Adult neural stem/progenitor cells in neurodegenerative repair

Limin MAO① John Q. WANG *
Division of Pharmacology① School of Pharmacy① University of Missouri-Kansas City① 2411 Holmes St① Rm. M3-225① Kansas City① Missouri 64108① USA

Abstract  Although the mammalian brain has long been thought to be entirely postmitotic① the recent discovery has confirmed an existence of neural stem or progenitor cells in various regions of the adult mammalian brain. Like embryonic stem cells① adult neural progenitor cells possess the capacity of self-renewal and differentiation potential for neurogenesis or gliogenesis. In addition to the subventricular zone and hippocampus where active cell division naturally occurs① adult neural progenitors with neurogenic potential exist in the striatum and the vicinity of dopaminergic neurons in the substantia nigra. Normally① progenitors in those regions proliferate at a low level① and most proliferated cells remain uncommitted. In response to the selective lesion of nigrostriatal dopaminergic pathway by the neurotoxins① such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine① MPTP① or 6-hydroxydopamine① progenitors in the injured areas markedly increase their proliferation rate. Depending upon the magnitude and kinetics of the lesion① neurogenesis and gliogenesis were induced in the lesion sites at varying extents. A large number of growth and neurotrophic factors influence proliferation and/or differentiation of progenitor cells under normal and lesioned conditions. Some factors① epidermal and basic fibroblast growth factors and brain-derived neurotrophic factor① are facilitatory① while others① usually bone morphogenetic proteins① are inhibitory① for controlling division and fate of neuronal or glial progenitors. Expression of endogenous factors and their respective receptors in existing and newborn cells are also subject to be altered by the lesion. These genomic responses are considered to be important elements for the formation of a local molecular niche for a given phenotypic cell regeneration. Taken together① adult neural progenitor cells in the nigrostriatal dopaminergic system have the ability to respond to the lesion to repopulate missing cells. The regenerative neuro- or gliogenesis in situ can at least in part① endogenously compensate injured neural elements① and achieve a self-repair of neurodegenerative disorders such as Parkinson’s disease.

Key words: stem cells① striatum① nigra① neurogenesis① cytopogenesis① dopamine① Parkinson’s disease

Received 2003-01-15  Accepted 2003-03-02

The studies of the author mentioned in the review were supported by two R01 grants from the NIH① DA10355 and MH61469 to J. Q. W. ① and a grant from the American Heart Association① L. M. ①.

* Corresponding author. Division of Pharmacology① School of Pharmacy① University of Missouri-Kansas City① 2411 Holmes St① Rm. M3-225① Kansas City① Missouri 64108① USA ① Tel ① 816-235-1786 ① Fax ① 816-235-1776 ① E-mail ① wqiu@umkc.edu
A question as to what exactly a stem cell is has been somewhat contentious even after nearly three decades of debate. A prevailing view is that stem cells are cells with the capacity for unlimited or prolonged self-renewal when conditions are satisfied that can produce at least one type of highly differentiated descendant. Usually between the stem cell and its terminally differentiated progeny there are a series of intermediate populations of committed cells progenitor or precursor cells which usually possess limited proliferative capacity and restricted differentiation potential sometimes known as transit amplifying cells. The neural stem cell is loosely referred to those that 1 can generate neural tissues or are derived from the central or peripheral nervous system 2 and 3 can give rise to one specific phenotype or more likely multiple types of neural other than themselves through asymmetric cell division.

It has long been thought that the mammalian brain is entirely postmitotic. That is shortly after birth brain cells no longer undergo mitosis and no new cells are produced in the brain throughout the rest of lifetime. Thus it becomes a surprise when stem cells are recently discovered in unexpected areas of the adult brain. Following the identification of stem cells in hematopoietic bone marrow and epithelial and liver tissues neural stem cells derived from the adult central nervous system came on the scene recently. There are at least two sites in the all adult mammalian brains where active cell division naturally occurs the subventricular zone SVZ and the granule cell layer GCL of the dentate gyrus of the hippocampal formation. Recently a list of areas showing stem cell activity expanded to spinal cord prefrontal cortex retina striatum and substantia nigra. More areas can be expected to add to this list rapidly in the future. The exact primitive stage of these cells in these areas is not yet defined. However a recent set of papers clearly documented that these cells in adult brains could self-renew and differentiate into newborn neural cells which could be either newborn neurons neurogenesis or newborn glial cells gliogenesis. Thus these cells can be at least described as adult neural progenitors therefore the term progenitor cells will be used thereafter in the rest part of this review.

