Mechanism of neurogenesis in adult avian brain

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Summary. Adult neurogenesis in birds offers unique opportunities to study basic questions addressing the birth, migration and differentiation of neurons. Neurons in adult canaries originate from discrete proliferative regions on the walls of the lateral ventricles. They migrate away from their site of birth, initially at high rates, along the processes of radial cells. The rates of dispersal diminish as the young neurons invade regions devoid of radial fibers, probably under the guidance of other cues. The discrete sites of birth in the ventricular zone generate neurons that end up differentiating throughout the telencephelon. New neurons may become interneurons or projection neurons; the latter connect two song control nuclei between neostriatum and archistriatum. Radial cells, that in mammals disappear as neurogenesis comes to an end, persist in the adult avian brain. The presence of radial cells may be key to adult neurogenesis. Not only do they serve as guides for initial dispersal, they also divide and may be the progenitors of new neurons.

Key words. Radial glia; radial cell; ventricular zone; tanycytes; neuroblast; neuronal migration.

Neurogenesis is generally thought of as a developmental process that happens when the brain is growing, terminating early during postnatal life. This concept, which is largely derived from studies in mammals[17, 32, 62], suggests that the birth, migration and differentiation of neurons takes place within an immature but specialized brain parenchyma. Neurons are born far from their final destination on the walls of the brain ventricles. Radial glia provide a scaffolding of processes that guide the migration of young neurons from their site of birth to their final destination[28, 59, 63]. The scaffolding is dismantled at the end of development when neurogenesis ceases and radial glia convert into astrocytes[69, 78]. This scenario, however, may not apply to all vertebrates.

Adult canaries and other birds continue to add new neurons to many regions of their telencephalon[3, 11, 23, 46, 52]. The brain has stopped growing and neuronal density does not seem to increase; thus, new neurons must replace older ones[46]. Neuronal development follows a complex path. Neuronal birth is restricted to the walls of the ventricles from where the young neurons migrate to distant locations to differentiate. The size and complexity of the adult brain parenchyma raises the question of how new neurons migrate from their site of birth in the ventricular zone (VZ) to their final location. Here, I review recent findings and suggest ways in which this happens. I will discuss the following observations: 1) Radial cells persist in adult avian brain; 2) Cells closely attached to radial fibers are young migrating neurons; 3) The migration pattern of young neurons suggests a dispersal strategy; and finally 4) Multiple types of neurons are produced in adult birds. The functional implications of adult neurogenesis on behavior and brain plasticity are beyond the scope of this review. This very interesting aspect of adult neurogenesis has been recently reviewed elsewhere[44, 46].

Radial cells persist in the adult avian brain

Cell processes (or fibers) originating in the VZ and penetrating the brain parenchyma have been identified both during development and in adulthood. The cells that give rise to these processes have been referred to in the literature by a variety of names; as radial cells[38], epithelial cells[66], tanycytes[30], faserglia[19, 30], ependymal astrocytes[34, 75], and typical ependymal cells[71]. Rakic first showed that cells of this morphology, which he called radial glia, guide the migration of young neurons during cortical development[59, 65]. In mammals, radial glia disappear at the end of development as they transform into astrocytes[66, 69, 78]. The radial glia of birds were also thought to disappear at the end of development (p. 834[66]). However, as shown below, many remain into adulthood. I will refer to these cells as radial cells and to their extensions as radial fibers or radial processes.

Monoclonal antibody (40E-C) recognizes a special form of vimentin and preferentially stains radial cells in adult avian brain[2]. In mammals this antibody recognizes radial cells only in the developing brain; in the adult, 40E-C stains astrocytes[2]. In birds, radial cells are most prominent in, if not unique to, the telencephalon. They have a round cell body that lies in the ventricular zone and a long unbranched process that penetrates into the adult telencephalon. Processes from radial cells seem to terminate in a staggered manner suggesting that their lengths vary. In some cases the process of a single radial cell can be followed up to 2 mm[5].

There seem to be at least two types of cells of analogous structure that originate in the walls of the avian ventricles: radial cells and tanycytes, both of which stain positively with antibody 40E-C[2]. The term tanycyte was originally used by Horstmann[30] in a general sense, to describe elongated cells (including radial cells) in the walls of the ventricles from selachians. It is now generally reserved for a specific cell type: ependymal cells with a process that connects the walls of the ventricle with blood

vessels and other subventricular structures. Tanycytes seem to belong to a distinct category of VZ cells different from radial cells [1, 57, 73]. These cells are very common in the infundibular region of the hypothalamus and are probably related to the transport of ions and/or neuroactive peptides [18, 57]. Tanycytes are also present in other ventricles and the central canal [2, 10, 31, 58].

