Brief Review

Adult neural stem/progenitor cells in neurodegenerative repair

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Abstract: Although the mammalian brain has long been thought to be entirely postmitotic, the recent discovery has confirmed an existence of neural stem or progenitor cells in various regions of the adult mammalian brain. Like embryonic stem cells, 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 occurs, adult neural progenitors with neurogenic potential exist in the striatum and the vicinity of dopaminergic neurons in the substantia nigra. Normally, progenitors in those regions proliferate at a low level, and most proliferated cells remain uncommitted. In response to the selective lesion of nigrostriatal dopaminergic pathway by the neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine, progenitors in the injured areas markedly increase their proliferation rate. Depending upon the magnitude and kinetics of the lesion, 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 factors (epidermal and basic fibroblast growth factors and brain-derived neurotrophic factor) are facilitatory, while others (usually bone morphogenetic proteins) are inhibitory, 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 together, 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 part, endogenously compensate injured neural elements, and achieve a self-repair of neurodegenerative disorders such as Parkinson's disease.

Key words: stem cells; striatum; nigra; neurogenesis; cytogenesis; dopamine; Parkinson's disease

成体神经干(前体)细胞在中枢神经系统退行性病变中的修复作用

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摘 要: 尽管传统概念长期认为成体哺乳动物中枢神经系统缺乏再生增殖能力, 但近年来发现, 在成体若干脑区内确实存在具有再生与分化能力的神经干或神经前体细胞。这些干细胞在正常情况下仅表现较低的再生分化活动。不过, 在神经退行性病变中,病灶区内的干细胞可被动员、激活, 并以较高的速率分裂分化以及取代坏死的神经元或胶质细胞,达到自身原位修复的作用。许多神经生长和营养因子具有增强或抑制干细胞分裂和/或分化的能力, 在神经退行性病变中,病灶区内外成熟或新生细胞即可通过表达这些因子, 有效调节干细胞的活动和干细胞主导的修复过程。总之, 成体神经干细胞可以积极参与急性或慢性神经组织损伤的修复, 通过再生来提供新的神经元以及其他必需的细胞, 以促进功能的恢复。

关键词: 神经干细胞; 纹状体; 黑质; 神经元再生; 细胞再生; 多巴胺; 帕金森病

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A question as to what exactly a stem cell is has been somewhat contentious even after nearly three decades of debate[1,2]. 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[3]. 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) have self-renewal capacity, and (3) can give rise to one specific phenotype, or more likely multiple types, of neural cells other than themselves through asymmetric cell division[4].

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[5,6]. 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[7-11]. 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[12-18]. Recently, a list of areas showing stem cell activity expanded to spinal cord[18,19], prefrontal cortex[20], retina[21], striatum[22] and substantia nigra[23-25]. 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 (cytogenesis) which could be either newborn neurons (neurogenesis) or newborn glial cells (gliogenesis)[24,26-28]. 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 tissues (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[29]. The knowledge on the exact kinetic profile of neurogenesis and gliogenesis is currently lacking. It has been suggested that, conservatively, 1 neuron be produced each day for every 2000 existing neurons in rat and mouse[30] or 6% of total hippocampal granule cells be generated each month[31]. The rate of neurogenesis and gliogenesis declines with age, but cytogenesis does persist in many brain areas of elderly rodents and humans throughout adulthood[32,33]. 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 h[34]. The other population, which has a relatively long cell cycle (~15 d or more), is known as the quiescent cell population[35,36]. The constitutively proliferating cells are the progeny of the relatively quiescent population[35]. The quiescent cells proliferate in response to growth factors *in vitro* to give rise to clonal cell aggregates (neurospheres) containing neuronal and glial progenitor cells and thus are thought to represent the endogenous neural progenitor cell population *in vivo*[17,35,37].

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 vivo* through the use of retroviruses[38] or thymidine autoradiography[32,33]. 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[4]. The highest density of progenitor cells is found in the SVZ (Fig. 2*A*). Neuronal progenitors in the SVZ migrate tangentially (sagittally) along the rostral migratory stream into the olfactory bulb, where they differentiate into granule and periglomerular neurons[39,40]. In contrast, glial progenitors in

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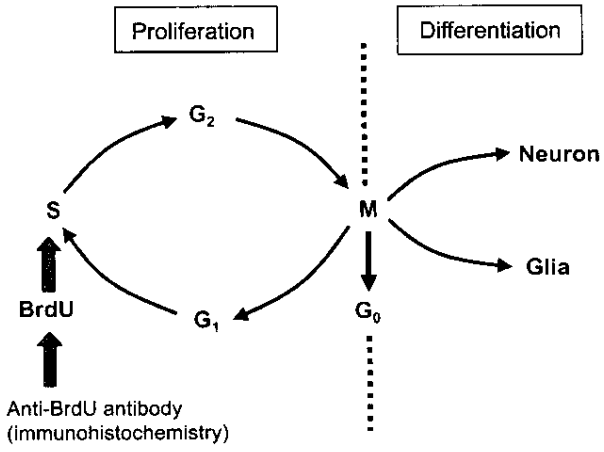