As compared to embryonic stem cells which tend to proliferate at high levels and spontaneously differentiate into all kinds of tissue adult neural progenitors usually show low levels of cell division under normal conditions and have already made a commitment to become neural tissue either neurons or non-neuronal cells. Moreover the proliferation and differentiation of adult neural progenitors can be substantially altered in response to environmental changes induced by growth factors or other external cues see below.

Progenitor cells can divide symmetrically to expand their numbers or asymmetrically to give rise to a differentiated progeny. The knowledge on the exact kinetic profile of neurogenesis and gliogenesis is currently lacking. It has been suggested that conservatively neuron be produced each day for every 2000 existing neurons in rat and mouse or 6% of total hippocampal granule cells be generated each month. The rate of neurogenesis and gliogenesis declines with age but cytogenesis does persist in many brain areas of elderly rodents and humans throughout adulthood. The relationship between the birth of new neurons and the death of older ones is an interesting issue. Some types of balance presumably exist between the two events. Whether more cells are born or died in a given region of the adult brain probably depends upon environmental requirements. Cell cycle analysis of the proliferative population residing near the ventricle in the adult mouse forebrain reveals that there are at least two distinct groups of dividing cells. One population the constitutively proliferating population has a cell cycle time of approximately 12.7 hours. The other population which has a relatively long cell cycle ~15 d or more is known as the quiescent cell population. The constitutively proliferating cells are the progeny of the relatively quiescent population. The quiescent cells proliferate in response to growth factors in vitro to give rise to clonal cell aggregates containing neuronal and glial progenitor cells and thus are thought to represent the endogenous neural progenitor cell population.

**Adult neural progenitor cells in the forebrain**

Adult neural progenitor cells in the SVZ and hippocampus represent the most thoroughly investigated and best characterized ones in the forebrain. These progenitor cells are often detected in vitro through the use of retroviruses or thymidine autoradiography. Recently a thymidine analog bromodeoxyuridine BrdU is used as a tracer of new DNA synthesis to label dividing cells in brain Fig. 1. There are advantages and disadvantages of those methods. The highest density of progenitor cells is found in the SVZ Fig. 2A. Neuronal progenitors in the SVZ migrate tangentially along the rostral migratory stream into the olfactory bulb where they differentiate into granule and periglomerular neurons. In contrast glial progenitors in
Fig. 1. Mammalian adult neural progenitor cell cycle and BrdU immunohistochemical detection of newborn cells. The BrdU that penetrates the blood-brain barrier after systemic administration can be incorporated into the newly synthesized DNA. Using anti-BrdU antibodies the newborn cells with BrdU-incorporated DNAs can be detected immunohistochemically.

The SVZ migrate radically into neighboring brain areas such as striatum\[40\] corpus callosum\[41\] and neocortex\[42\]. Adult neural progenitors in the hippocampus are distributed throughout the medial dentate gyrus at all rostrocaudal levels\[43\]. They are typically observed in a thin lamina between the hilus and the granule cell layer\[44\] i.e. the subgranular zone\[45\] as well as within the granule cell layer and hilus\[46\]. Approximately a half of newborn cells in the hippocampus are believed to differentiate into neurons 3 to 4 weeks after their birth according to their characteristic morphology of granule neurons and co-expression of the neuronal markers\[47\] such as neuron specific enolase\[48\] NSE\[49\] microtubule-associated protein-3\[50\] MAP2\[51\] or neuronal nuclear antigen\[52\] Neun\[53\]. A small fraction of newborn cells \( \sim 15\% \) adopt glial fate as detected by their association with the astrocytic marker\[54\] glial fibrillary acidic protein\[55\] GFAP\[56\] or SI00\[57\] or the oligodendrocytic markers\[58\] see Table 1 for a summarization of the frequently-used phenotype markers\[59\]. Newborn neurons in the adult dentate gyrus can migrate to the functional site where they execute the programmed missions and connect appropriately into the circuitry of the hippocampus by developing synapses and axonal projections to receive and deliver signals\[60\] respectively\[61\].

