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## Adult Neurogenesis and local neuronal progenitors in the striatum

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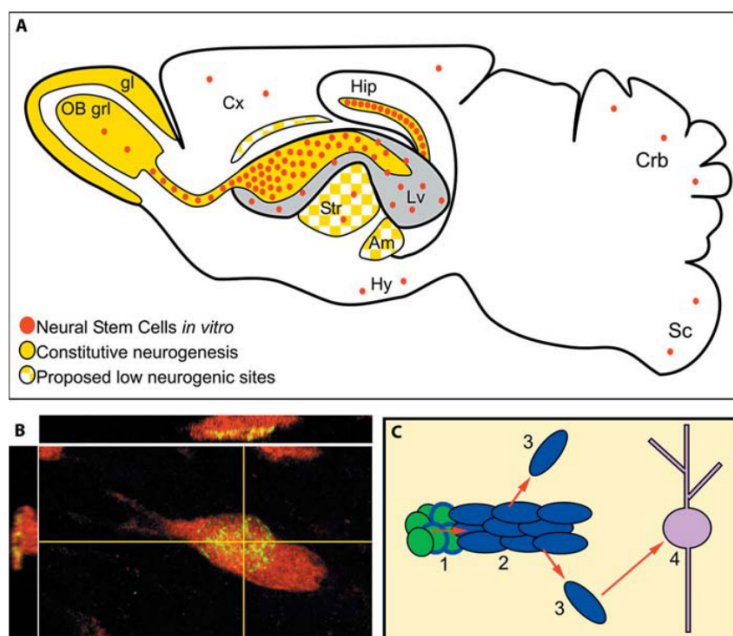
### Abstract

Mechanisms underlying neurogenesis in the subventricular zone-olfactory-bulb system and dentate gyrus of the hippocampus are beginning to be delineated and show common regulative features. In both regions neurogenesis is attributable to progenitor cells whose progeny progressively matures to functional neurons under genetic and epigenetic influence. Persistence of endogenous neuronal progenitors and integration of new neurons in preexisting circuits provide an appealing model of study to develop therapy strategies for neurodegenerative diseases. Interestingly, comparative analysis in mammals indicates that low neurogenic activity is also present in regions classically considered nonneurogenic in both normal and pathological conditions. Neurogenesis in these regions can be due to progenitors derived from the subventricular germinal zone and/or local parenchymal progenitors. Although, *in vivo*, the origin, identity and putative function of parenchymal progenitors are still obscure, *in vitro* studies suggest that many regions of the adult central nervous system potentially contain multipotent parenchymal progenitors. The aim of this review is to delineate the common regulative features underlying adult neurogenesis in the main neurogenic regions and in the striatum focusing on our recent data concerning the existence of local parenchymal progenitors in the caudate nucleus of the adult rabbit.

### Structural Organization of the Adult Constitutive Neurogenic Regions

In adult mammals, constitutive neurogenesis occurs in the subventricular-zone-olfactory-bulb (SVZ-OB) system and in the dentate gyrus of the hippocampus [1, 2] (fig. 1A). Morphological and physiological data indicate that this activity gives rise to new neurons which functionally integrate in the mature preexisting circuits [2]. In both regions adult neurogenesis has been correlated to both learning and memory formation mechanisms, however, the specific role of newly formed neurons in the adult brain remains as yet unresolved.

Fig. 1. A Schematic representation, in a medial view of a rodent brain, of the constitutive neurogenic regions (SVZ-OB system and SGZ of hippocampus), and proposed low neurogenic sites in different mammalian species (squares). Dots indicate the putative distribution of neural stem cells as determined by *ex vivo* analyses. B Newly generated NeuN, BrdU double immunolabeled neuron in the striatum of adult rabbit 2 months after BrdU injection. C Neurogenesis in the caudate nucleus of adult rabbit (schematic representation). Four major steps can be hypothesized. Chains of neuronal precursors (2) are produced from Ki67 clusters that express both glial and neuronal antigens (1). Individual neuronal precursors leave the chains (3) and ultimately differentiate into mature neurons (4). Am = Amygdala; Crb = cerebellum; Cx = cerebral cortex; gl = glomerular layer of the OB; Hip = hippocampus; Hy = hypothalamus; Lv = lateral ventricle; OB grl = granular layer of the OB; Sc = spinal cord; Str = striatum.