Fig. 1. Mammalian adult neural progenitor cell cycle and BrdU immunohistochemical detection of newborn cells. The BrdU that penetrates the blood-brain barrier after systemic administration can be incorporated into the newly synthesized DNA. Using anti-BrdU antibodies, the newborn cells with BrdU-incorporated DNAs can be detected immunohistochemically.

the SVZ migrate radically into neighboring brain areas such as striatum, corpus callosum, and neocortex[41]. Adult neural progenitors in the hippocampus are distributed throughout the medial dentate gyrus at all rostrocaudal levels[14,42]. They are typically observed in a thin lamina between the hilus and the granule cell layer, i. e., the subgranular zone, as well as within the granule cell layer and hilus[14,42] (Fig. 2*B*). 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, such as neuron specific enolase (NSE), microtubule-associated protein-2 (MAP2), or neuronal nuclear antigen (NeuN)[43]. A small fraction of newborn cells (~15%) adopt glial fate as detected by their association with the astrocytic marker, glial fibrillary acidic protein (GFAP) or S100β, or the oligodendrocytic markers (see Table 1 for a summarization of the frequently-used phenotype markers). 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, respectively[44].

Besides the SVZ and the dentate gyrus, 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[22,24]. After BrdU injection, dividing cells assayed by BrdU incorporation were consistently observed in the dorsal and ventral striatum (Fig. 2*C*). These cells were scattered throughout the area, and could survive beyond 60 d, with a graduate increase in their body size and processes[22,24]. Although a small fraction of cells exhibited the morphological characteristics of radial glia 3 weeks after their birth, the vast majority of newborn cells showed no obvious morphology of either projection neurons or glia. Parallel with the morphological observation, 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

Phenotypes	Markers
Neuronal cells	β-tubulin type Ⅲ (TuJ1；immature neurons)
	NeuN (mature neurons)
	MAP2ab (mature neurons)
	NSE (mature neurons)
Glial cells	
Astrocyte	GFAP (mature astrocyte)
	S100β (mature astrocyte)
Oligodendrocyte	CNP (immature oligodendrocyte)
	O4 (immature oligodendrocyte)
Microglia	Mac-1
	Ox42
Glial progenitors	NG2
Multipotent neural progenitors	Nestin

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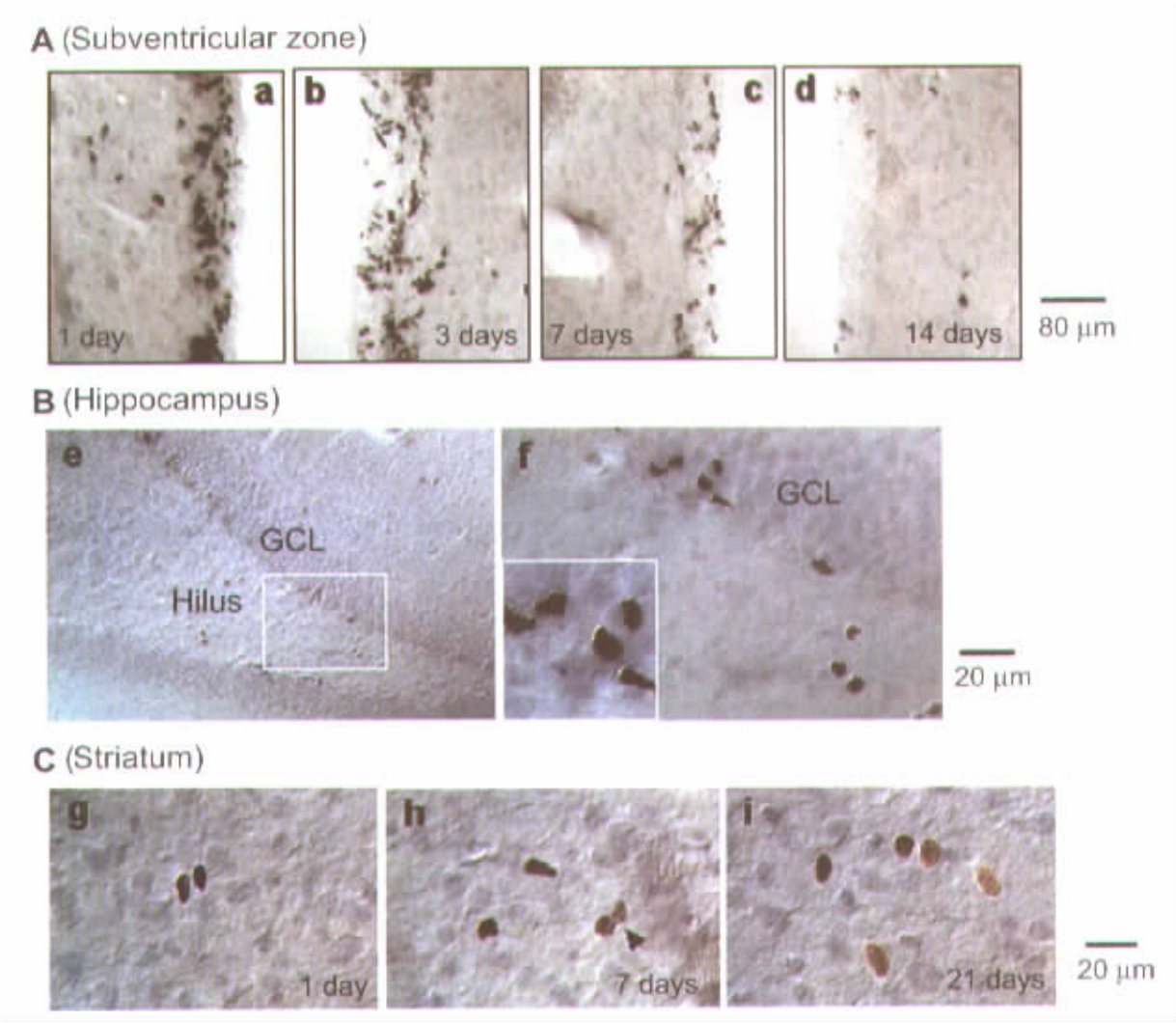
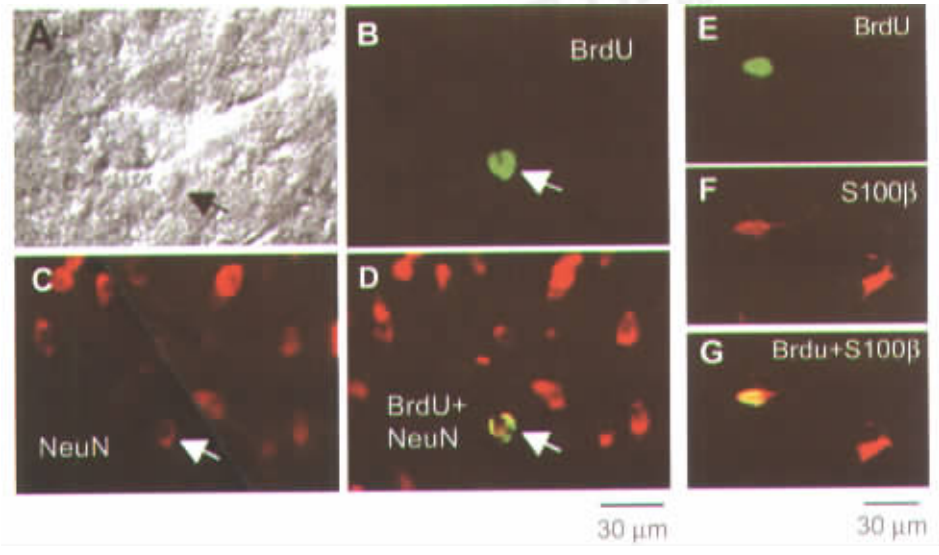