It is hard to distinguish tanycytes from radial cells solely on anatomical grounds. However, in canaries tanycytes are observed to target blood vessels to form specialized endings [2]. Radial cells project further and only occasionally contact blood vessels 'en passant' as revealed by a thickening in their processes [2]. The functional significance of these 'en passant' specializations is unknown. A further difference between tanycytes and radial cells in adult avian brain is that the former are most prominent in parts of the brain where neurogenesis has not been reported, such as the hypothalamus. Radial cells occur in the telencephalon where they are associated with neurogenesis (see below).

In adult mammals, tanycytes persist but cells equivalent to the radial cells of birds are absent. During mammalian development, probably all radial cells differentiate into glia [14, 29, 69, 78]. It is not known if fewer astrocytes or other glia are generated in birds at the expense of maintaining a cohort of radial cells.

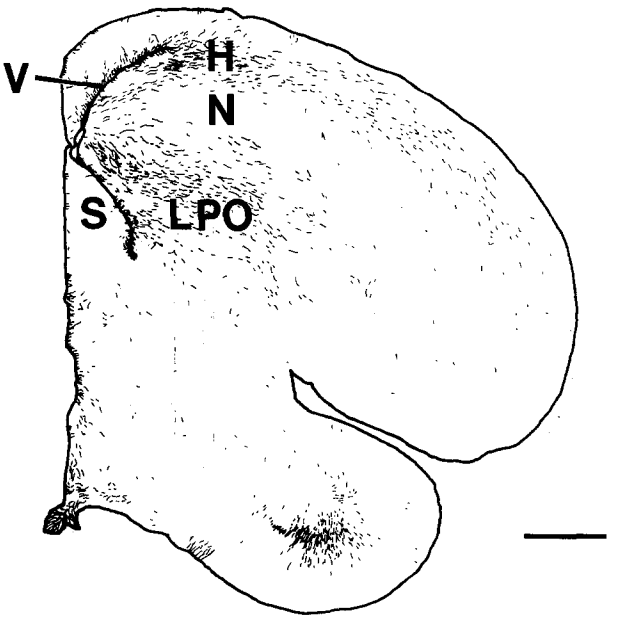

Figure 1. Distribution of radial processes in 6 µm frontal hemisection of canary brain at the level of the anterior commissure; left is medial, up is dorsal. Fibers staining with antibody 40E-C were mapped with the aid of a computer-microscope [7]. Radial cells have their cell body in the walls of the lateral ventricle (V) and a long process that penetrates laterally into the telencephalon. Note the high density of radial fibers in the hyperstriatum (H) and lobus parolfactorius LPO. The neostriatum (N) and septum (S) are practically devoid of processes from radial cells. Calibration bar = 1 mm.

Organization of radial cells in adult canaries

Our studies in canaries have concentrated on the radial cells in the telencephalon, since it is only in this region that new neurons are generated [3, 46]. Radial cells are preferentially oriented in the medio-lateral plane [5]. Many more fibers are observed in frontal than in sagittal sections. In coronal sections the medio-lateral orientation is confirmed and small cohorts of radial cells are observed projecting rostrally at the anterior (medial and lateral) borders of the lateral ventricle. The distribution of radial cells and their processes in the telencephalon is not homogeneous. Patches of radial fibers are observed in the hyperstriatum and lobus parolfactorius, whereas the anterior neostriatum is practically devoid of these fibers. Radial processes exit and stream out from the dorsal-lateral tip of the lateral ventricle and bend towards the lateral telencephalon [5] (fig. 1).

The alignment of radial cells in the medio-lateral plane is reminiscent of early development, when radial cells are oriented like spokes on a wheel around the embryonic telencephalic vesicle. However, when seen in frontal sections of the brain, radial cells are not oriented towards the surface of the brain but instead are deflected ventrolaterally into the telencephalon. The massive and differential growth of striatal structures in the avian brain may progressively bend and distort the original ontogenetic orientation of radial fibers. Similarly, regions like the anterior neostriatum and the higher vocal center (HVC, also known by its initial misnomer of hyperstriatum ventralis pars caudalis [47]) have few radial fibers, and may have shifted radial cells to their sides as a consequence of late onset of growth (HVC appears late [49]). This would happen if the arrangement of radial cells was laid out early during development and maintained as a continuum into adulthood. If this is the case, the distribution of radial cells in the adult bird could reflect the ontogenetic history of the telencephalon. This developmental aspect has not been studied.

