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New neurons in the adult striatum: from rodents to humans

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Abstract

Most neurons are generated during development and are not replaced during adulthood, even if they are lost to injury or disease. It is firmly established, however, that new neurons are generated in the dentate gyrus of the hippocampus of virtually all adult mammals, including humans [1]. Many questions still remain, however, regarding adult neurogenesis in other brain regions and particularly in humans, where standard birthdating methods are not generally feasible. Exciting recent evidence indicates that calretinin-expressing interneurons are added to the adult human striatum at a substantial rate [2]. The role of new neurons is unknown, but studies in rodents will be able to further elucidate their identity and origin and then begin to understand their regulation and function.

Keywords

Adult neurogenesis; striatum; GABAergic interneurons; subventricular zone; humans

Sites of adult neurogenesis in humans

For nearly 15 years, the dentate gyrus was the only brain region in which adult neurogenesis had been demonstrated in humans [3]. This situation recently changed due to the development of a novel technique for retrospective cellular birthdating in humans that takes advantage of changes in levels of the isotope carbon-14 following cold war atomic weapons testing. The level of carbon-14 in genomic DNA closely parallels atmospheric levels and can therefore be used to reliably determine the time at which DNA was synthesized, and populations of cells that were generated, without the use of exogenous markers [4]. This technique has provided evidence for robust neurogenesis in the adult human striatum [2]. Sorting to exclude DARPP32-expressing projection neurons indicated that the regenerating population comprised interneurons, and immunostaining of doublecortin (DCX)-expressing

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immature neurons further narrowed down the identity of these new neurons to specific subpopulations of GABAergic interneurons. Roughly 30% of the young interneurons expressed calretinin (CR) and an equal number expressed neuropeptide Y (NPY) [2]. It is not clear whether the CR+ and NPY+ populations are distinct or overlapping, but neurogliaform neurons in mice express both CR+/NPY+ [5], suggesting a possible neurogliaform identity for the adult-born striatal neurons.

Striatal adult neurogenesis in different species

The discovery of adult neurogenesis in the human striatum has been portrayed as demonstrating a fundamental difference between humans and rodents [6], based on an early study reporting adult-born striatal medium-sized spiny neurons in a rat stroke model [7]. However, more recent studies have indicated that new neurons are generated in adult rats under both normal and post-stroke conditions and that these new neurons are primarily CR+ interneurons [8–10], as seen in the normal human brain. These small “granule cell-like” CR+ interneurons are also generated in adult rabbits [11], and are concentrated in the dorso-medial caudate-like association area of the striatum [10,12]. These adult-born neurons have not been identified in untreated mice [13,14], suggesting a potentially important species difference. A distinct population of adult-born neurons has been identified in the ventral striatum, within the Islands of Calleja (ICj), poorly understood accumulations of granule cells expressing several olfactory bulb granule cell markers but not CR [15–17]. It is not yet known whether these cells show ongoing neurogenesis in humans.

The identity of adult-born striatal neurons

CR does not define a particular interneuron subclass [5,18], so the specific identity of the adult-born striatal neurons is still undetermined. Further complicating identification, CR could be only transiently expressed in new striatal interneurons, as it is in adult-born dentate gyrus granule cells [19]. The total number of CR-expressing neurons peaks and then declines during postnatal development [20], suggesting that CR may in fact be transient in some immature striatal populations.

Morphology can provide additional clues to interneuron identity and physiological function [21]. Neither dendrites nor axons have been observed in the adult-born striatal neurons in humans. Even in rodents, the morphology of adult-born striatal neurons has not been examined in depth, using methods that fill the entire cell enabling tracing of the axon or full dendritic tree. However, immunostaining with CR suggests that the adult-born neurons in the striatum have a single primary dendrite [10,22], similar to the granule neurons in the olfactory bulb and dentate gyrus. Intriguingly, the small CR+ interneurons added to the adult striatum also seem to have a similar appearance to the small interneurons born in the adult rat neocortex, which express CR and/or calbindin as well as the 5HT3A receptor [10,22]. 5HT3AR+/CR+ cells born in the neocortex during the early postnatal period have been described as “small axonless neurons” with a granule cell-like morphology [23]. However, some postnatally-born neurons in the anterior cingulate cortex have a similar granule cell-like morphology but also appear to have either an axon or basal dendrites [24]. Granule cells with axons are found in the dentate gyrus, while those in the olfactory bulb lack an axon. Basal dendrites are not found on either of the well-studied granule cell populations but are a

