infected with a lentivirus carrying the *gfp* gene. 21 days after infection, GFP positive cells were found in the OB. Merged picture shows that the GFP positive cell is also positive for the neuron marker NeuN, representing a newly generated neuronal cell

advent of new methods for labeling dividing cells, (such as 5-bromo-2'-deoxyuridine or retroviral labeling), and the improvement in imaging techniques, investigators confirmed that neurogenesis takes place in discrete areas of the rodents brain throughout adulthood (Cameron et al. 1993; Corotto et al. 1993; Luskin 1993; Lois and Alvarez-Buylla 1994; Kuhn et al. 1996; van Praag et al. 2002). Findings are reassessed and evidence presented that adult neurogenesis also occurs both in human and non-human primates (Gould et al. 1998; Eriksson et al. 1998; Kornack and Rakic 2001). The confirmation that neurogenesis occurs in the adult brain and neural stem cells reside in the adult central nervous system (CNS) (Reynolds and Weiss 1992; Gage et al. 1995) have profound implications for our understanding of brain development and functioning, as well as for cellular therapy in the CNS (Temple and Alvarez-Buylla 1999).

Stem cell diversity

Despite a growing interest, a census of any mammalian organism's stem cells would still be far from complete.

Stem cells in the blood (Ivanova et al. 2002), skin (Blanpain et al. 2007), intestine (Marshman et al. 2002), gonad (Nakagawa et al. 2007) and brain (Lledo et al. 2006) of adults have long been known, and evidence increasingly supports their presence in several tissues and organs such as breast (Clayton et al. 2004), muscle (Lyngbaek et al. 2007; Martin et al. 2006), lung (Aliotta et al. 2005) and kidney (Morigi et al. 2006). However, to definitively characterize known stem cells and find those that remain undescribed, better methods are needed. Label-retaining cells following a pulse of BrdU or thymidine do not reliably denote stem cells. Many stem cells are now known to proliferate regularly, whereas others act as reserve, and might not divide at all during the pulse. The ability of explanted cells to proliferate extensively in culture is also not a reliable indicator of the stem cell state.

On the other hand, stem cells have not been found to express a unique repertoire of genes that might serve as universal stem cell markers (*stemness genes*) but, rather, show diverse genetic imprints shared with non-stem cells. Moreover, stem cell gene expression varies with the organism's physiological state and environment in ways that can be interpreted only after stem cell identity is

established. Hope that diagnostic gene markers or fixed programs of low proliferation can be used to unequivocally identify stem cells is fading as our knowledge of stem cell diversity increases.

Lineage-labeling methods (see Glossary) represent the gold standard of stem cell identification. In mammals, cell marking has been used to trace the origin of neural stem cells in the subventricular zone (SVZ) near the lateral wall of the lateral ventricles or to demonstrate that pancreatic islet cells are derived in the adult from symmetrical divisions within a population of insulin-expressing cells. These general methods of lineage labeling have revealed new stem cells, even in long-studied tissues such as the ovary and intestine. However, this method has its limitations in part due to the fact that progeny from labeled progenitors are in some cases a minority among other dividing cells and appear scattered in the tissue. Additional lineage specific markers are, therefore required to reveal and characterize more precisely stem cells.

Neurogenic permissiveness in the adult brain

Adult neurogenesis exemplifies an unforeseen regenerative capacity of the mature mammalian CNS and raises an intriguing question: why is active neurogenesis retained and restricted only to a few neurogenic regions in adult mammals? The term *neurogenic* implies at least two things: first, the presence of immature precursor cells from which new neurons can develop, and second, a certain type of microenvironment that is permissive for neurogenesis to occur. In the adult mammalian brain, there are two known neurogenic regions: the dentate gyrus subgranular zone at the hippocampus (SGZ) and the SVZ/olfactory system (Gage 2000; Alvarez-Buylla and Garcia-Verdugo 2002; Lledo PM et al. 2006). We refer to the rest of the brain as *non-neurogenic*, although this categorization might ultimately turn out to be premature, and such terms as *potential neurogenic* or *reactive neurogenic* zones might be more appropriate (Fig. 2). There is still an ultimate test for qualifying a region as neurogenic: a neural precursor cell implanted in a neurogenic region should develop into a neuron and when grafted into a non-neurogenic region it should become a glial cell or die. Thus, the definition of ‘*neurogenicity*’ is based on a general and physiological neurogenic permissiveness rather than on the presence or absence of a neural precursor cell alone. The key questions become, then, what makes a brain region neurogenic? How is neurogenic permissiveness defined on a molecular and cellular level?