Fig. 2. BrdU-labeled nuclei in the lateral subventricular zone (*A*), hippocampus (*B*) and striatum (*C*). *A*. BrdU-positive nuclei in the lateral subventricular zone 1 (a), 3 (b), 7 (c) and 14 (d) d after a single injection of BrdU (100 mg/kg). Note that a large number of BrdU cells are present 1 – 3 d, and dramatic reduction of BrdU cells occurred 7 – 14 d, 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 1 (g), 7 (h) and 21 (i) d after BrdU injection. GCL, granule cell layer.



(Fig. 3)

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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 groups[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, isolated nigral progenitor cells were found to possess a neurogenic potential *in vitro*[25]. 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, proneuronal 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, 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[45-47]. 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 D_1/D_2 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[23] in mice with damaged nigrostriatal dopamine system by an acute injection of neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP can result in the selective lesion of the nigrostriatal dopaminergic pathway (dopaminergic terminals in the dorsal striatum and dopaminergic cell bodies in the substantia nigra), and therefore is extensively used as an excellent animal model for human Parkinson's disease. In our recent study, subacute injections of MPTP (25 mg/kg, once daily for 5 d) 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, 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) or neuronal (round or oval nulcei 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.

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Fig. 3. Immunofluorescent images showing co-expression of BrdU with a neuronal marker NeuN in a newborn cell (arrowed in *A-D*) and with a glial marker S100β (*E-G*) in the striatum of adult rat. Co-expression of BrdU with NeuN or S100β indicates a new production of neuronal cells (neurogenesis) or glial cells (gliogenesis), respectively.

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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[23,24]. Among many complex compensatory responses to neurodegeneration in the brain, one noticeable response to the lesion of the nigrostriatal dopaminergic projection is reactive astrogliosis: the accumulation of large, swollen, so-called 'reactive' astrocytes within the region of degenerative axon terminals (the dorsal striatum)[49]. The origin of these reactive astrocytes can be considered in the following three possibilities. First, the reactive astrocytes are newborn cells that are generated via local progenitors waken by injury. Second, they are the consequence of migration of matured or newborn astrocytes from elsewhere to the injured site. Lastly, they are local astrocytes that are triggered to express, or increase expression of, immunohistochemically detectable astrocytic markers, such as S100β. The BrdU incorporation provides a tool to distinguish newborn and pre-existing astrocytes. Since most S100β-positive astrocytes showed the incorporation of BrdU[24], astrogenesis represents a major component of the reactive astrocytic 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) and clusters of new astrocytes are often seen in the area[24], an indicator of local proliferation with limited migration.