Besides the SVZ and the dentate gyrus\[62\] active adult neurogenesis and/or gliogenesis exist in other regions of the forebrain. The striatum that receives dopaminergic afferents from the midbrain neurons is among those regions where cell proliferation and differentiation have been noticed and characterized in the recent work performed in this laboratory\[63\]. After BrdU injection\[64\] dividing cells assayed by BrdU incorporation were consistently observed in the dorsal and ventral striatum\[65\]. These cells were scattered throughout the area\[66\] and could survive beyond 60 days with a graduate increase in their body size and processes\[67\]. Although a small fraction of cells exhibited the morphological characteristics of radial glia 3 weeks after their birth\[68\] the vast majority of newborn cells showed no obvious morphology of either projection neurons or glia. Parallel with the morphological observation\[69\] approximately 10 – 20% of BrdU-labeled cells were immunoreactive to an astrocyte-

Table 1. A summarization of the chemical markers frequently used in immunohistochemistry for the identification of phenotypes of newly generated cells in the central nervous system

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal cells</td>
<td>β-tubulin type [60] TuJ1[61] immature neurons[62]</td>
</tr>
<tr>
<td></td>
<td>NeuN[63] mature neurons[64]</td>
</tr>
<tr>
<td></td>
<td>MAP2a[65] mature neurons[66]</td>
</tr>
<tr>
<td></td>
<td>NSE[67] mature neurons[68]</td>
</tr>
<tr>
<td>Glial cells</td>
<td></td>
</tr>
<tr>
<td>Astrocyte</td>
<td>GFAP[69] mature astrocyte[70]</td>
</tr>
<tr>
<td></td>
<td>S100[71] mature astrocyte[72]</td>
</tr>
<tr>
<td>Oligodendrocyte</td>
<td>CNP[73] immature oligodendrocyte[74]</td>
</tr>
<tr>
<td></td>
<td>O4[75] immature oligodendrocyte[76]</td>
</tr>
<tr>
<td>Microglia</td>
<td>Mac-1[77]</td>
</tr>
<tr>
<td></td>
<td>OX42[78]</td>
</tr>
<tr>
<td>Glial progenitors</td>
<td>NG2[79]</td>
</tr>
<tr>
<td>Multipotent neural progenitors</td>
<td>Nestin[80]</td>
</tr>
</tbody>
</table>
Fig. 2. BrdU-labeled nuclei in the lateral subventricular zone [A] hippocampus [B] and striatum [C]. A. BrdU-positive nuclei in the lateral subventricular zone [a] 1 day, [b] 3 days, [c] 7 days and [d] 14 days after a single injection of BrdU (100 mg/kg). Note that a large number of BrdU cells are present 1 – 3 days and dramatic reduction of BrdU cells occurred 7 – 14 days after BrdU injection. B. BrdU cells are primarily distributed in the hilus and the bottom line of the GCL in the hippocampus. C. BrdU-positive cells in the striatum [g] 1 day, [h] 7 days and [i] 21 days after BrdU injection. GCL granule cell layer.
associated marker S100β and a few BrdU cells were double-labeled with a neuron-associated marker NeuN [Fig. 3]. Thus it appears that gliogenesis naturally occurs in the intact striatum at a small scale whereas neurogenesis is minimal. The vast majority of newborn cells normally remain undifferentiated in this brain area. The exact primitive stage of those dividing cells in the striatum is not yet defined. However the aforementioned study clearly demonstrates that progenitor cells in the adult striatum could self-renew and give rise to at least glia.

The substantia nigra pars compacta in the midbrain where dopaminergic neurons reside is another forebrain area containing natural cell genesis[24]. In a recent report from Gage’s group[25] BrdU-positive cells were detected throughout the entire midbrain including the nigra indicating a population of proliferating cells present in this region. The presence of locally dividing cells was confirmed by injection of Moloney murine leukemia virus-based GFP retroviruses that infect only dividing cells. Using glia-associated markers[12,9] of newborn cells differentiated into oligodendrocytes and 1.4% into astrocytes. Few newborn cells in the nigra were microglia. Multiple BrdU-positive nuclei seemed to be associated with the neuron-associated protein NeuN. However careful analysis by confocal z-series of each of those cells revealed that BrdU-labeled nuclei belonged to cells that were in close proximity to the nuclei of NeuN-positive neurons. Thus convincing evidence for in vivo neurogenesis in the nigra is lacking. Moreover the result emphasizes the importance of careful confocal microscopy when it comes to identify neurogenesis using double immunofluorescent labeling.