The presence and distribution of radial cells in the adult canary suggested a role in adult neurogenesis. It was this hypothesis that we set out to test. If, as in the embryonic mammalian brain, adult canaries used radial cells to guide the migration of young neurons, then we might be able to identify cells associated with radial processes that could correspond to migrating young neurons.

Radial processes reveal elongated cells

When canary brain sections are simultaneously stained with antibody 40E-C and cresyl violet, the relation of cell nuclei to the radial fibers can be studied. Mature cells of neuronal or glial morphology seem randomly distributed with respect to the fibers of radial cells. However, an elongated cell with unique morphological characteristics was frequently aligned and contiguous with 40E-C positive processes (fig. 2). Such elongated cells have relatively pale nucleoplasm and dark nucleoli. Where the elongated

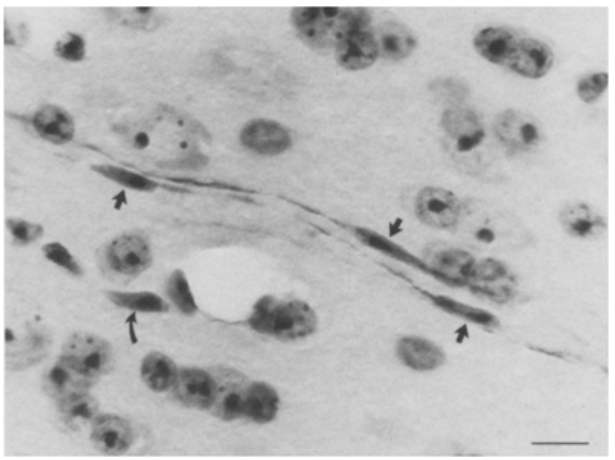

Figure 2. Migrating young neurons stained with cresyl violet (straight arrows) coursing along 40E-C stained radial fibers. A fourth migrating young neuron (curved arrow) is not contiguous with a radial fiber at this level but shows similar orientation as those on the radial track. Polyethylene glycol embedded canary brain sectioned at 3 µm. Calibration mark = 10 µm.

cells were not contiguous with 40E-C positive processes, their long axes were oriented parallel to the neighboring processes.

The morphology of these elongated cells was distiguishable from other cells even in the absence of the vimentin label for radial cells. This simplified the task of mapping the distribution of elongated cells throughout the brain [5]. Results show that this type of elongated cell is virtually restricted to the telencephalon. Very few, if any, were found in the diencephalon, mesencephalon or hindbrain. As mentioned above, it was in the telencephalon that we expected to find migrating neurons and for this reason we suspected that the elongated cells were related to neurogenesis.

The elongated cells are migrating young neurons

More than three decades ago, (^{3}H)-thymidine was introduced to neurobiology as a tool for the determination of neuronal birth dates [7,0]. Cells tagged with (^{3}H)-thymidine, which is incorporated into DNA during the S phase of the cell cycle, can then be followed by autoradiography. Using this technique we have shown that the elongated cells described above are born in adulthood [3]. Futhermore their positions changed at different survival times after (^{3}H)-thymidine administration indicating that they were moving. It is clear from this type of analysis that the elongated cells migrate away from the VZ, laterally into the telencephalon.

New cells with well-differentiated neuronal morphology appear labeled with (^{3}H)-thymidine only 20 days after injection of the nucleotide. The chronology is as follows: VZ cells appear labeled first. These cells are initially concentrated in 'hot spots', precisely in the hyperstriatum and lobus parolfactorius where radial cells are common [5]. As the number of labeled VZ cells begins to decrease, labeled elongated cells increase in number, first making their appearance close to the sites of VZ cell proliferation. The labeled migrating elongated cells progressively become dispersed throughout the telencephalon. The number of labeled elongated cells reaches a maximum 20 days after (^{3}H)-thymidine, decreasing thereafter, concomitant with the appearance of labeled neurons (fig. 3). Labeled non-neuronal cells do not appear to increase in number with extended survival time after (^{3}H)-thymidine. These data suggest that cells born in the VZ become elongated as they migrate into the telencephalon where they differentiate into neurons [3].

