Opinion

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New neurons in the adult striatum: from rodents to humans

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

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 [1]. This situation recently changed due to the development of a novel technique for retrospective cellular birth-dating in humans that takes advantage of changes in levels of the isotope carbon-14 (14C) following Cold War atomic weapons testing. The level of 14C in genomic DNA closely parallels atmospheric levels and, therefore, can be used to reliably determine the time at which DNA was synthesized, and populations of cells were generated, without the use of exogenous markers [2]. This technique has provided evidence for robust neurogenesis in the adult human striatum [3]. Sorting to exclude projection neurons, identified by their expression of dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa (DARPP-32), indicated that the regenerating population comprised interneurons, and immunostaining of doublecortin (DCX)-expressing immature neurons in tissue sections further narrowed down the identity of these new neurons to specific subpopulations of GABAergic interneurons. Approximately 30% of the young interneurons expressed calretinin (CR) and an equal number expressed neuropeptide Y (NPY) [3]. It is not clear whether the CR+ and NPY+ populations are distinct or overlapping, but neurogliaform neurons in mice express both CR+ and NPY+ [4], suggesting a possible neurogliaform identity for 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 [5], based on an early study reporting adult-born striatal medium-sized spiny neurons in a rat stroke model [6]. However, more recent studies have indicated that new neurons are generated in adult rats under both normal and poststroke conditions and that these new neurons are primarily CR+ interneurons [7–9], as seen in the normal human brain. These small 'granule cell-like' CR+ interneurons are also generated in adult rabbits [10], and are concentrated in the dorsomedial caudate-like association area of the striatum [9,11]. These adult-born neurons have not been identified in untreated mice [12,13], 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), which are poorly understood accumulations of granule cells expressing several olfactory bulb granule cell markers but not CR [14–16]. 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 [4,17]; therefore, 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 [18]. The total number of CR-expressing neurons peaks and then declines during postnatal development [19], suggesting that CR is in fact transient in some immature striatal populations.

Morphology can provide additional clues to interneuron identity and physiological function [20]. 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 to enable 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 [9,21], similar to the granule neurons in the olfactory bulb and dentate gyrus. Intriguingly, the small CR+ interneurons

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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 5-Hydroxytryptamine (serotonin) receptor 3A (5HT3A) receptor [9,21]. 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 [22]. However, some postnatally born neurons in the anterior cingulate cortex not only have a similar granule cell-like morphology, but also appear to have either an axon or basal dendrites [23]. Granule cells with axons are found in the dentate gyrus, while those in the olfactory bulb lack an axon. Basal dendrites are not found in 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 are 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 [9]. However, the widespread localization and relative paucity of these new neurons under normal conditions in the adult brain, particularly in mice [12,13], 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 [9,21,24]. 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 [25]. However, more recent studies revealed widespread neuronal migration from the early postnatal SVZ into neocortical and striatal areas [24,26]. 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, similar to olfactory bulb granule cells and CR-positive interneurons generated in the adult striatum [21]. Subcortical migration of neuroblasts from the ventral SVZ (vSVZ) occurs in a widespread 'shower', forming the ventral migratory mass (VMM), comprising an important fraction (approximately 20%) of perinatal SVZ neuroblasts and generating granule cells of the ICj [26].

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 in adult and postnatal stages [7,8,28] 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 [29], as do CR-positive neocortical neurons generated in the early postnatal SVZ [30], 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 similar to those in rodents [10]. This has not yet been observed in normal rodents, but generation of new striatal neurons from local astrocytes was described after ectopic expression of SRY (Sex Determining Region Y)-Box 2 (SOX2) or blocking of Notch signaling [31,32]. Altogether, these results suggest that both local and SVZ progenitors contribute to adult striatal neurogenesis (Figure 1). 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 [33] and striatum [34] are generated prenatally and originate in the ganglionic eminences (GEs). However, most CR-positive olfactory bulb interneurons are generated from Empty spiracles homeobox 1 (*Emx1*)-expressing progenitors in the SVZ [35,36]. Emx1 is a transcription factor largely restricted to the pallium during early development [37], indicating a cortical origin, distinct from most GABAergic interneurons. Following cerebral ischemia in early postnatal mice, newborn striatal CR-positive interneurons also derive from SVZ *Emx1*-expressing progenitors [38], 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 [39]. A later study found that a subpopulation of *Emx1*-lineage cells originating in the pallium migrates to the developing striatum during early prenatal development [40] and differentiates primarily into DARPP-32-positive medium-sized spiny neurons, but also generates a small number of CR-positive (but no other) striatal interneurons [41]. 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 [42,43]. 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 [44]. This directly contradicts the 14C evidence from Ernst [3] and also appears incompatible with studies suggesting that, in humans, more neocortical