feature of immature dentate gyrus granule cells, suggesting that the basal dendrites observed in 10-day-old anterior cingulate cortex neurons may be transient. Taken together, it seems likely that most neurons born in adulthood throughout the brain share a unipolar granule cell-like morphology, with variation in features such as axons.

The origin of new striatal neurons

Local striatal or SVZ progenitors?

The morphologies of new neurons in the adult rat striatum and changes in location with time both suggest a possible origin in the SVZ [10]. However, the widespread localization and relative paucity of these new neurons under normal conditions in the adult brain, particularly in mice [13,14], have hampered direct investigation of their origin via fate-mapping studies. During early postnatal development, a period of increased SVZ neurogenesis, several fate-mapping and/or time-lapse imaging studies have clearly demonstrated that newborn striatal CR-positive interneurons originate in the SVZ [10,22,25]. The early postnatal SVZ is also the main site of gliogenesis, but whereas glioblasts migrate extensively into cortical layers, neuroblasts were long believed to migrate only to the olfactory bulb [26]. More recent studies, however, revealed widespread neuronal migration from the early postnatal SVZ into neocortical and striatal areas [25,27]. In 1–4-week-old 5-HT3R-EGFP transgenic mice, EGFP⁺ neuroblasts were observed in the SVZ and spreading along elongations of the callosal system. These 5-HT3R-EGFP⁺ neurons differentiated into CR-positive GABAergic interneurons with simple morphology, very similar to olfactory bulb granule cells and CR-positive interneurons generated in the adult striatum [22]. Subcortical migration of neuroblasts from the ventral SVZ (vSVZ) occurs in a widespread “shower”, forming the ventral migratory mass (VMM), comprising an important fraction (about 20%) of perinatal SVZ neuroblasts and generating granule cells of the ICj [27].

In the adult brain, cerebral ischemia can increase neurogenesis enough to allow viral lineage tracing studies. Under these conditions, new striatal neurons originate in the SVZ, both at adult and postnatal stages [8,9,28] and migrate along blood vessels [29]. Olfactory bulb precursors generated in the untreated adult rodent SVZ use a blood vessel scaffold within the olfactory bulb [30], as do CR-positive neocortical neurons generated in the early postnatal SVZ [31], suggesting a SVZ origin and common mode of vasophilic migration for many postnatally- and adult-generated neurons. Another possibility is that new striatal neurons in the adult brain originate from local neural progenitors in the striatum (possibly detached from the SVZ during development), as described in the caudate nucleus of adult rabbits, which incorporates new CR-positive interneurons strikingly similar to those in rodents [11]. This has not yet been observed in normal rodents, but generation of new striatal neurons from local astrocytes has been described after ectopic expression of SOX2 or blocking of Notch signaling [32,33]. Altogether, these results suggest that both local and SVZ progenitors can contribute to adult striatal neurogenesis. Future studies will be needed to clarify the contributions of local and SVZ neuronal precursors and to determine whether there are differences in the anatomical and functional properties of newborn neurons deriving from these different niches.