Adult neurogenesis is attributable to the activity of progenitor cells located in the SVZ of the lateral ventricles and in the subgranular zone (SGZ) of the hippocampus [1], respectively. Interestingly, while the SVZ more evidently retains embryonic features of primitive germinal layers, maintaining direct contact with the ventricles and extending along the primitive olfactory ventricles, the SGZ loses this contact after the 'rolling in' of the hippocampus during development [3]. Thus, the SGZ represents a parenchymal germinal layer located between the dentate gyrus and the hilus [1, 2, 4] (fig. 1A). Primary progenitors display features of astroglial cells, similar to the development period [5], and have been described as a subpopulation of astrocytes which populate the neurogenic regions [1, 4, 6]. Indeed, SVZ and SGZ astrocytes represent a peculiar class of cell which show unique morphological, molecular and functional properties [1, 2, 6–9]. Besides this primary role in adult neurogenesis, several data indicate that astroglial cells of the SVZ-OB system and the hippocampus directly participate in controlling the microenvironment, which can house and regulate the activity of neural stem cells and their progeny, the so-called neurogenic niche [1, 10–12].

In the SVZ-OB system and hippocampus, primary precursors give rise to transit-amplifying cells (type C or D cells in the SVZ and hippocampus, respectively), which in turn generate neuroblasts. Transit-amplifying cells are the most actively proliferating elements in the neurogenic regions and are arranged in small clusters of cells juxtaposed to the immature neurons [1]. These cells have peculiar ultrastructural and molecular characteristics which lie midway between those of the primary progenitors and neuroblasts [1]. Noteworthy is the fact that these cells divide less frequently in the hippocampus than in the SVZ, and at least 3 different subtypes, showing progressive neuronal lineage, have been described [2, 4].

Neurogenesis is local in the dentate gyrus, therefore, the new granule neurons differentiate where they are generated, while neuroblasts born in the rodent SVZ undergo a long-distance migration to the OB [1, 13]. During their migration toward the OB, SVZ neuroblasts are organized in longitudinally oriented chains and express molecules such as the polysialylated neural cell adhesion molecule (PSA-NCAM) and doublecortin (DCX) [1, 14].

Chains of neuroblasts are ensheathed by a dense meshwork of astrocytic cell bodies and processes forming long channels called glial tubes [13]. Rather than being directly involved in the migratory mechanism, this peculiar organization of the astrocytic glia, recognizable in rodents only from the third postnatal week of life [8], separates the migrating neuroblasts from the mature brain parenchyma and contributes to the secretion of neurogenic factors [1, 10–12]. Once the core of OB has been reached, the chains and glial tubes disaggregate, and neuroblasts displace radially as single elements into the granule and glomerular layers, where they differentiate into interneurons [13].

### *Mechanisms Controlling Adult Neurogenesis*

An increasing number of studies demonstrate that multiple signals are involved in the control of adult neurogenesis. Growth factors, hormones, neurotransmitters, morphogens, physical activity and aging have been included as regulators of several phases of adult neurogenesis [1, 10]. The relationships between these various factors as well as their specific mechanisms and steps in which they act are only partially characterized. However, several data suggest a common regulative pattern for adult neurogenesis, namely integration of new neurons in the preexisting circuits besides activity, strongly depends on functional demand. Quantitative analyses indicate that most selective processes involved in regulating the new neuron integration occur at the differentiation and survival level of newly generated cells [2, 15]. Indeed, within 2 weeks from genesis, about half of the newly formed cells are eliminated in both systems. Interestingly, selection occurs soon after neuroblasts mature and develop synaptic spines, suggesting an intriguing functional role for a transient population of relatively undifferentiated cells [16].