In sum, neurogenic regions are characterized by: (1) the presence of neural precursor cells, (2) the presence of a microenvironment consisting of cell-cell contacts and

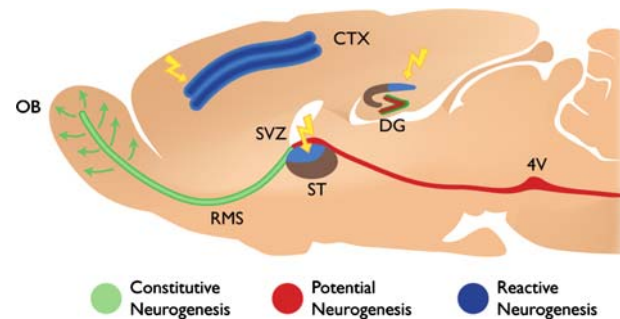


Fig. 2 Three forms of adult neurogenesis. Schematic diagram showing the two constitutively neurogenic regions of the adult mammalian CNS (green; SVZ/olfactory bulb and hippocampal dentate gyrus), and some of the principal regions where populations of neural precursors have been identified (red; potential neurogenesis) which include the subgranular zone of the dentate gyrus, and rostro-caudally from the anterior subventricular zone along the neuraxis through the central canal of the spinal cord. Precursors have also been isolated in smaller numbers from several parenchymal regions. The diagram also indicates selected regions in which limited neurogenesis can be induced experimentally (blue; reactive neurogenesis) following cell damage (yellow arrows). While isolated and sometimes controversial reports of neurogenesis in other regions exist, these are omitted from the figure for simplicity. CTX: cortex; DG: dentate gyrus of the hippocampus; OB: olfactory bulb; RMS: rostral migratory stream; ST: striatum; SVZ: subventricular zone; 4v: fourth ventricle

diffusible factors promoting neural development of the precursor cells and (3) a neurogenic potential that can be tested by the implantation of neural precursor cells into this region. Consequently, non-neurogenic regions may contain precursor cells, but lack distinctive germinative cell clusters as well as the permissive microenvironment that under physiological conditions would promote neurogenesis from local or implanted precursor cells. So far, transplantation into the adult brain has yielded neurons only in the olfactory system and the hippocampus, although the same precursor cells could give rise to neurons under appropriate in vitro conditions (Temple and Alvarez-Buylla 1999). This makes matters even more complex: how much of adult neurogenesis lies in the precursor cells and how much is dictated by the cellular microenvironment?

At the core of the concept of *neurogenic permissiveness* is the assumption that precursor cells in the neurogenic zones are embedded into a microenvironment with which they form a functional unit, the so-called *stem cell niche*. The idea that somatic stem cells reside within specific anatomical locations was first suggested on the basis of transplantation studies of hematopoietic progenitors in the 70's (Schofield 1978). Different studies in several model systems, such as *Drosophila* germline and mammalian skin, intestine and bone marrow have provided cellular and functional descriptions of niches as microenvironments that not only anatomically house stem cells, but also

functionally control their development in vivo (reviewed in Li and Xie 2005). In the adult mammalian brain, we are just beginning to identify these cellular and molecular elements that characterize specifically neurogenic niches either in the SVZ or in SGZ at the hippocampus, and the mechanisms by which the full range of adult neural stem cells development is regulated. In both cases, these niches consist of the precursor of cell itself, astrocytes, endothelial cells, microglia or macrophages, extracellular matrix, and close contact with the basal membrane, but all of these elements are present in the SVZ and the hippocampus with unique proportions (Lim et al. 2007). We now know that germinative niches serve two functions: the maintenance of the stem and progenitor cell activity, and the promotion of neuronal differentiation. In non-neurogenic regions, precursor cells appear to be maintained in a different, niche-independent manner and no neuronal development occurs.