In contrast to the predominant BrdU-positive astrocytes in glial reaction in the striatum, reactive astroglia were not BrdU-positive in the nigra after acute injection of MPTP[23]. Some midbrain cells co-expressed BrdU and Mac-1, a microglial marker[23]. Most BrdU cells in the nigra failed to express markers for microglia, astroglia, or oligodendroglia[23], 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[24]. In general, 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 (see below).

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[23,25]. Similarly, convincing evidence showing co-expression of BrdU-containing cells with a neuronal marker (NeuN) has not been collected after a subacute treatment with MPTP[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[50]. Dopamine content and uptake in the striatum were also rapidly recovered[24]. Thus, limited and transient damage to nigral cells may not raise an adequate call to neurogenesis. Recently, 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[50]. Interestingly enough, in response to this profound damage, a significant scale of neurogenesis was seen in both the striatum and nigra approximately eight weeks after the lesion (Mao et al., unpublished observations). Thus, 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 (TH)-immunoreactive dopaminergic neurons have been spotted in the intact striatum[51,52]. The MPTP lesion caused a 3.5-fold increase in TH-immunoreactive cells in the mouse dorsal striatum[53]. Similar results were also observed in rats after the 6-OHDA lesion[52,54]. 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 dopamine denervation[55,56]. Alternatively, they could result from 'birth' of new TH-phenotypic neurons through a local progenitor mechanism. The absence of an aging pigment, lipofuscin, in TH cells when it is present in most of the matured striatal projection neurons in the monkey[53] seems to favor this notion. However, during the full course of the subacute MPTP lesion, we could not confirm that striatal TH cells are newborn ones due to their dissociation from BrdU[24]. Thus, increased TH cells more likely represent pre-existing striatal cells in which TH gene expression is triggered or enhanced to a level detectable immunohistochemically. 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, due to the novelty of research in this area, very limited experiments have been

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attempted to unravel this issue. However, it can be speculated that certain alterations in local environment occur following the lesion[57,58], 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-2 (FGF-2, bFGF) show the power of significantly altering the proliferation and differentiation of progenitors in the SVZ, 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[37,59-62]. Moreover, the two mitogens influenced the fate of cells, usually resulting in more glial cells than neurons[37,59,61,63]. Increased systemic levels of FGF-2 by subcutaneous injection also increased cell proliferation in both the SVZ and hippocampus of neonatal and adult rats[64]. 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[64,65]. 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, a goal of 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[66]. 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 at 5 weeks when the terminals are regenerated[67,68]. After a 6-OHDA lesion in rats, a sustained and strong increase in FGF-2 mRNA was seen in the ipsilateral nigra and striatum[69]. Moreover, the number of glial 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 [70]). Among these trophins, 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[71,72]. BDNF also protected the survival of dopaminergic neurons against the toxic effects of MPTP and 6-OHDA in primary cultures[73,74]. Similar to the trophism observed *in vitro*, icv injection of BDNF or adenovirus bearing BDNF increased cell proliferation or neurogenesis in the rat striatum[75,76]. 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[77-80]. 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 mechanic denervation of dopamine system increased BDNF and TrkB mRNA levels in the injured striatum and nigra[81-83]. 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 β (TGFβ) superfamily (for review, see [84,85]). The multiple functions of BMPs involve not only embryogenesis but also a-

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dult cytogenesis (for review, see [86]). In the forebrain, BMP4 was demonstrated to be a strong inhibitor of neurogenesis both *in vitro* and *in vivo*[87,88]. BMPs are also abundantly expressed in the adult brain, including striatal and nigral areas, from early embryogenesis throughout adult life[86,89]. 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 nigra show a moderate level of type IA mRNA and minimal levels of type IB and II mRNAs[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, see [91]). However, in the intact striatum and nigra, Noggin expression is minimal as opposed to a high level of Noggin in the hippocampus[88]. The variable levels of Noggin in different areas may be responsible, at least in part, for variable levels of natural neurogenesis in those regions[25]. 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 (CNTF) and glial cell line-derived neurotrophic factor (GDNF), exhibit the trophic effect on striatal or midbrain neurons at a varying degree[92,93]. 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 adrenalectomy increased proliferation of progenitor population in the hippocampus, and systemic application of glucocorticoids antagonized this influence[13,95,96]. 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 (NMDA) 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 non-neuronal 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[39,104] 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].

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Under pathophysiological conditions, inducible cytogenesis can play dual roles in a given pathophysiological process. On the one hand, cytogenesis 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[44,106]. However, the epilepsy-induced neurogenesis sends axon collaterals back onto the dentate gyrus that forms recurrent collaterals contributing to enhanced local activity for epilepsy[44,107]. On the other hand, cytogenesis can be wakened to repair (rescue or compensate) chronic neurodegenerative loss, such as in Parkinson's disease[108]. In this scenario, the repopulation of missing cells by increased endogenous neurogenesis in the diseased site could be an ideal '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

[1] Morrison SJ, Shah NM, Anderson DJ. Regulatory mechanisms in stem cell biology. Cell 1997; 88: 287 – 298.

[2] Potten CS, ed. Stem Cells, Academic Press, London, 1997.