Early embryonic origins

Most information about neuronal lineage comes from studies looking at early development. Assuming adult-born interneurons share a lineage with a CR-positive interneuron population born embryonically, it may be informative to ask about the origin of those earlier neurons. In rodents, most GABAergic interneurons in the cortex [34] and striatum [35] are generated prenatally and originate in the ganglionic eminences (GEs). However, the majority of CR-positive olfactory bulb interneurons are generated from *Emx1*-expressing progenitors in the SVZ [36,37]. *Emx1* is a transcription factor largely restricted to the pallium during early development [38], indicating a cortical origin, distinct from the majority of GABAergic interneurons. Following cerebral ischemia in early postnatal mice, newborn striatal CR-positive interneurons also derive from SVZ *Emx1*-expressing progenitors [39], suggesting a possible pallial origin for adult-generated striatal interneurons as well. However, developmental fate-mapping studies revealed that *Emx1*-expressing cells generate excitatory, but not inhibitory, neurons in the neocortex and striatum [40]. A later study found that a subpopulation of *Emx1*-lineage cells originating in the pallium migrates to the developing striatum during early prenatal development [41] and differentiates primarily into DARPP-32-positive medium-sized spiny neurons but also a small number of CR-positive (but no other) striatal interneurons [42]. The pallium has been proposed as the main source of CR+ interneurons in the primate neocortex—and the explanation for the specific expansion of this interneuron subtype in primates [43,44]. It is not yet clear whether any or all adult-born striatal interneurons derive from the *Emx-1* lineage in the normal rodent, but these young neurons would represent a small proportion of the interneurons or *Emx-1*-derived neurons in the rodent striatum and could easily be overlooked.

One recent study suggests, based on the expression pattern of the transcription factor Sp8 that all striatal interneurons in primates originate in the medial ganglionic eminence (MGE). and that this region shows no adult neurogenesis [45]. This directly contradicts the 14C evidence from Ernst [2] and also appears incompatible with studies suggesting that in humans, many more neocortical GABAergic interneurons, including CR+ interneurons, have a pallial origin, arising from the VZ/SVZ and enlarged outer SVZ during midgestation [46].

Relative rates of neurogenesis across species

Technical considerations

Many features of adult neurogenesis are remarkably similar across species, but dramatic differences in the rates of neurogenesis have been described [6,47]. It is difficult, however, to determine with any certainty how rates compare across species. Radiocarbon-14 dating cannot be used in rodents due to their relatively short lifespan, while bromodeoxyuridine (BrdU), the gold standard for cell birthdating, is rarely used in humans. Endogenous markers of immature neurons, such as DCX have been tremendously useful for identifying young neurons in many species and brain regions [10,48], but they are unsuitable for cross-species rate comparisons due to differential rates of cell death, maturation and consequent downregulation of DCX, and postmortem stability across species [49–51].

The radiocarbon-14 birthdating method has provided an important window into adult neurogenesis in humans, but it does not provide cellular resolution. Because of its low sensitivity, it can only be used to detect large or highly enriched adult-born populations. This low sensitivity may explain the inability to detect new neurons in the human neocortex [52], where rodent studies suggest that newborn neurons are likely to be widely distributed and represent a very small fraction of the neuronal population [53]. If adult neurogenesis occurs in the human neocortex, it could potentially be detected after removing the pyramidal neurons and enriching for interneurons or the correct subclass of interneurons.

Difficulties in comparing cell counts

Beyond any technical difficulties, it is not entirely clear what constitutes equivalent rates of neurogenesis. One can compare the total number of neurons generated, the density of young neurons, the turnover rate relative to all neurons in a region, or the replacement rate relative to the particular class of neurons that is renewable. Equal replacement rates may be the best approximation of functional equivalence, but this type of comparison requires more knowledge about the identity of the new neurons than is available outside the dentate gyrus and olfactory bulb. New neuron density may be a reasonable alternative. Similar densities of new neurons have been found in the neocortex of rats and nonhuman primates [10,54], but density information is not available for the human neocortex or striatum.