Cellular niches for neural stem cells

The cell types, lineage, and architecture of the germinal zones in the adult SVZ and the SGZ have been extensively studied (Doetsch et al. 1997; Seri et al. 2004; Garcia Verdugo et al. 1998). Current evidence suggests that some stem cells in these neurogenic regions retain attributes reminiscent of radial glia and would be identified as astrocytes by their morphological and histological characteristics, yet the true identities of adult neural stem cells still remain controversial (Morshead et al. 1994; Johansson et al. 1999; Spassky et al. 2005). In accordance with the general stem cell lineage, primary neural stem cells in the adult SVZ transit from quiescent to active state and give rise to migratory neuroblasts through transient-amplifying progenitors. The radial glia-like astrocytes express glial fibrillary acidic protein (GFAP), but not S100 β , both of which are astrocyte markers; thus, they might represent a unique astrocytic population in the SVZ. The *bona fide* astrocyte, expressing both GFAP and S100 β , also constitute essential components of the local environment, keeping in close contact with all other cell types in the adult SVZ. Notably, a large population of astrocytes forms a glial tunnel that guides the migration of neuroblasts through the rostral migratory stream (RMS) to the olfactory bulb. Considering the heterogeneity and complexity of astrocytes, it remains to be determined whether the same type of ‘astrocytic’ cells function simultaneously as stem cells and cells that constitute part of the neurogenic niche or if these two roles are temporally and/or spatially segregated. This possible dual functionality of astrocytes presents an intriguing anatomical feature that might facilitate the construction and operation of the niche.

In the dentate gyrus, at least two types of GFAP reactive astrocytes have been characterized: *horizontal* and *radial* astrocytes (hAs and rAs respectively) (Seri et al. 2004, 2001). hAs extend highly branched processes along the border of SGZ and do not express nestin, a marker for immature progenitors; thus, they represent traditional astroglia. In comparison, rAs possess prominent radial projections into the granule cell layer and thin lateral processes intercalating nearby granule neurons. Many proliferative rAs are found to be in close proximity to blood vessels. A subset of rAs express nestin and probably function as stem cells that give rise to neuroblasts and eventually to new granule neurons (Seri et al. 2001). Serial-section reconstructions by electron microscopy showed that SGZ astrocytes harbor extensive basal processes and form basket-like structures that cradle the clustered neuroblasts (Seri et al. 2004). Some of the neuroblasts generated from rAs send out apical neurites and migrate along the prominent radial processes of rAs.

In addition to providing structural support, astrocytes are known to express secreted and membrane-associated molecules, including cytokines, growth factors, and neurotransmitters, in response to physiological and pathological stimuli (Ridet et al. 1997; Lafon-Cazal 2003). Astrocytes are also well suited to integrate local environmental signals because of their unique syncytial structure formed via gap junctions between astrocytes, through which intercellular signaling might propagate (Schipke and Kettenmann 2004). Naturally coupled to astrocytes through astrocytic endfeet, endothelial cells are also important components of the niche structure and maintain close coordination with astrocytes to regulate adult neurogenesis (Palmer et al. 2000; Shen et al. 2004) (Fig. 3). In vivo studies showed that proliferation hotspots in the SGZ are concentrated around blood vessels (Palmer et al. 2000). In accordance, endothelial cells greatly promote self-renewal of fetal neural stem cells in co-culture (Shen et al. 2004). Surprisingly, adult neural stem cells might even differentiate into the endothelial lineage in vitro (Wurmser et al. 2004). These findings highlight the complexity of cellular interactions within the niche and raise the intriguing possibility that adult neural stem cells are not only regulated by their niche but also, when necessary, able to populate their niche with glial and endothelial cells, forming a likely unitary ensemble for local adult neurogenesis.