[3] Watt FM, Hogan BM. Out of Eden: stem cells and their niches. Science 2000; 287: 1427 – 1430.

[4] Gage FH. Mammalian neural stem cells. Science 2000; 287: 1433 – 1438.

[5] Temple S. CNS development: The obscure origins of adult stem cells. Curr Biol 1999; 9: R397 – R399.

[6] Temple S, Alvarez-Buylla A. Stem cells in the adult mammalian central nervous system. Curr Opin Neurobiol 1999; 9: 135 – 141.

[7] Gage FH, Ray J, Fisher LJ. Isolation, characterization, and use of stem cells from the CNS. Annu Rev Neurosci 1995; 18: 159 – 192.

[8] Gage FH. Stem cells of the central nervous system. Curr Opin Neurobiol 1998; 8: 671 – 676.

[9] Kuhn HG, Svendsen CN. Origins, functions, and potential of adult neural stem cells. BioEssays 1999; 21: 625 – 630.

[10] McKay R. Stem cells in the central nervous system. Science 1997; 276: 66 – 71.

[11] Shihabuddin LS, Palmer TD, Gage FH. The search for neural progenitor cells: prospects for the therapy of neurodegenerative disease. Mol Med Today 1999; 5: 474 – 480.

[12] Smart I. The subependymal layer of the mouse brain and its cell production as shown by radioautography after thymidine-H^3 injection. J Comp Neurol 1961; 116: 325 – 338.

[13] Cameron HA, Gould E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. Neuroscience 1994; 61: 203 – 209.

[14] Gage FH, Kempermann G, Palmer TD, Peterson DA, Ray J. Multipotent progenitor cells in the adult dentate gyrus. J Neurobiol 1998; 36: 249 – 266.

[15] Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult old world primates. Proc Natl Acad Sci USA 1999; 96: 5263 – 5267.

[16] Kornack DR, Rakic P. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc Natl Acad Sci USA 1999; 96: 5768 – 5777.

[17] Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 1992; 255: 1707.

[18] Weiss S, Christine D, Hewson J, Wohl C, Wheatley M, Peterson AC, Reynolds BA. Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. J Neurosci 1996; 16: 7599 – 7609.

[19] Horner PJ, Power AE, Kempermann G, Kuhn HG, Palmer TD, Winkler T, Thal LJ, Gage FH. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. J Neurosci 2000; 20: 2218 – 2228.

[20] Gould E, Reeves AJ, Graziano MSA, Gross CG. Neurogenesis in the neocortex of adult primates. Science 1999; 286: 548.

[21] Tropepe V, Coles BLK, Chiasson BJ, Horsford DJ, Elia AJ, McInnes RR, van der Kooy D. Retinal stem cells in the adult mammalian eye. Science 2000; 287: 2032 – 2036.

[22] Mao L, Wang JQ. Gliogenesis in the striatum of the adult rat: alteration in neural progenitor population after psychostimulant exposure. Dev Brain Res 2000; 130: 41 – 51.

[23] Kay JN, Blum M. Differential response of ventral midbrain and striatal progenitor cells to lesions of the nigrostriatal dopaminergic projection. Dev Neurosci 2000; 22: 56 – 67.

[24] Mao L, Lau YS, Petroske E, Wang JQ. Profound astrogenesis in the striatum of adult mice following nigrostriatal dopaminergic lesion by repeated MPTP administration. Dev