In this context, cell death acts the same as during development, that is, as a prominent factor which regulates the incorporation of new neurons by eliminating a surplus of newly generated cells. However, in adult neurogenesis this mechanism seems optimized according to functional request.

Accordingly, sensory enrichment or deprivation strongly modulates the integration of new neurons in the adult OB [15, 17]. Moreover, recent studies on the hippocampus have added new important information in understanding how new neurons mature and develop working connections with the preexisting neurons, suggesting that electrical activity is key to survival [18, 19].

Therefore, while the functional contribution of adult neurogenesis in both the SVZ-OB system and hippocampus remains highly debated [21], the mechanisms leading the primary progenitors toward functional integrated neurons in the adult central nervous system (CNS) begin delineation. This is critical for developing potential brain repair strategies involving manipulation of endogenous progenitors.

### **Adult Neurogenesis in Other CNS Sites**

If persistence of neurogenesis in the hippocampus and SVZ-OB is now widely accepted, and these areas are therefore considered the ‘neurogenic regions’ of the adult mammalian brain, the addition of new neurons occurring in other areas of the adult CNS remains a matter of debate. Nevertheless, both old and new studies performed following several forms of brain injury [23], or studies on the intact brain of different mammalian species [20, 24–26, 29], indicate that genesis of new neurons can also be detected in classically considered ‘nonneurogenic regions’ [29] (fig. 1A). It is important to highlight that both physiological and induced neurogenesis in these areas ends up with the integration of very few mature neurons compared to SVZ and hippocampal neurogenesis. Furthermore, their functional role, if it were to exist, has not been so far clarified. These studies aim at clarifying the sites, methods and function of neurogenesis in the adult brain with the final goal of unraveling mechanisms to mobilize endogenous progenitors that might be used to develop strategies for brain repair in adult animals.

#### *Induced Neurogenesis*

A number of studies have recently demonstrated that selective neuronal death or degeneration in regions such as the cerebral cortex, striatum and nonneurogenic areas of the hippocampus of adult mammals can induce modest levels of neurogenesis [22, 23]. These studies suggest that nonneurogenic regions of the brain, in pathological conditions, become more permissive to neurogenic processes, possibly trying to compensate for the loss of neurons. Both transplanted or endogenous progenitors can proliferate, migrate and ultimately differentiate in the injured region with different efficiency depending on the age of progenitors (if transplanted), type of lesion, region considered and if growth factors are infused in parallel [22, 23]. In order to develop neuronal replacement therapies, there are obvious advantages in manipulating endogenous precursors over transplantation-based approaches due to many technical, but also ethical and political, reasons. The primary source of endogenous progenitors in the adult CNS is the germinative SVZ. Indeed, most of the above-mentioned studies of induced neurogenesis agree that SVZ neuroblasts do migrate toward the injured areas. Nevertheless, the existence of local putative endogenous progenitors is suggested by *ex vivo* studies which provide evidence that multipotent progenitors can be isolated from diverse regions of the adult CNS, including septum, striatum, cortex, spinal cord and optic nerve [22] (fig. 1A). Although the origin, identity and multipotentiality of these cells *in vivo* need to be clearly established, the occurrence of this population may indicate the existence of a physiological low-rate mechanism of neuronal turnover whose stimulation can be potentially used to reduce the effects of neurodegenerative diseases.

#### *Physiological Neurogenesis*

Apart from induced neurogenesis, studies performed in rodents, primates and lagomorphs indicate that genesis of new neurons can also be detected, under normal conditions, in several classically considered nonneurogenic regions of the mature brain, such as the visual cortex [20], neocortex

[24, 25] , amygdala [26] and striatum [29, 30] (fig. 1A). These reports, in particular those regarding addition and functional integration of new neurons in the neocortex of adult primates, generated a general excitement at first, which was later followed by serious criticisms concerning the methodological and experimental approaches used. Furthermore, when quantitative studies are performed, they indicate, similar to induced neurogenesis, an extremely low number of mature newly generated neurons in these regions. Thus, it is difficult to hypothesize a significant functional contribution of these cells in the complex structure of a normal mature brain. Nevertheless, under physiological conditions this low neurogenic activity, consistent with the above data of induced neurogenesis, suggests that many regions of the mature brain potentially retain populations of latent progenitor cells. Moreover, differences observed between mammals and occurrence of neurogenesis in regions of particular pathological interest for humans, such as the corpus striatum, would justify further and more detailed investigations concerning the reason and possible role of such activity in the mature brain.