Neurogenesis in adulthood

Although recent estimates suggest that the quantity of newly produced neurons in adulthood is much greater than previously thought, the rate of the adult neuronal production still remains lower than during development. As a

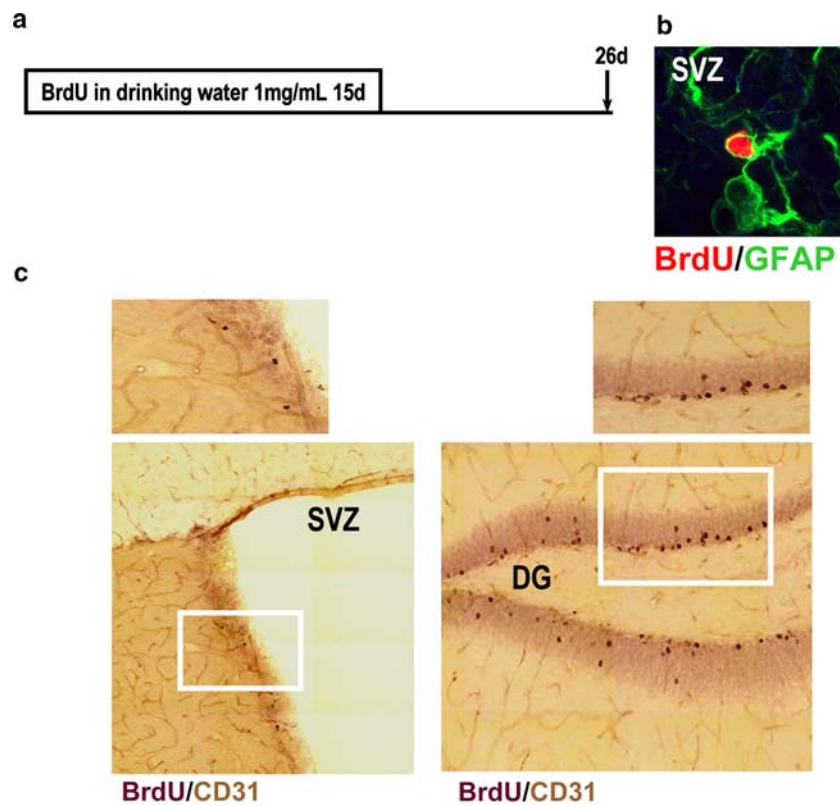


Fig. 3 Neurogenic niches in the adult brain are highly irrigated by blood vessels. 5-bromo-2'-deoxyuridine (BrdU) labeling is a standard method for studying different aspects of neurogenesis (Miller and Nowakowsky 1998). BrdU was administered to animals for 2 weeks in drinking water. 26 days after BrdU administration, animals were sacrificed and brain sections were processed for immunohistochemistry. In these label retaining experiments it is considered that labeled cells in the neurogenic zones are good candidates to be stem cells.

(b) Adult stem cells express GFAP, a marker also assigned to mature astrocytes. The image shows a BrdU positive cells in the SVZ, also positive for GFAP. (c) Sagittal sections of adult mouse brain stained with BrdU (violet) and CD31, the classical endothelial cell marker (brown). It is shown that both in the SVZ and DG of the hippocampus, BrdU positive cells receive irrigation from blood vessels. Insets show a detail of the framed area

result, if the functional properties brought by adult-generated neurons are similar to those brought by neurons generated in early life, then adult neurogenesis has to be considered insignificant (Nottebohm 2002). In contrast, if adult-generated neurons have unique properties that increase their impact relative to more mature neurons, then one can hypothesize that their constant integration into the functional circuitry has tremendous effects. Recent observations made both in the hippocampus and the olfactory bulb support the second hypothesis. Young granule cells in the adult dentate gyrus appear to exhibit robust plasticity that, in contrast to mature granule cells, cannot be inhibited by GABA. These newborn neurons may respond preferentially to modulation by stress hormones. Learning has been shown to increase the number of new neurons in the hippocampus. Running increases both the number of new dentate gyrus cells and performance on a hippocampal-dependent task whereas a decrease in the number of new granule neurons is correlated with impaired performance for such a task (reviewed in Kempermann 2002). It is thus