Although natural neurogenesis was not seen in the nigral region[26] isolated nigral progenitor cells were found to possess a neurogenic potential in vitro[27]. Transplantation of freshly isolated nigral progenitor cells into the adult hippocampus showed that these cells also have a neuronal potential under in vivo conditions. These results suggest that progenitor cells in the adult nigra can give rise to new neurons when exposed to appropriate environmental signals. Perhaps under normal conditions[28] neuronal signals are absent and/or inhibitory signals of neuronal differentiation are present in the adult nigra which prevents sizeable neurogenesis in this region.

The origination of neural stem/progenitor cells is an interesting issue. While the majority of progenitor cells in adult brain are believed to be provided by the local source[29] recent evidence shows an alternative source of neural progenitor cells from the tissue outside the central nervous system. Mezey’s group shows that transplanted bone marrow cells can enter the brain of mice or human subjects and differentiate into neurons or glia[25-47]. This raises the possibility that some neuronal and glial progenitor cells in adult brain may arise from a precursor that is a normal constituent of adult bone marrow.

**Proliferative reaction of progenitor cells to dopamine lesions**

Decreased dopaminergic tone significantly alters proliferation of progenitor cells in the striatum and nigra. Pharmacological blockade of dopamine D1/D2 receptors with a specific antagonist haloperidol increased cell proliferation in the gerbil hippocampus[48]. Similar results were seen in the recent work reported by Kay and Blum[29] in mice with damaged nigrostriatal dopamine system by an acute injection of neurotoxin 1-methyl-4-phenyl-1-2-pyridyl-β-tetrahydropyridine (MPTP). MPTP can result in the selective lesion of the nigrostriatal dopaminergic pathway[50] dopaminergic terminals in the dorsal striatum and dopaminergic cell bodies in the substantia nigra[51] and therefore is extensively used as an excellent animal model for human Parkinson’s disease. In our recent study[52] subacute injections of MPTP 25 mg/kg once daily for 5 d[53] caused a robust proliferative response in striatal and nigral regions of adult mice[24]. The newborn cells were not associated with blood vessels indicating that these cells were produced through local neural progenitor cells but not endothelial cells. A large number of newborn cells could survive more than 60 d[54] indicating a potential of differentiation into neuronal or glial cells. Indeed some of newborn cells show morphological characteristics of glial triangular or irregular cell bodies with long radial processes[55] or neuronal round or oval nuclei in medium-sized bodies cells. Using another neurotoxin 6-hydroxydopamine[6-OHDA] that selectively produces the dopaminergic lesion an apparent increase in the number of dividing cells was seen in the lesioned side as compared with the unlesioned control side[25]. Taken together nigrostriatal dopaminergic lesions significantly increase proliferation of neural progenitor cells in the affected sites. Those newborn cells may differentiate into neuronal or glial cells for the sake of compensating the loss of dopamine content.

---

Fig. 3. Immunofluorescent images showing co-expression of BrdU with a neuronal marker NeuN in a newborn cell[56] arrowed in A + D and with a glial marker S100β[57] E + G in the striatum of adult rat. Co-expression of BrdU with NeuN or S100β indicates[58] the presence of neuronal cells neurogenesis[59] or glial cell[60] gliogenesis[61] respectively.
Differentiation of newborn cells after dopamine lesions