Comparisons across species in striatum and other brain regions

One measure that has been used to compare rates of neurogenesis across species is lifetime replacement rate. This type of comparison is only available for the dentate gyrus but may be illustrative of conclusions that can be drawn, and problems faced, in the striatum as well. One study has reported that only 10% of dentate gyrus granule neurons are replaced in adulthood in mice, while another found that 40% of dentate gyrus granule neurons are replaced in rats [47,55,56]. This difference could reflect differences in methodology, which are significant. BrdU-based estimations of precursor population size and cell cycle time, as used in rats, involve several calculations, each with inherent assumptions and variability [55], but the pharmacogenetic estimate in mice assumes that the nestin promoter drives expression in self-renewing stem cells [56], which appears not to be the case [57]. However, it could also reflect a true species difference, as mice have approximately 5x lower relative rates of dentate gyrus and neocortical adult neurogenesis than rats [49]. This species difference is consistent with reports on striatal adult neurogenesis, where few if any new striatal neurons have been observed in normal adult mice [14,28], in contrast to significant striatal adult neurogenesis found in rats and rabbits [10,11]. It has been estimated that 100% of dentate gyrus granule neurons turn over in adulthood in humans [47,58]; this high rate could also reflect either a real difference from rodents or the use of different methods. It is important to note that it is unclear whether the proportion of cells replaced over the lifetime of an organism is functionally relevant or whether it is more appropriate to compare the proportion of cells replaced over a fixed time, e.g., cells per month, regardless of lifespan. The answer to this question will depend on how new neurons alter functional circuits, which has not yet begun to be investigated.

Looking at replacement within a specific time window, the replacement rate of CR+ interneurons in the rat striatum is estimated to be 7 times higher than that of dentate gyrus granule cells in the same animals [10]. In humans, turnover rates of 2.7% of neurons each year in the striatum and 1.75% each year in the hippocampus have been reported [2,58]. These values likely underestimate the difference in replacement rate between these two regions, since the renewing populations, CR+ interneurons and granule cells, respectively, comprise different proportions of the neuronal populations in these two regions [58–60]. But in any case, data from both species point to greater replacement in the striatum than the dentate gyrus, though of a less numerous population. Whether generation of striatal interneurons is greater in human than in rodents is less clear. Intriguingly, the proportion of striatal and neocortical interneurons that are CR-positive greatly increases across species, from less than 1% in rodents to 10% in humans, where they represent the predominant interneuron subtype [43,44,61,62]. The size of the vSVZ-derived ICj is also substantially greater in primates than in rodents [17,63]. If the size of these populations is larger in humans, there would be more new neurons generated in absolute terms, even if the rate of neurogenesis relative to the parent population is equivalent. However, it should be noted that CR+ interneurons are a diverse group, and it is unclear whether the specific class of small interneurons that are born in adulthood increases in number.

Although it is still impossible to compare rates of striatal neurogenesis across species, one important conclusion that can be drawn from the available data is that substantial numbers of new neurons are generated in humans. A second is that adult striatal neurogenesis in rats and rabbits is significant enough to study but that lower rates of neurogenesis in mice may preclude the use of this species under control conditions.

Possible functional significance of adult striatal neurogenesis

Functional features as olfactory bulb granule cells?

The function of newborn striatal neurons is unknown. Knowledge of striatal CR+ interneurons as a whole is limited to morphological and neurochemical descriptions, since they have never been recorded, much less silenced or eliminated [5,18]. There is only limited knowledge of the functional properties of ICj granule cells as well [64]. The tightly apposed granule cells forming the ICj are connected via gap junctions [65]; there are no data about the existence of similar electrical connections between striatal CR+ interneurons, newborn or otherwise, though they appear partly clustered. The best clues to date about their functional profile may come from the analysis of similar postnatally-generated CR+ interneurons in deep cortical layers [23]. These granule cell-like neurons lack an axon (and have been named “small axonless neurons”), show a characteristic firing pattern and slow functional maturation, and communicate with their neuronal partners via dendrodendritic synapses [23]. Such features are strikingly similar to those of olfactory bulb granule cells, which are generated into adulthood, lack an axon, form dendrodendritic synapses with their neuronal partners [66], and display delayed maturation of spiking activity [67]. In fact, all granule cells share key physiological properties [21], suggesting that the granule cell-like neurons born in the adult striatum and neocortex are likely to share these features as well. Interestingly, there is a coincidence of subthreshold global and local (i.e., presynaptic and