万方数据

Brain Res 2001;131 57 – 65.
[25] Lie DC, Dziewczapolski G, Willhoite AR, Kaspar BK, Shults CW, Gage FH. The adult substantia nigra contains progenitor cells with neurogenic potential. J Neurosci 2000;22 6639 – 6649.
[26] Chiasson BJ, Tropepe V, Morshead CM, van der Kooy D. Adult mammalian forebrain ependymal and subependymal cells demonstrate proliferative potential, but only subependymal cells have neural stem cell characteristics. J Neurosci 1999;19 4462 – 4471.
[27] Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 1999;97: 703 – 716.
[28] Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Rrisen J. Identification of a neural stem cell in the adult mammalian central nervous sytem. Cell 1999;96 25 – 34.
[29] Martens DJ, Tropepe V, van der Kooy D. Separate proliferation kinetics of fibroblast growth factor-responsive and epidermal growth factor-responsive neural stem cells within the embryonic forebrain germinal zone. J Neurosci 2000; 20 1085 – 1095.
[30] Kempermann G, Kuhn HG, Gage FH. Genetic influence on neurogenesis in the dentate gyrus of adult mice. Prod Natl Acad Sci USA 1997;94 10409 – 10414.
[31] Cameron HA, McKay RD. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 2001;435 406 – 417.
[32] Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 1965;124 319 – 335.
[33] Altman J, Das GD. Postnatal neurogenesis in the guinea pig. Nature 1967;214 1098 – 1101.
[34] Morshead CM, van der Kooy D. Postmitotic death is the fate of constitutively proliferating cells in the subependymal layer of the adult mouse brain. J Neurosci 1992;12 249 – 256.
[35] Morshead CM, Reynolds BA, Craig CG, McBurney MW, Staines WA, Morassutti D, Weiss S, van der Kooy D. Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells. Neuron 1994;13 1071 – 1082.
[36] Morshead CM, Craig CG, van der Kooy D. *In vivo* clonal analyses reveal the properties of endogenous neural stem cell proliferation in the adult mammalian forebrain. Development 1998;125 2251 – 2261.
[37] Craig CG, Tropepe V, Morshead CM, Reynolds BA, Weiss S, van der Kooy D. *In vivo* growth factor expansion of endogenous subependymal neural precursor cell populations in the adult mouse brain. J Neurosci 1996;16 2649 – 2658.
[38] Price J, Thurlow L. Cell lineage in the rat cerebral cortex: a study using retroviral-mediated gene transfer. Development 1988;104 473 – 482.
[39] Lois C, Alvarez-Buylla A. Long-distance neuronal migration in the adult mammalian brain. Science 1994;264: 1145 – 1148.
[40] Luskin MD. Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron 1993;11 173 – 189.
[41] Levision SW, Chuang C, Abramson BJ, Goldman JE. The migrational patterns and developmental fates of glial precursons in the rat subventricular zone are temporally regulated. Development 1993;119 611 – 622.
[42] Cameron HA, Woolley CS, McEwen BS, Gould E. Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. Neuroscience 1993;56 337 – 344.
[43] Mullen RJ, Buck CR, Smith A. NeuN, a neuronal specific nuclear protein in vertebrates. Development 1992;116: 201 – 211.
[44] Markakis E, Gage FH. Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. J Comp Neurol 1999; 406 449 – 460.
[45] Eglitis MA, Mezey E. Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice. Proc Natl Acad Sci USA 1997;94 4080 – 4085.
[46] Mezey E, Chandross KJ, Harta G, Maki RA, McKercher SR. Turning blood into brain: cells bearing neuronal antigens generated *in vivo* from bone marrow. Science 2000; 290 1779 – 1782.
[47] Mezey E, Key S, Vogelsang G, Szalayova I, Lange GD, Crain B. Transplanted bone marrow generates new neurons in human brains. Proc Natl Acad Sci USA 2003;100 1364 – 1369.
[48] Dawirs PR, Hildebrandt K, Teuchert-Noodt G. Adult treatment with haloperidol increases dentate granule cell proliferation in the gerbil hippocampus. J Neural Transm 1998;105 317 – 327.
[49] Ridet JL, Malhotra SK, Privat A, Gage HH. Reactive astrocytes: Cellular and molecular cues to biological function. Trends Neurosci 1997;20 570 – 577.
[50] Petroske E, Meredith GE, Callen S, Totterdell S, Lau, YS. Mouse model of parkinsonism: a comparison between subacute MPTP and chronic MPTP/probenecid treatment. Neuroscience 2001;106 141 – 153.
[51] Dubach M, Schmidt R, Kunkel D, Bowden DM, Martin R, German DC. Primate neostriatal neurons containing tyrosine hydroxylase: immunohistochemical evidence. Neurosci Lett 1987;75 205 – 210.
[52] Tashiro Y, Sugimoto T, Hattori Y, Uemura I, Nagatsu H, Kikuchi H, Mizuno N. Tyrosine hydroxylase-like immunoreactive neurons in the striatum of the rat. Neurosci Lett 1989;97 6 – 10.
[53] Betarbet R, Turner R, Chockkan V, DeLong MR, Allers KA, Walters J, Levey AI, Greenamyre JT. Dopaminergic neurons intrinsic to the primate striatum. J Neurosci 1997; 17 6761 – 6768.
[54] Meredith GE, Kellaghan FP, Tan Y, Zahm DS, Totterdell S. Immunocytochemical characterization of catecholaminergic neurons in the rat striatum following dopamine-depleting lesions. Eur J Neurosci 1999;11 3585 – 3596.
[55] Du X, Iacovitti L. Synergy between growth factors and transmitters required for catecholamine differentiation in brain neurons. J Neurosci 1995;15 5420 – 5427.
[56] Du X, Stull ND, Iacovitti L. Brain-derived neurotropic factor works coordinately with partner molecular to initiate tyrosine hydroxylase expression in striatal neurons. Brain Res 1995;680 229 – 233.
[57] Carvey PM, Ptak LR, Nath ST, Sierens DK, Mufsen EJ, Goetz CG, Klawans HL. Striatal extracts from patients with Parkinson's disease promote dopamine neurons growth in mesencephalic cultures. Exp Neurol 1993;120 149 – 152.
[58] Shen Y, Yu Y, Tang Z, Guo H, Yu ESX, Zhou J. Identi-

万方数据

fication and comparative analysis of differentially expressed proteins in rat striatum following 6-OHDA lesions of nigrostriatal pathway: upregulation of amyloid precursor like-protein 2 expression. Eur J Neurosci 2002; 16: 896 – 906.

[59] Calzà L, Giardino L, Pozza M, Bettelli C, Micera A, Aloe L. Proliferation and phenotype regulation in the subventricular zone during experimental allergic encephalomyelitis: *in vivo* evidence of a role for nerve growth factor. Proc Natl Acad Sci USA 1998; 95: 3209 – 3214.