Profound astrogenic differentiation of newborn cells was found in the striatum in recent in vivo studies following acute and subacute MPTP lesions\(^2\) \(^{24} \). Among many complex compensatory responses to neurodegeneration in the brain, one noticeable response to the lesion of the nigrostriatal dopaminergic projection is reactive astrogliosis\(^2\) the accumulation of large, swollen so-called 'reactive' astrocytes within the region of degenerative axon terminals\(^2\) the dorsal striatum and nigra. \(^4\) The origin of these reactive astrocytes can be considered in the following three possibilities. First\(^2\) the reactive astrocytes are newborn cells that are generated via local progenitors wakened by injury. Second\(^2\) they are the consequence of migration of mature or newborn astrocytes from elsewhere to the injured site. Lastly\(^2\) they are local astrocytes that are triggered to express or increase expression of immuno-histochemically detectable astrocytic markers such as S100B. The BrdU incorporation provides a tool to distinguish newborn and pre-existing astrocytes. Since most S100B-positive astrocytes showed the incorporation of BrdU\(^2\) \(^{24} \) astrogenesis represents a major component of the reactive astrogliotic response to MPTP lesions. The new astrocytes are more likely born locally in the striatum rather than the result of active migration of the newborns from elsewhere because the large fraction of newborn cells rapidly differentiated into astrocytes within 10 d after birth\(^2\) and clusters of new astrocytes are often seen in the area\(^2\) \(^{24} \) an indicator of local proliferation with limited migration.

In contrast to the predominant BrdU-positive astrocytes in glial reaction in the striatum\(^2\) reactive astrogliosis were not BrdU-positive in the nigra after acute injection of MPTP\(^2\) \(^{24} \). Some midbrain cells co-expressed BrdU and Mac-1\(^2\) a microglial marker. Most BrdU cells in the nigra failed to express markers for microglia\(^2\) astroglia or oligodendroglia\(^2\) \(^{24} \) suggesting that they still remain as uncommitted progenitors. Similar results were also seen in the nigra in our recent study following the subacute lesion with MPTP\(^2\) \(^{24} \). In general\(^2\) the differentiation response of progenitors in the nigra is different from that of progenitors in the striatum. Since most newborn cells remain uncommitted exogenous growth or neurotrophic factors may exert powerful influences on their fate adaptation\(^2\) see below\(^2\).

Neurogenesis after the MPTP lesion is worth a particular attention. A single dose of MPTP or 6-OHDA did not cause reliable neurogenesis in the striatum and nigra\(^2\) \(^{23}\) \(^{25} \). Similarly\(^2\) convincing evidence showing co-expression of BrdU-containing cells with a neuronal marker\(^2\) \(^{23}\) \(^{25} \) not been collected after a subacute treatment with MPTP\(^2\) \(^{24} \). The lack of neurogenesis may be related to the extent of loss of midbrain dopaminergic neurons by the acute and subacute administration of neurotoxins. An acute or subacute MPTP lesion caused a marginal loss of dopaminergic cells in the nigra as revealed by unbiased stereology\(^2\) \(^{50} \). Dopamine content and uptake in the striatum were also rapidly recovered\(^2\) \(^{24} \). Thus\(^2\) limited and transient damage to nigral cells may not raise an adequate call to neurogenesis. Recently\(^2\) a novel chronic MPTP model involving five-week repeated treatments with MPTP was therefore developed in this laboratory which showed more prolonged and profound loss of nigral cells\(^2\) \(^{50} \). Interestingly enough\(^2\) in response to this profound damage\(^2\) a significant scale of neurogenesis was seen in both the striatum and nigra approximately eight weeks after the lesion\(^2\) Mao et al.\(^2\) unpublished observations\(^2\). Thus\(^2\) the chronic MPTP lesion appears to be able to induce the environmental change that is particularly favorable for the birth of neuronal cells.

Intrinsic tyrosine hydroxylase\(^2\) TH\(^-\) immunoreactive dopaminergic neurons have been spotted in the intact striatum\(^2\) \(^{21}\) \(^{32} \). The MPTP lesion caused a 3.5-fold increase in TH-immunoreactive cells in the mouse dorsal striatum\(^2\) \(^{50} \). Similar results were also observed in rats after the 6-OHDA lesion\(^2\) \(^{52}\) \(^{41} \). The increase in TH cells is believed to be a compensatory response to decreased dopaminergic inputs for restoring the dopamine balance. The origin of increased TH cells may be due to de novo expression of the normally quiescent TH gene in noncatecholaminergic striatal neurons under the condition of dopaminergic denervation\(^2\) \(^{55}\) \(^{56} \). Alternatively\(^2\) they could result from the birth of new TH-phenotypic neurons through a local progenitor mechanism. The absence of an aging pigment lipofuscin\(^2\) in TH cells when it is present in most of the matured striatal projection neurons in the monkey\(^2\) \(^{50} \) seems to favor this notion. However\(^2\) during the full course of the subacute MPTP lesion\(^2\) we could not confirm that striatal TH cells are newborn ones due to their dissociation from BrdU\(^2\) \(^{24} \). Thus\(^2\) increased TH cells more likely represent pre-existing striatal cells in which TH gene expression is triggered or enhanced to a level detectable immuno-histochemically. Turning non-TH cells into TH cells seems to be a more rapid response than relatively time-consuming TH neurogenesis to timely compensate dopamine loss at the early stage of the lesion.