possible that since new neurons are structurally plastic, they are highly susceptible to changes in the animal's environment and to different life experiences. This suggests that adult neurogenesis is functionally important since its result is a continual influx of neurons that are, at least temporarily, immature with unique physiological properties. As described elsewhere, bulbar interneurons play an essential role in shaping the olfactory information that reaches the olfactory cortex (Gheusi and Lledo 2007). Since adult-generated cells born in the SVZ differentiate exclusively into olfactory bulb interneurons, they probably contribute to essential aspects of olfactory processing. Although experimental studies and modeling have already provided arguments in favor of a role for newborn granule cells in olfactory discrimination, a more general function remains to be characterized. It is noteworthy that the functional benefit derived from adult neurogenesis cannot be acute since it takes several weeks to generate a functionally integrated new interneuron. We have shown that newborn cells extend neurites within a couple of weeks

after cell birth and it is obvious that the new connections cannot constitute a response to the particular functional event that triggered neurogenesis since these connections will only be in place well after the triggering event is over. Thus, adult neurogenesis of the olfactory system has to be considered as a long-term rather than as a short-term adjustment of the bulbar circuitry to a higher level of experience governed by olfaction.

The rejuvenating adult human olfactory bulb

Forty years since the initial discovery of neurogenesis in the postnatal rat hippocampus, investigators have now firmly established that active neurogenesis from neural progenitors continues throughout life in discrete regions of the CNS of mammals. However, the extrapolation of neurogenesis studies to the human case is still matter for discussion. As a result, one might ask today how much of what has been described in non-human models is relevant to the human situation? This is a major issue because research on adult neurogenesis is to a large degree justified, to funding agencies and the tax-paying public, by the belief that adult neurogenesis can occur in humans and that its exploration will lead undeniably to progress in modern medicine. Thus, significant progress has been made over the past few years in understanding the developmental process and regulation of adult neurogenesis, including proliferation, fate specification, neuronal maturation, targeting, and synaptic integration of new neurons into the hippocampus. About 8 years ago, adult neurogenesis was demonstrated to occur in humans when BrdU incorporation was detected in the hippocampus (Eriksson et al. 1998). Strikingly, a few years later it was found that the second neurogenic niche described in rodents, the so-called SVZ, was missing in humans (Rakic 2004; Sanai et al. 2004). Because the SVZ provides the first central relay of the olfactory system with newly-generated neurons in rodents, this finding discouraged not only researchers embarked in understanding how the brain processes olfactory information *per se*, but also for those tempted by promoting new strategies based on cell replacement therapy using endogenous neural stem cells in humans. However, the recent discovery of the existence of a RMS in human brain (Curtis et al. 2007), has opened new perspectives in the study and the promotion of therapeutic applications of human neurogenesis.

In rodents, newborn neurons integrating the olfactory bulb are produced near the lateral ventricles in a region denominated SVZ. The absence of neurogenic features in the human SVZ was interpreted as resulting from the obvious regression of olfaction in humans. Hence, one of the oldest beliefs about human perception is that we have a

poor sense of smell (Rakic 2004). At a first glance, this general belief seems to have a scientific background as recent human genetic studies showed a decline in the number of functional olfactory receptor genes through primate evolution to humans (Rouquier et al. 2000; Gilad et al. 2004). According to this view, the use of an arboreal habitat and the adoption of an erect posture during human evolution have led to the gradual ascendance of vision and concomitant reduction of smell.