[60] Ciccolini F, Svendsen CN. Fibroblast growth factor 2 (FGF-2) promotes acquisition of epidermal growth factor (EGF) responsiveness in mouse striatal precursor cells: identification of neural precursors responding to both EGF and FGF-2. J Neurosci 1998; 18: 7869 – 7880.

[61] Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci 1997; 17: 5820 – 5829.

[62] Palmer TD, Markakis EA, Willhoite AR, Safar F, Gage FH. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. J Neurosci 1999; 19: 8487 – 8497.

[63] Gritti A, Frolichsthal-Schoeller P, Galli R, Parati EA, Cova L, Pagano SF, Bjornson CR, Vescovi AL. Epidermal and fibroblast growth factors behave as mitogenic regulators for a single multipotent stem cell-like population from the subventricular region of the adult mouse forebrain. J Neurosci 1999; 19: 3287 – 3297.

[64] Wagner JP, Black IB, DiCicco-Bloom E. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. J Neurosci 1999; 19: 6006 – 6016.

[65] Tao Y, Black IB, DiCicco-Bloom E. Neurogenesis in neonatal rat brain is regulated by peripheral injection of basic fibroblast growth factor (bFGF). J Comp Neurol 1996; 376: 653 – 663.

[66] Villares J, Faucheux B, Herrero MT, Obeso JA, Duyckaerts C, Hauw JJ, Agid Y, Hirsch EC. [^{125}I] EGF binding in basal ganglia of patients with Parkinson's disease and progressive supranuclear palsy and in MPTP-treated monkeys. Exp Neurol 1997; 154: 146 – 156.

[67] Leonard S, Luthman D, Logel J, Luthman J, Antle C, Freedman R, Hoffer B. Acidic and basic fibroblast growth factor mRNAs are increased in striatum following MPTP-induced dopamine neurofiber lesion: assay by quantitative PCR. Mol Brain Res 1993; 18, 275 – 284.

[68] Rufer M, Wirth SB, Hofer A, Dermietzel R, Pastor A, Kettenmann H, Unsicker K. Regulation of connexin-43, GFAP, and FGF-2 is not accompanied by changes in astroglial coupling in MPTP-lesioned, FGF-2-treated parkinsonian mice. J Neurosci Res 1996; 46: 606 – 617.

[69] Chadi G, Cao Y, Pettersson RF, Fuxe K. Temporal and spatial increase of astroglial basic fibroblast growth factor synthesis after 6-hydroxydopamine-induced degeneration of the nigrostriatal dopamine neurons. Neuroscience 1994; 61: 891 – 910.

[70] Glass DJ, Yancopoulos GD. The neurotrophins and their receptors. Trends Cell Biol 1993; 3: 262 – 268.

[71] Hyman C, Hoger M, Barde YA, Juhasz M, Yancopoulos GD, Squinto SP, Lindsay RM. BDNF is a nuerotrophic factor for dopaminergic neurons of the substantia nigra. Nature 1991; 350: 230 – 233.

[72] Knusel B, Winslow JW, Rosenthal A, Burton LE, Seid DP, Nikolics K, Hefti F. Promotion of central cholinergic and dopaminergic neuron differentiation by brain-derived neurotrophic factor but not neurotrophin-3. Proc Natl Acad Sci USA 1991; 88: 961 – 965.

[73] Beck KD, Knusel B, Hefti F. The nature of the tropic action of brain-derived neurotrophic factor, des(1-3)-insulin-like growth factor-1, and basic fibroblast growth factor on mesencephalic dopaminergic neurons developing in culture. Neuroscience 1993; 52: 855 – 866.

[74] Spina MB, Squinto SP, Miller J, Lindsay RM, Hyman C. Brain-derived neurotrophic factor protects dopamine neurons against 6-hydroxydopamine and N-methyl-4-phenylpyridinium ion toxicity: Involvement of the glutathione system. J Neurochem 1992; 59: 99 – 106.

[75] Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. J Neurosci 2001; 21: 6718 – 6731.

[76] Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. J Neurosci 2001; 21: 6706 – 6717.

[77] Frim DM, Uhler TA, Galpera WR, Beal MF, Breakefield XO, Isacson O. Implanted fibroblasts genetically engineered to produce brain-derived neurotrophic factor prevent 1-methyl-4-phenylpyridinium toxicity to dopaminergic neurons in the rat. Proc Natl Acad Sci USA 1994; 91: 5104 – 5108.

[78] Hung HC, Lee EH. The mesolimbic dopaminergic pathway is more resistant than the nigrostriatal dopaminergic pathway to MPTP and MPP + toxicity: role of BDNF gene expression. Mol Brain Res 1996; 41: 14 – 26.

[79] Levivier M, Przedborski S, Bencsics C, Kang UJ. Intrastriatal implantation of fibroblasts genetically engineered to produce brain-derived neurotrophic factor prevents degeneration of dopaminergic neurons in a rat model of Parkinson's disease. J Neurosci 1995; 15: 7810 – 7820.

[80] Pearce RK, Costa S, Jenner P, Marsden CD. Chronic supranigral infusion of BDNF in normal and MPTP-treated common marmosets. J Neural Transm 1999; 106: 663 – 683.