Molecular niche for neurogenesis and gliogenesis

Mechanisms underlying neurogenesis and gliogenesis in the striatum and nigra of lesioned animals are unknown. As a matter of fact\(^2\) due to the novelty of research in this area\(^2\) very limited experiments have been
attempted to unravel this issue. However, it can be speculated that certain alterations in local environment occur following the lesion which ultimately leads to changes in cytogenesis. One of scenarios concerning environmental changes is that the facilitatory signals of cell regeneration are enhanced and/or that the inhibitory signals are reduced in the lesion sites. When the balance of facilitatory and inhibitory signals leans towards cell regeneration significant neurogenesis and gliogenesis occur accordingly. Several growth factors and neurotrophic factors have been demonstrated to function as pro- or inhibitory signals to cell birth in the adult rodent brain. Changes in their activities either endogenously or exogenously can integrate local molecular niche for neurogenesis or gliogenesis.

Epidermal growth factor (EGF) and basic fibroblast growth factor (FGF-2) bFGF show the power of significantly altering the proliferation and differentiation of progenitors in the SVZ[1] hippocampus and striatum of rodents. Although EGF and FGF-2 show a various degree of effects on proliferation and differentiation of neuronal or glial progenitors they predominantly act as proglial and/or proneuronal signals. Infusion of EGF and FGF-2 into the lateral ventricle of adult rats or mice profoundly increased proliferation of cells in the SVZ but not in the dentate gyrus of hippocampus. Moreover, the two mitogens influenced the fate of cells usually resulting in more glial cells than neurons[2]. Increased systemic levels of FGF-2 by subcutaneous injection also increased cell proliferation in both the SVZ and hippocampus of neonatal and adult rats. The effects of intraventricular FGF-2 are age-dependent much more increases in neurons in the neonate than those in the adult were induced following FGF-2 application. These data suggest that exogenously-administered factors alter proliferation and differentiation of progenitors in a facilitatory manner. It is therefore intriguing to investigate whether and how these exogenous factors affect the response of neural progenitors to the dopamine lesion in the current study in this laboratory.

Endogenous EGF and FGF-2 levels may be altered and sufficient to adjust the response of neural progenitors to the dopamine lesions. Increased EGF receptor binding sites in the striatum were observed in chronic parkinsonian syndromes but not in acute models of the disease. In response to lesions by acute MPTP in mice FGF-2 mRNA was increased in the striatum at 1 week post-lesion and the increased FGF-2 mRNA returned to control levels 5 weeks when the terminals are regenerated. After a 6-OHDA lesion in rats a sustained and strong increase in FGF-2 mRNA was seen in the ipsilateral nigra, olfactory tubercle, and striatum. Moreover, the number of gliocatal cells expressing the FGF-2 mRNA was increased and FGF-2 immunoreactivity was increased primarily in the nuclei of astrocytes. These data provide evidence that expression of EGF or FGF-2 or their receptors in the lesion sites are vulnerable to dopamine lesions. Altered expression may participate in the formation of a molecular niche for distinct cytogenesis. It is currently unknown whether newborn cells express those factors or receptors. Such an expression allows a close regulation of newborn cells via mechanisms involving auto- or intercellular interactions.