postsynaptic) activation of olfactory bulb granule cell spines, suggested as possible novel mechanism for Hebbian synaptic plasticity within the spine microcircuit [68]. Similar to striatal CR+ interneurons, the function of ICj granule cells is unknown; it could be that they undergo as well slow functional maturation, since they express throughout life high levels of immaturity markers, such as Bcl2 [69] and doublecortin-like (DCL) [70]. Future studies will need to clarify, whether newborn striatal CR+ interneurons and ICj granule cells exhibit similar functional properties during their development and retain features of immaturity and increased plasticity throughout life.

Striatal adult neurogenesis was found in control human brains, suggesting a normal physiological function for these new neurons. Changes in adult neurogenesis from normal levels could potentially play a role in etiology of and/or protection from illness. We will briefly address two pathological situations: cerebral ischemia, where upregulation of neurogenesis could potentially minimize damage, and psychiatric disorders, where neurogenesis could potentially increase susceptibility to illness or aid in its treatment.

Cerebral ischemia

It was demonstrated that cerebral ischemia increases SVZ neurogenesis and migration of neuroblasts into the adjacent striatum both in the juvenile and adult brain [8,9]. Recent cell fate reprogramming studies have demonstrated induced conversion of local striatal astrocytes into neurons [32,33,71,72], suggesting exciting strategies for increasing brain repair. Although most fate shifting studies have not determined what type(s) of neurons are generated, one recent study showed predominant conversion of striatal astrocytes to CR+ interneurons in mice injected with SOX2 virus and treated with brain-derived neurotrophic factor (BDNF) or valproic acid [32]. However, in the absence of external reprogramming, striatal astrocytes do not generate post-ischemia new neurons, which instead derive from the SVZ [28]. Ischemia studies indicate that also SVZ-derived striatal neuroblasts differentiate into only one subtype of neurons, CR+ GABAergic interneurons [8,9]. This apparently restricted fate of adult-generated striatal neurons suggests a limited capacity for brain repair that will at best require complex strategies to overcome. In any case it remains to be determined if, and how, such newborn striatal interneurons can replace lost neurons and restore local circuitry/function.

Psychiatric disorders

In contrast to the lateral “motor” striatum, the medial striatum, where most of the newborn neurons are found in rats and rabbits, is part of the limbic emotional circuitry, with afferents from the medial prefrontal and cingulate cortices [10–12,73]. Parallels across species suggest that a similar localization pattern will be found in humans. Rodent models of psychiatric treatment such as electroconvulsive therapy (ECT) vigorously stimulate SVZ and striatal neurogenesis, without modifying the phenotype of newborn CR-positive GABAergic interneurons [74]. The significance of this process for neuropsychiatric disorders requires to be determined, but since endogenous electrical fields normally guide the migration of neuroblasts out of the SVZ [75], these treatments may act by enhancing a normally-occurring process. Similarly, 5-HT3R expressed by neuroblasts from the postnatal/adult SVZ may modulate their migration into the striatum, as recently shown for embryonic

migration of neocortical interneuron precursors [76]. Future studies will need to determine whether serotonergic antidepressants influence migration in adulthood and evaluate the possible significance for the treatment of mood disorders. Finally, the ICj, which also show ongoing neurogenesis in rodents, expresses high levels of the dopamine D3 receptor [77] and the schizophrenia susceptibility risk factors *erbB4* and *neuregulin-1* receptor [78] and have been implicated in peri-adolescent developmental disorders associated with striatal hyperdopaminergia in schizophrenia [79].