It is noteworthy that in other vertebrate classes such as reptiles and birds, adult neurogenesis normally occurs in several areas including the homologous of mammalian striatum [27, 28] . These data suggest, as for the hippocampus and olfactory system, that persistence of neurogenic activity in specific regions of the mammalian brain could also be related to ancient regional characteristics. Wide and detailed comparative investigations could help shed light on the role and function of adult mammalian neurogenesis.

### **Neurogenesis in the adult striatum is produced by parenchymal progenitors**

Evidence of the presence and activity of local parenchymal progenitors in a normal, untreated, adult mammalian brain has come from our recent studies performed on the rabbit [29]. Previous comparative investigations on several species of rodent, lagomorph and primate (human included) demonstrated striking differences in terms of the organization of adult germinal zones and neurogenesis [30] . For instance, we found that the SVZ chains of neuroblasts in the young adult rabbit brain are not exclusively directed toward the OB, but some of them migrate within the mature brain parenchyma toward cortical and subcortical areas of the temporal hemisphere [31]. These data led us to investigate the occurrence of neurogenesis in the telencephalic subcortical region and, in particular, within the striatum of normal, untreated, adult rabbits. This region, which lies beneath the germinative SVZ, is generally considered nonneurogenic during adulthood under physiological conditions.

As described in detail below, we have demonstrated that the caudate nucleus (the most medial-dorsal part of the striatum) of the adult rabbit is neurogenic under normal conditions. Strikingly, our *in vivo* and *in vitro* data indicate that the addition of new neurons in this region is attributable to the proliferative activity of progenitor cells located in the nucleus.

#### *Occurrence of New Neurons in the Striatum*

The occurrence of newly formed NeuN-positive neurons in the caudate nucleus was demonstrated by means of 5-bromo-2-deoxyuridine (BrdU) injections and confocal analyses performed at different survival times from the treatment (fig. 1B). The stereological time course analysis indicated that BrdU/NeuN-positive cells were detectable only at the longer survival times considered and that after 2 months only 0.7% of the surviving BrdU cells corresponded to neogenerated neurons. Additional confocal phenotypic analyses showed that about 1/6 of newly formed neurons differentiated into the calretinin striatal interneurons. Interestingly, although the number of newly formed interneurons found is extremely low, if we refer to the whole striatal calretinin population, the percentage of newly generated calretinin cells, obtained after 5 BrdU injections, reaches the nonnegligible value of about 0.1%. Therefore, these results demonstrate both the persistence of low neurogenic activity in the striatum of adult rabbit and that neurogenesis in this region is at least partly devoted to replacing and/or adding cells within the small subpopulation

of calretinin striatal interneurons. As to the remaining fraction of newly formed neurons without a specific striatal phenotype (5/6 of the total BrdU/NeuN cells), one possibility which has not been addressed in our study is the fact that these cells could become dopaminergic neurons. Indeed, several data [32] indicate that cells expressing tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of catecholamines, occur in the striatum of several mammalian species, including humans. Interestingly, the number of striatal tyrosine-hydroxylase-positive cells increases both in parkinsonian patients and in animal models of Parkinson's disease. These data, previously explained as a phenotypic switch of the striatal neurons to restore the striatal dopamine levels, may have to be reconsidered as a result of the occurrence of adult neurogenesis in the striatum in both induced and physiological conditions [32].