The neurotrophic factor is another mitogenic factor family that influences progenitor’s behaviors. Neurotrophins refer to a family of proteins comprising nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) for review see[4]. Among these BDNF is best characterized in its potential to promote dopaminergic cell development, neuroproliferation and neurodifferentiation and restoration of dopaminergic degeneration, neuroprotection and neuroregeneration. For example BDNF promoted dopaminergic neuron differentiation in embryonic mesencephalic cultures[5]. BDNF also protected the survival of dopaminergic neurons against the toxic effects of MPTP and 6-OHDA in primary cultures[6]. Similar to the tropism observed in vitro[7] icv injection of BDNF or adenovirus bearing BDNF increased cell proliferation or neurogenesis in the rat striatum[8]. Direct intrastriatal or intranigral infusion of BDNF or implantation of fibroblasts genetically engineered to produce BDNF prevented MPTP- or 6-OHDA-induced degeneration of dopaminergic neurons in adult rodents[9, 10]. Thus, exogenous BDNF possesses the ability to reduce cell damage. However, to date the mechanism underlying the protective effect of BDNF is poorly understood. It is possible that BDNF exerts its trophic action via a mechanism involving neural progenitors. That is, BDNF promotes local neuronal and/or glial regeneration which in turn protects or restores the damage to dopaminergic neurons. Endogenous BDNF and the high-affinity receptor for BDNF the TrkB receptor are highly sensitive to the dopamine lesion. The toxic or mechanical denervation of dopamine system increased BDNF and TrkB mRNA levels in the injured striatum and nigra[11-13]. It is believed that increased BDNF/TrkB expression constitutes an important element in the compensatory response to the lesion.

Increasing evidence indicates that the proliferation and particularly fate of neural progenitors are regulated by members of the bone morphogenetic protein (BMP) subclass of the transforming growth factor (TGF-β) superfamily[4] for review see[14]. The multiple functions of BMPs involve not only embryogenesis but also a-
dult cytogenesis for review se 86]. In the forebrain BMP4 was demonstrated to be a strong inhibitor of neurogenesis both in vitro and in vivo[97,98]. BMPs are also abundantly expressed in the adult brain including striatal and nigral areas from early embryogenesis throughout adult life[86,90]. Two subtypes of BMP receptors type I IA and IB and type II are also expressed in the adult mouse brain at variable levels in different regions[90]. The striatum and niga show a moderate level of type IA mRNA and minimal levels of type IB and II mRNA[90]. BMP actions are regulated in vivo by proteins such as Noggin which antagonizes BMP signaling by directly binding BMPs and blocking ligand activity for review se 91]. However in the intact striatum and niga Noggin expression is minimal as opposed to a high level of Noggin in the hippocampus[86]. The variable levels of Noggin in different areas may be responsible at least in part for variable levels of natural neurogenesis in those regions[250]. To date no data are available regarding genomic responses of BMP the BMP receptor and Noggin in the forebrain to MPTP lesions. Those genomic responses if there are any could be equally important as EGF FGF and BDNF responses for the understanding of formation of molecular niche for neurogenesis after MPTP lesions.

Each of the above-mentioned factors and their respective receptors are members of their large families. Emerging evidence shows that other subtypes in their families can also regulate adult neuro- or gliogenesis in a similar or distinctive fashion. For example the other neurotrophins such as NGF NT-3 ciliary neurotrophic factor NT-4 and glial cell line-derived neurotrophic factor GDNF exhibit the trophic effect on striatal or midbrain neurons at a varying degree[92,93,94]. Roles of BMPs may be more complex and distinctive depending upon the subtype of BMPs involved and specific stages of lesions[94]. The subtypes of receptors may also be the determinant of the trophic effect of factors. Challenging and massive work seems inevitable to define roles of each individual member in the regulation of cell regeneration.

There are many other intrinsic factors that could influence adult neuro- and/or gliogenesis under normal or lesioned conditions. For example hormones significantly influence neurogenesis. Glucocorticoids inhibit proliferation of progenitors as evidenced by the fact that adenohypophyseal increased proliferation of progenitor population in the hippocampus and systemic application of glucocorticoids antagonized this influence[14,96,98]. In contrast estrogen stimulated neurogenesis in the hippocampus of adult rats[97] indicating a sex-specific regulation of neurogenesis. Neurotransmitters also modulate adult progenitor’s activity. Glutamate is the first one studied in this regard. Glutamatergic deafferentation and blockade of glutamate receptors[98] NMDA[98] caused an increase in all aspects of hippocampal neurogenesis[98-101]. In contrast activation of NMDA receptors caused a dramatic decrease in proliferation of progenitors in the dentate gyrus[98-100]. Thus glutamate affects adult neurogenesis in an inhibitory fashion as opposed to a facilitatory role of serotonin in the production of new neurons via activation of the 5HT1A receptor[102]. Under the real in vivo condition the above hormones and neurotransmitters are believed to vigorously interact each other or with the growth and neurotrophic factors to form a molecularly-synchronized niche for either neuro- or gliogenesis or both at varying degrees corresponding to the magnitude and kinetics of the lesion.