Conclusions

The human striatum generates CR-positive GABAergic interneurons into adulthood, similar to what occurs in rats and rabbits. There are still conflicting data regarding the origin of these neurons in the adjacent SVZ and their turnover rate. Studies in rodents have shown that the generation of these interneurons occurs at high levels at early postnatal stages in the SVZ and decreases but is maintained at a lower level in the adult. Therefore, rodents, especially rats, are a good model for postnatal and adult human striatal neurogenesis. Additionally, at perinatal and possibly also at later stages the vSVZ generates other “granule cell”-like, CR-negative GABAergic interneurons that form the ICj. No data are yet available about adult neurogenesis in the human ICj, which show a striking increase in size/number compared to rodents. CR+ GABAergic interneurons are not well characterized, but indications that their proportion increases considerably in primates relative to rodents and that their origin differs from that of other interneurons suggest that these are important neurons that should be the focus of future investigation.

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Outstanding Questions

- **Which interneuron subclass(es) do new striatal neurons belong to?** Specifically identifying the new neurons is critical for determining their function, by linking these new cells to a population whose properties have already been described and/or by enabling direct targeting of this subclass for future study.
- **Where do the precursors for adult-born striatal neurons reside and what are their features?** Being able to identify and target the precursors for adult-born neurons is necessary for studying the regulation of adult neurogenesis and for genetic targeting to trace or eliminate new neurons. Several possible origins have been described, but which one predominates in the normal adult.
- **Do new striatal interneurons share subclass identity, origin and regulation with new neurons in the neocortex, hypothalamus, amygdala and other regions?** Common features of new neurons across brain regions suggest common functions, at least at the circuit level. Available data suggests many parallels across regions, but the full extent of the similarities and differences is not known because many features have not yet been determined.
- **Are there true differences in the rate of new neurons across species?** Increased rates of neurogenesis in humans relative to rodents would suggest that this phenomenon is especially important to human brain function, while decreased rates might indicate the opposite. It is very difficult to accurately compare rates across species, but comparisons between closely-related rodent species suggest that there may be significantly more striatal adult neurogenesis in rats than in mice under normal conditions, pointing to rats as a better model for studying this phenomenon.

Highlights

- Recently, adult neurogenesis was shown to occur in the normal human striatum
- Similar newborn specific striatal interneurons were described in different species
- Adult-generated striatal neurons may derive from the pallium/subventricular zone
- Adult striatal neurogenesis could be of relevance for neuropsychiatric disorders

Figure 1.

Schematic representation of postnatal and adult striatal neurogenesis in rodents versus humans. **(A)** The putative neuronal migration routes from the ventral subventricular zone (vSVZ) generating new neurons in the postnatal and/or adult striatum of rodents and humans. In rodents most postnatally/adult-generated neuroblasts migrate from the anterior SVZ to the olfactory bulb (OB), with a significant intra-striatal migration at early postnatal stages from the vSVZ that generates dispersed calretinin (CR)+ GABAergic interneurons (IN) and clustered CR-islands of Calleja (ICj). In humans, the OB is sharply diminished, however, the vSVZ, ICj as well as the proportion of striatal CR+ IN significantly increase compared to rodents (in the case of CR+ IN from less than 0,5% to 10% of all striatal interneurons). **(B)** Most postnatally/adult born striatal IN may derive from pallial vSVZ progenitors in rodents; however, generation of new striatal neurons from local astrocytes appears possible upon manipulation. The origin of newborn striatal interneurons in humans is unknown. **(C)** Adult-generated striatal interneurons in rats belong to the subclass of CR+ “granule cell”-like IN. At postnatal stages also CR-GABAergic granule cells forming the ICj are generated in the vSVZ. Newborn neurons in the adult human striatum belong to GABAergic IN expressing CR (mainly) and neuropeptide Y (NPY). **(D)** The function of new striatal interneurons is both in rodents and humans unknown. Nevertheless, the analysis of similar postnatally-generated cortical CR+ IN suggest functional properties similar to adult-generated axonless granule cells in the OB that form dendrodendritic synapses. Adult striatal neurogenesis could be of importance for persistent plasticity in this structure and may play a role in the pathophysiology and treatment of neuropsychiatric disorders.