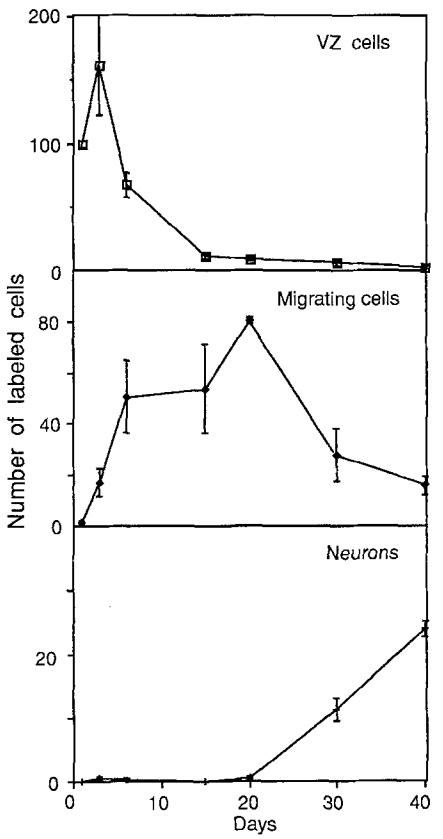

Figure 3. Number of (^{3}H)-thymidine labeled ventricular zone (VZ) cells, migrating cells and neurons at different survivals after the administration of the radioactive nucleotide [3]. Mean number of labeled cells per hemisection at the level shown in fig. 1 (n = 3; ± SEM). See text for interpretation.

Hot spots of VZ proliferation

Studies of the distribution of radial cells have directed our interest towards the VZ, where neurons are born. Until recently, the cells of the adult brain VZ were thought to have just an ependymal role related to substance transport and the circulation of ventricular cerebrospinal fluid. Now we know that in the telencephalon of adult birds the VZ cells are also involved in neurogenesis. Whether single cells share these two functions or different sets of cells exist is not known. As a first step

towards characterizing VZ cells related to neurogenesis, we have mapped the incidence of (^{3}H)-thymidine labeled cells at short survivals[6].

Proliferative regions were found only in the lateral ventricle and thus never outside of the telencephalon where neurogenesis does not occur. Likewise, labeled cells were very rare in the medial wall of the lateral ventricle, which faces telencephalic regions devoid of adult neurogenesis (e.g. the septum). Within the lateral walls, labeled VZ cells are concentrated in regions we have called 'hot spots'[6]. Interestingly, the most prominent hot spots coincide with regions of the telencephalon where many processes from radial cells originate and where new neurons begin migrating (e.g. in lobus parolfactorius and hyperstriatum).

Hot spots indicate regions where stem cells for adult neurogenesis reside. Surprisingly the most common cell proliferating within the hot spots is also positive to antibody 40E-C and many of these have a process typical of radial cells[6,51]. This observation suggests that radial cells may not only be present in adult avian brain as guides for migration but may also function as neuronal stem cells. Although this hypothesis is still developing, a similar scenario may also be true for the developing brain[41]. Radial cells of the developing murine telencephalon and spinal cord are also proliferative[20,42]. Radial cells in adult avian brain may be direct descendants of neuroepithelial cells. Their elongated profiles and potential to generate neurons may be a consequence of this ancestry.

Dispersal strategy of new neurons

It is interesting that such discrete neurogenic regions can give rise to neurons of several types (see below) which will end up widely dispersed throughout the telencephalon. As shown above many young migrating neurons are closely apposed to the processes of radial cells. This observation is reminiscent of neuronal migration in the developing mammalian neocortex, where radial cells guide the migration of young neurons[59,60]. However, unlike mammalian neocortex, where many radial cells span the entire thickness of the brain, radial cells in adult canaries do not reach the brain surface. The density of radial fibers, as revealed by 40E-C staining, decreases drastically 2–3 mm away from the lateral ventricle[5] (fig. 1). These processes are not directed towards the surface of the brain but instead dive into the lateral telencephalon.

Since migrating young neurons have been identified outside the scope of the radial fibers, these fibers can only guide part of the journey. Thereafter the migrating young neurons must follow other paths. Interestingly, two pathfinding strategies are also reflected in the rate at which the young neurons move away from the ventricular walls. Initially new cells move away at an average rate of 28 µm/h. This rate decreases to 8 µm/h, 2–3 mm away from the VZ at the point where radial fibers decrease sharply in number (fig. 4). Winding paths could account for slower progress despite similar speeds.