#### *Neuronal precursors are scattered within the caudate nucleus*

As in the classically considered adult neurogenic regions (see first paragraph), our data indicate that new neurons originate from a population of neuronal precursors characterized by transient expressions of early neuronal markers such as PSA-NCAM, DCX, class III beta-tubulin and HuC/D protein. Similarly to the SVZ-OB system, striatal neuronal precursors are initially organized as chains which in turn give rise to individual elements that ultimately differentiate into mature NeuN-positive neurons. Notably, at 2 months survival time, the individual neuronal precursors and the newly formed mature neurons represent less than 10% of the initial neuronal precursor population, indicating the occurrence of a strong selection. Comparison with the SVZ-OB system and hippocampus, where about 50% of the neuronal precursors became mature neurons (see first paragraph), indicates that neuroblast survival within the adult caudate nucleus is very low. However, strong selection and poor integration of new neurons within the striatum has also been described following lesion-induced neurogenesis [23]. Thus, adult striatum of mammals seems to represent an unfavorable environment for survival rather than genesis of the newly formed neurons.

#### *Relationships between striatal and SVZ chains*

Both the presence of numerous PSA-NCAM/DCX-positive chains in the parenchyma of the caudate nucleus, and evidence from the above-mentioned comparative studies as well as induced neurogenesis, led us to look for the origin of striatal chains within the adjacent SVZ. Surprisingly, by using 3-dimensional reconstruction analyses of thick consecutive sections of the SVZ-striatal region and intraventricular injections of a cell tracer (cell tracker green) to specifically label the SVZ-migrating neuroblasts, we found that striatal and SVZ chains represent 2 separate populations. In particular, the rendered image of SVZ-striatal region 3-dimensional analysis showed a consistent system of chains with great variability in length, diameter and orientation, mostly confined to the medial dorsal part of the caudate nucleus. Nevertheless, none of them came into contact with the SVZ and its neuroblasts. Consistently, analyses of CTG-labeled SVZ neuroblasts performed at different times after tracer injection showed SVZ-CTG-positive neuroblasts were never associated with the striatal chains.

#### *The striatal chains originate from the activity of proliferating cells located within the caudate nucleus*

By using the endogenous marker of cell proliferation Ki67 and examining sections from animals treated with BrdU 2 h before sacrifice, we found that part of the striatal proliferating cell population is arranged in small clusters of cells mainly distributed in the medial-dorsal part of the striatum. Quantitative studies and confocal analyses on thick sections demonstrated a close physical and numerical correlation between the number of striatal chains and proliferating clusters. Above all, we found that the Ki67-positive clusters represent specialized regions of the striatal chains. These results, therefore, suggest a population of striatal neuronal precursors originating locally from

the activity of proliferating cells, which act as amplifying elements. Genesis of neuroblasts directly from the mature striatal parenchyma was confirmed in vitro by culturing small strips of tissue obtained from striatum, SVZ and cortex of animals treated with BrdU 2 h before sacrifice. These results demonstrated the occurrence of migrating BrdU/DCX-positive neuroblasts from the explants of the caudate nucleus as well as SVZ but not from cortical explants.

### *Parenchymal Progenitors*

The above presented data indicate the presence of neuronal progenitors displaced within the mature parenchyma of the caudate nucleus of the adult mammalian species. Interestingly, phenotypic analyses indicate that about 85% of the proliferating clusters express the astroglial marker brain-lipid-binding protein. This protein is abundant in the radial glia, which serve as neuronal progenitors in all regions of the CNS and give rise to the adult SVZ and SGZ progenitors [33]. Moreover, nearly 60% of proliferating elements of the same cluster express the early neuronal marker DCX, indicating that some of the proliferating progenitors coexpress both markers, therefore suggesting a clonal relationship between brain-lipid-binding-protein and DCX-expressing cells. Thus, the neurogenic model here described (fig. 1C) share interesting similarities with both SVZ (i.e. chains of migrating neuroblasts) and hippocampal (local neurogenesis) adult neurogenic regions. Although we cannot rule out that local striatal progenitors might be peculiar to the rabbit, these data support the persistence in vivo of neuronal progenitors in various regions of the mature mammal CNS. Origin, regulation and putative functional role of this population, both in pathological and normal conditions, deserve further detailed investigations with the perspective of efficiently mobilizing endogenous progenitors to replace dying neurons in neurodegenerative diseases.

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