However, several overlooked human features such as the structure of the nasal cavity, retronasal smell, olfactory brain areas, and language call for reassessing the status of the sense of smell in human beings (Shepherd 2004). As systems biology taught us, there is not a one-to-one relationship between the number of genes and complex behaviors. Rather, behavior issued from multiple factors. This holds true for the olfactory system where olfactory receptor genes do not map directly onto olfactory capacities. For instance, when tested for thresholds to the odors of a series of straight-chain (aliphatic) aldehydes, dogs do better on the short chain compounds, but humans perform as well or slightly better than dogs on the longer chain compounds, and humans perform significantly better than rats (Laska et al. 2000). If human smell perception is better than we thought, it may have played a more important role in human evolution than is usually acknowledged. In this context, the very recent study from Curtis et al (2007) has to be considered as a major breakthrough both for olfaction and adult neurogenesis.

Together, these studies, indicate that humans are not poor smellers (a condition technically called microsmats), but rather are relatively good, perhaps even excellent, smellers (macrosmats) (Laska et al. 2000). This may come as a surprise to many people, though not to those who make their living by their noses, such as oenologists, perfumers, and food scientists. Anyone who has taken part in a wine tasting, or observed professional testing of food flavors or perfumes, knows that the human sense of smell has extraordinary capacities for discrimination.

Concluding remarks

Many tasks remain before we can better understand the fundamental biological significance of adult neurogenesis. First we have to know more about the physiological properties of the newborn neurons. When will these neurons contribute to the plasticity of the olfactory circuits? Do adult-generated neurons exhibit special properties during a limited time window or permanently? Secondly we need to know how extensively these neurons are involved in the existing neuronal circuits. This will require systematic anatomical analysis. What are the

sources of the inputs these new neurons receive? Do adult-generated neurons form circuits different from those produced during development? Thirdly we need to explore which aspects of behaviors are affected by, or are affecting, adult human neurogenesis. Fourthly experimental approaches have to be guided by neural modeling. For example, theoretical modeling predicts significant advantages of new neurons over mature neurons for both temporary storage and clearance of memories (Cecchi et al. 2001; Becker 2005).

Much about the sense of smell seems enigmatic and conflicting. This is partly because there is not yet a recognition of all the relevant mechanisms that are involved. It may be hoped that the plasticity discovered in human olfactory bulb can help to address and resolve the mystery of the apparent non-correlation of olfactory receptor gene numbers with smell acuity, and in doing so stimulate a major reassessment of human smell perception. This study indicates that the sense of smell is more important in humans than is generally realized, which in turn suggests that it may have played a bigger role in the evolution of human diet, habitat, and social behavior than has been appreciated. So far, all of these considerations should stimulate a greater interest in this neglected sense. A central question in the field of adult neurogenesis in the human olfactory system remains to be answered in the upcoming years: what is the functional significance of this well conserved biological phenomenon in humans?

Glossary

Adult stem cell

A cell that is the long-term progenitor of a tissue and that can undergo asymmetric, self-renewing divisions resulting in one stem cell and one non-stem daughter cell.

Lineage labeling

A technique in which expression of an enzyme that promotes site-specific recombination (for example, at a lox or an FRT site) activates a marker gene in an initial cell. This gene will subsequently be inherited and expressed in future progeny cells, thereby indicating that they have descended by division from the initial cell.

Niche

A specific location in a tissue whose microenvironment enables stem cells to reside for an indefinite period of time and produce progeny cells while self-renewing.

Transit cell

A short-lived (relative to the stem cell) dividing cell that typically undergoes symmetrical divisions to increase cell number within a tissue.

Acknowledgements We thank Cecile Moreau for help with the artwork. Our laboratory is supported by the Pasteur Institute, the Institut de France (Fondation NRJ), INSERM (Contract # CS0303), Fédération pour la Recherche sur le Cerveau, the Fondation pour la Recherche Médicale, the Agence Nationale de la Recherche (ANR-05-Neur-028-01), the CNRS, the European Neuroscience Institutes Network (ENI-NET; LSHM-CT-2005-019063) and the Groupe Arpège.

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