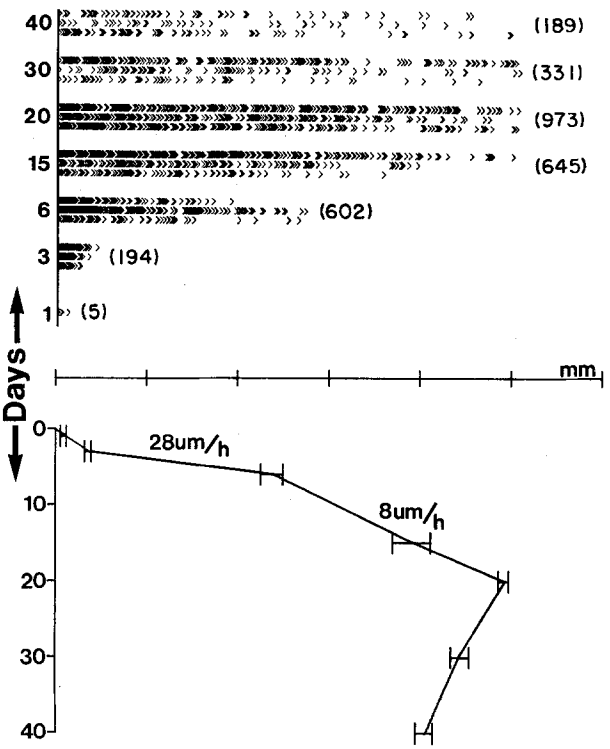

Figure 4. Dispersal of (^{3}H)-thymidine labeled young migrating neurons as a function of time (vertical axis). The horizontal axis shared between the upper and lower panels indicates distance between migrating neuron (>) and the closest VZ. Upper panel shows the position of all labeled migrating neurons mapped at the different survival times. Each row corresponds to migrating cells in 4 hemisections at the level of the anterior commissure (same level as in fig. 1) from one canary brain[3]. The lower panel plots the mean distance from the nearest VZ for the leading 5 migrating cells from each bird at each survival time (15 cells total, means ± SEM). The calculated rate of dispersal is indicated for intervals between 3–6 days and 6–15 days.

The relatively straight path provided by the processes of radial cells may serve as an expressway. Young migrating neurons appear to use this route to reach deep into the telencephalic parenchyma, allowing them to move away from the VZ as fast as possible. Local cues probably guide final homing. However, little information is available on how this might happen. Young migrating neurons may follow radial fibers, axons, dendrites or blood vessels, in this sense being 'multiphylic'[61], perhaps with a hierarchy of affinities. However, as much as structures such as radial fibers or neurites may provide a path, there should also be cues that specify direction. Young migrating neurons may be equipped with an endogenous navigational system and/or sense for chemical gradients. The surface of the guiding path could also be polarized to indicate directionality.

It is not known what determines where within the structure of the functioning adult brain parenchyma new neurons will finally settle. They may be attracted to sites requiring new neurons due to cell loss or demands for

additional circuit elements. Alternatively, they may force themselves into a location, overpowering neurons already there. One crucial distinction between adult neurogenesis and that in the embryo is that in the former, new neurons are inserted into established functional circuits [53]. They are doing this through a vast volume of telencephalon that is probably involved in many different tasks.

How is it then that the VZ determines how many and what types of young neurons to launch? This may not be necessary if neurons are produced in excess. Those that find a site for differentiation survive while the others die. The number of labeled migrating cells versus differentiated neurons after (^{3}H)-thymidine supports this view [3]. For every three labeled migrating young neurons only one differentiates (fig. 3). Degenerating cells labeled with (^{3}H)-thymidine are occasionally found in migratory paths, suggesting that some of the migrating young neurons die. It has been proposed that the migratory capacity of young neurons during cerebellar development is regulated by an internal clock [76]. If a similar clock were to operate in adult birds it could limit the length of time a young migrating neuron remains migratory. If within this period no adequate site for differentiation were found, then the young migrating neuron would die. Thus, a surplus would ensure a steady supply of young neurons. However, neurogenesis need not be regulated just by the culling of migrating neurons; there may as well be cues that induce neurogenesis, and these cues could vary over different parts of the telencephalon and for different types of neurons. Modulation of the neuronal type produced has been recently suggested in the developing frog retina [67].