[81] Aliaga E, Carcamo C, Abarca J, Tapia-Arancibia L, Bustos G. Transient increase of brain derived neurotrophic factor mRNA expression in substantia nigra reticulata after partial lesion of the nigrostriatal dopaminergic pathway. Mol Brain Res 2000; 79: 150 – 155.

[82] Numan S, Seroog KB. Increased expression of trkB mRNA in rat caudate-putamen following 6-OHDA lesions of the nigrostriatal pathway. Eur J Neurosci 1997; 9: 489 – 495.

[83] Venero JL, Viuete ML, Revuelta M, Vargas C, Cano J, Machado A. Upregulation of BDNF mRNA and trkB mRNA in the nigrostriatal system and in the lesion site following unilateral transection of the medial forebrain bundle. Exp Neurol 2000; 161: 38 – 48.

[84] Kingsley DM. The TGF-β superfamily: new members, new receptors, and new genetic tests of function in different organisms. Genes Dev 1994; 8: 133 – 146.

[85] Hogan BLM. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. Genes Dev 1996; 10: 1580 – 1584.

[86] Mehler MF, Mabie PC, Zhang D, Kessler JA. Bone mor-

万方数据

phogenetic proteins in the nervous system. Trends Neurosci 1997 20 309 – 315.

[87] Gross RE, Mehler MF, Mabie PC, Zang Z, Santschi L, Kessler JA. Bone morphogenetic proteins promote astroglial lineage commitment by mammalian subventricular zone progenitor cells. Neuron 1996 17 595 – 606.

[88] Lim DA, Tramontin AD, Trevejo JM, Herrera DG, Garcia-Verdugo JM, Alvarez-Buylla A. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. Neuron 2002 28 713 – 726.

[89] Furuta Y, Piston DW, Hogan BLM. Bone morphogenetic proteins (BMPs) as regulators of dorsal forebrain development. Development 1997 124 2203 – 2212.

[90] Zhang D, Mehler MF, Song Q, Kessler JA. Development of bone morphogenetic protein receptors in the nervous system and possible roles in regulating trkC expression. J Neurosci 1998 18 3314 – 3326.

[91] Cho KW, Blitz IL. BMPs, Smads and metalloproteases: extracellular and intracellular modes of negative regulation. Curr Opin Genet Dev 1998 8 443 – 449.

[92] Akerud P, Alberch J, Eketjall S, Wagner J, Arenas E. Differential effects of glial cell line-derived neurotrophic factor and neurturin on developing and adult substantia nigra dopaminergic neurons. J Neurochem 1999 73 70 – 78.

[93] Hagg T. Neurotrophins prevent death and differentially affect tyrosine hydroxylase of adult rat nigrostriatal neurons *in vivo*. Exp Neurol 1998 149 183 – 192.

[94] Mabie PC, Mehler MF, Kessler JA. Multiple roles of bone morphogenetic protein signaling in the regulation of cortical cell number and phenotype. J Neurosci 1999 19 7077 – 7088.

[95] Alonso G. Proliferation of progenitor cells in the adult rat brain correlates with the presence of vimentin-expressing astrocytes. Glia 2001 34 253 – 266.

[96] Gould E, Cameron HA, Daniels DC, Woolley CS, McEwen BS. Adrenal hormones suppress cell division in the adult rat dentate gyrus. J Neurosci 1992 12 3642 – 3650.

[97] Tanapat P, Hastings NB, Reeves AJ, Gould E. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. J Neurosci 1999 19 5792 – 5801.

[98] Cameron HA, McEwen BS, Gould E. Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. J Neurosci 1995 15 4687 – 4692.

[99] Gould E, Cameron HA, McEwen BS. Blockade of NMDA receptors increases cell death and birth in the developing rat dentate gyrus. J Comp Neurol 1994 340 551 – 565.

[100] Gould E, Tanapat P. Lesion-induced proliferation of neuronal progenitors in the dentate gyrus of the adult rat. Neuroscience 1997 80 427 – 436.

[101] Nacher J, Rosell DR, Alonso-Llosa G, McEwen BS. NMDA receptor antagonist treatment induces a long-lasting increase in the number of proliferating cells, PSA-NCAM-immunoreactive granule neurons and radial glia in the adult rat dentate gyrus. Eur J Neurosci 2001 13 512 – 520.

[102] Gould E. Serotonin and hippocampal neurogenesis. Neuropsychopharmacology 1999 21 46S – 51S.

[103] Alvarado AS, Newmark PA. The use of planarians to dissect the molecular basis of metazoan regeneration. Wound Repair, Regen 1998 6 413 – 420.

[104] Lois C, Garcia-Verdugo JM, Alvarez-Buylla A. Chain migration of neuronal precursors. Science 1996 271 978 – 981.

[105] Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. Neurogenesis in the adult is involved in the formation of trace memories. Nature 2001 410 372 – 376.

[106] Stanfield BB, Trice JE. Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp Brain Res 1988 72 399 – 407.

[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 3727 – 3738.

[108] Snyder EY, Yoon C, Flax JD, Macklis JD. Multipotent neural precursors can differentiate toward replacement of neurons undergoing targeted apoptotic degeneration in adult mouse neocortex. Proc Natl Acad Sci USA 1997 94 11663 – 11668.

万方数据