Functional roles of adult neural progenitors

The adult brain has long been thought to be entirely postmitotic. So functional roles of adult neural stem cells or neural progenitors in the CNS are unclear at present. It has been suggested that they are vestiges of evolution from more primitive organisms like fish[103] in which organ and tissue self-renewal provides survival advantages in an inhospitable environment. However along with emerging in vivo studies on this issue functional roles of adult neurogenesis started to be noticed. Under physiological conditions cytogenesis may replace normal programmed dead cells to remain full functional capability of replacing cells even though such a replacement is considered to be very limited in adult brains. More importantly the adult mammalian nervous system needs to retain the capacity of adapting to new demands of brain functions such as learning memory and neural plasticity in response to environmental changes. It is therefore essential for a local generation of new neuronal or nonneuronal cells in the responsible brain structures which contributes to the formation or integration of new memories and neuroadaptation. As to region-specific roles the SVZ is more like a stem/progenitor cell factory conveniently located in the brain. Through proliferation it manufactures progenitor cells infinitely and delivers them to the destinations all over the brain. The newborn neurons in adult subependyma have been shown to migrate along a sagittal pathway to the olfactory bulb of rodents[19,104] and putatively along an unknown pathway to the association cortex of nonhuman primates[20]. As compared to the SVZ where proliferation happens at high levels with limited differentiation cytogenesis in the hippocampus occurs at a relatively low level. However newly generated cells in this region could effectively signify their presence whenever a call is made for new memory or neuroadaptive formation[105].
Under pathophysiological conditions inducible cyrogenesis can play dual roles in a given pathophysiological process. On the one hand cyrogenesis can be provoked abnormally to process aberrant functions. For example the neurons that are formed through normal ongoing neurogenesis do not send processes to the CA3 region of the hippocampus. However the epilepsy-induced neurogenesis sends axon collaterals back onto the dentate gyrus that forms recurrent collaterals contributing to enhanced local activity for epilepsy. On the other hand cyrogenesis can be wakened to repair rescue or compensate chronic neurodegenerative loss such as in Parkinson’s disease. In this scenario the repopulation of missing cells by increased endogenous neurogenesis in the diseased site could be an idea self-repair. The newborn cells after differentiation in situ may partially or completely take on the exact function of the cells they replace. Studies on these regenerative neurogenesis and gliogenesis are just emerging. It can be anticipated that the provoked cell regeneration via a progenitor mechanism could provide a promising target for the future treatment of Parkinson’s disease and other neurodegenerative disorders.

Summary

The review summarizes the recent progress in a novel field about neural progenitor cells in the adult rodent brain. These cells are confirmed to exist in the vicinity of midbrain dopaminergic neurons and their projection region striatum. Normally there is a low level of proliferation and astrogenetic differentiation naturally occurred in these regions. The selective lesion of nigrostriatal dopaminergic pathway with neurotoxins such as MPTP or 6-OHDA resulted in a marked increase in the proliferation rate of neural progenitors in the injured striatum and nigra. Neurogenesis and gliogenesis was induced at varying extent depending upon treatment paradigms. A number of growth and neurotrophic factors are involved in the regulation of natural and lesion-induced neuro- and gliogenesis as either pro- or inhibitory signals. Expression of endogenous factors and their respective receptors may be altered in the lesion sites to form a molecular niche for cell regeneration. Taken together neural progenitor cells in the diseased sites respond to the dopamine lesion and provide ideal self-repair for neurodegenerative diseases such as Parkinson’s disease.

REFERENCES

22. Liu Y, Lusis S, Petrose E, Wang QJ. Proximal glioneurogenesis in the striatum of adult mice following nigrostriatal dopaminergic lesion by repeated MPTP administration. Dev
Brain Res 2001;931:R7 – 65.


86 Mehler MF, Magie PC, Zhang D, Kessler JA. Bone mor-


107] Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. J Neurosci 1997;17:7277 – 7378.