Specification in the adult VZ

The radial unit hypothesis recently proposed by Rakic [64, 65], states that the VZ which gives rise to cortex, has predetermined proliferative units that correspond to presumptive target areas were neurons will ultimately migrate and differentiate. In some developing structures, like neocortex in mammals [13, 21, 69, 78] or the optic tectum of birds [25, 26], many radial processes extend from the VZ to the pial surface. Alignment between the VZ and the migration target in these structures is thus ensured by these radial processes [64]. Young migrating neurons within these developing structures may adhere to strict radial migration, since radial processes provide reliable targeting. This appears to be true in the avian optic tectum [25–27] and the mammalian neocortex [37, 39]; although considerable migratory scattering has also been described for cortex [56, 79] (for further discussion see Walsh and Cepko [80]). However, in other regions of the developing brain, or in the case described here for the adult avian brain, radial processes do not span the entire migratory route.

New neurons in adult avian brain originate mainly in the hot spots. These relatively small regions generate neurons for a vast volume of telencephalon. During the first 6 days of migration there is a good correlation between the position of the hot spots and that of the young neurons. However, this correlation is blurred at longer survivals, when many young neurons invade regions with no recognizable (i.e. 40 E-C positive) radial processes [3]. New neurons may end up differentiating in regions of the brain that are topographically disjoined from the hot spots [3, 46]. This probably happens when the young neurons give up radial migration and follow other cues.

Taken together these observations suggest that there is no detailed VZ specification for the number of new neurons nor positions where new neurons differentiate. There could be, however, a predisposition for neurons born in dorsolateral reaches of the lateral ventricle to end up taking positions in lateral or dorsal telencephalon. Conversely, those born in ventrolateral reaches of the same ventricle might preferentially end up in ventral and medial telecephalon [5]. This is probably due to the initial bias imposed by the orientation of radial processes and not by a system of point to point addresses.

Embryonic brain chimeras between chick and quail support the notion that lax radial migration is not unique to adult brain. Borders between chick and quail tissue in the telencephalon of these chimeras are not distinct. Grafted neurons from one species invade (orthogonally to the radial processes) neighboring parenchyma from the host species [8]. Recent experiments with the retroviral tracing method, suggest a similar conclusion for the developing chick telencephalon [26, 27]. Therefore, young neurons do not follow a strict radial pattern of migration during assembly of the avian telencephalon, or during adult neurogenesis. The radial unit hypothesis may therefore only apply to specific regions of the developing brain. Phenomena that in the cortex could be explained by this hypothesis, such as regulation of cell number and topographical plan, require new interpretations in structures where radial cells do not bring the young migrating neurons to their final destination.

Types of neurons produced in adulthood

The range of potential phenotypes for neurons born in adulthood may be limited. If this is the case, then stem cells in the adult VZ could already be determined to a certain degree. Developing brains teach us that the birth of different neuronal types follows astonishing punctuality. The birthdate of distinct neuronal classes can therefore be traced to specific ontogenetic periods [32, 35, 40, 68]. We know that many neurons are produced in song birds during development [4]. This happens over a short period of time but at a very high rate. The rate of neurogenesis drops soon after hatching but in most of the telencephalon continues into adulthood [3, 4, 46]. Since neurogenesis now occurs over months instead of days, low post-

hatching rates of neurogenesis could dramatically alter the neuronal composition of specific target areas[4, 33, 45]. In canaries the brain stops growing at one month of age and brain morphogenesis cannot explain continued neurogenesis. Neurons from paleostriatum, septum and nontelencephalic regions of the brain are produced only during development. Thus, the assembly of major regions of the avian brain follows different strategies.

What then is the nature of the neurons produced during development versus those produced in the adult avian brain? Our experiments address this question in this same area of the telencephalon where adult neurogenesis was first described[23]: the higher vocal center (HVC). Nucleus HVC plays a major role in the production of learned song and its connectivity is well known[48, 50]. There are at least three types of neurons in HVC: large neurons projecting to area X of lobus parolfactorius, medium sized interneurons, and small neurons that project to nucleus robustus archistriatalis (RA)[4, 54]. In addition, there may be subclasses of neurons within each of these groups[4, 43, 52].

Following injection of Fluoro-gold into area X or RA, the neurons in HVC that project to these two target zones can be distinguished from one another. Combining this technique with autoradiography, the time of birth of the two types of neurons can be determined. Most if not all of area X-projecting neurons are born between embryonic day (E) 9 and E 12. At this time the production of RA-projecting cells is negligible. Instead, RA-projecting neurons are born throughout post-hatching development and into adulthood[4, 45]. Similarly interneurons (i.e. neurons not backfilled by fluorogold either from RA or area X) continue to be added from early development to adulthood[4, 54]. Different types of interneurons may also have scheduled birthdates. It has been suggested that the production of GABA-positive HVC interneurons stops at some point during development[52].

Very little is known about the phenotype of neurons born outside HVC. Some of the neurons produced in caudal neostriatum are positive to DARP-32[52], a phosphoprotein present in cells containing D-1 dopamine receptors. These cells are also surrounded by axonal 'baskets' stained with tyrosine hydroxylase antibodies[52]. These dopaminoceptive cells born in adulthood are absent or very rare in HVC. The neurotransmitters and projection patterns used by new neurons in other parts of the telencephalon are not known. However given the variety of locations in which new neurons differentiate in adult canary brain we infer that functional specification is diverse.

Thus new neurons of several types may be generated in adult avian brain. Most perplexing is that both interneurons and projection neurons continue to be generated. The migrating young neurons are either multipotent, or many young migrating neurons of different potential phenotypes are generated. However, from the experiments in HVC it is clear that certain restrictions apply. Neurons like those projecting to area X are only produced during fetal development. Whether the birth of area X-projecting neurons can be induced in adulthood remains to be determined. Meanwhile, it appears that multiple neuronal types probably belonging to one category are generated in adult canary brain.

Conclusion

The entire brain originates in the VZ. Cytogenetic functions are segregated temporally and spatially so that VZ cells produce neurons and glia. As these cells migrate away from the VZ to differentiate and extend their own processes, the parenchyma outside of the VZ grows and the VZ is soon overgrown by its progeny. In adult birds the neurogenic VZ is reduced to a tiny epithelial wall less than 50 μm in thickness that forms part of the walls of the lateral ventricle. In adult mammals a neurogenic VZ might disappear altogether.

Nevertheless, in many adult birds this narrow band of VZ continues to generate neurons of several types. Neurogenic areas of the VZ are segregated into discrete regions we call hot spots. Adult birds retain radial cells that project long processes into the telencephalon. These cells are concentrated in the hot spots. Most interesting is that some radial cells divide and may serve as the stem cells for neurogenesis.

The young migrating neurons develop a distinct elongated morphology as they migrate away from the VZ. This initial dispersal happens at high rates along processes of radial cells. However, migration is not strictly radial. Young neurons may follow other cues as they detach from the radial path to invade regions of the telencephalon devoid of radial cells. Neuronal differentiation takes place 20–40 days later in regions far from the initial birth site. Several neuronal types may be produced. In the vocal control nucleus HVC, both interneurons and projection neurons are added. However not all types of neurons are generated in adulthood: HVC's area X projecting neurons are produced only during development.

The specification of neuronal type, number of new neurons and final location for differentiation may not happen only at the level of the VZ. However, this is an inference that will have to be tested by following the fate of the progeny of small labeled patches or clones of VZ stem cells. Many young migrating neurons die during migration or as they begin differentiation. Selective death may play a role in the regulation of adult neurogenesis.

It has been known for almost a century, that many species of poikilotherms maintain cells on the walls of the brain ventricles with long processes that penetrate the adjacent parenchyma[15, 30, 71, 74, 77]. We have suggested that, as in canaries, radial cells of cold-blooded vertebrates might be related to neurogenesis[2]. In fact examples of adult neurogenesis have been described in fish, amphibians, and reptiles[9, 12, 16, 22, 36, 55]. In addition ra-

dial cells in fish have been shown to divide [72]; as suggested for canaries, radial cells in poikilotherms may serve as stem cells for neurogenesis. More frequently, however, the radial cells found in these animals during adulthood have been associated with a different function; they are considered a form of glia or ependyma, involved in the transport of electrolytes and other substances between different compartments of the brain and the ventricles [15, 18, 19]. Functions related to neurogenesis and substance transport need not be mutually exclusive [24].

The picture of the adult avian telencephalon that emerges is one of a very dynamic structure where new neurons are produced and older ones are replaced. Cell migration and the differentiation of new neurons demands constant structural modification of the adult brain. Young neurons must push their way through adult brain parenchyma. Dendrites and axons must grow and debris from cell death must be removed. These classical developmental phenomena can now be studied in the adult avian brain.

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