Review Article

Strategies for Regenerating Striatal Neurons in the Adult Brain by Using Endogenous Neural Stem Cells

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Currently, there is no effective treatment for the marked neuronal loss caused by neurodegenerative diseases, such as Huntington’s disease (HD) or ischemic stroke. However, recent studies have shown that new neurons are continuously generated by endogenous neural stem cells in the subventricular zone (SVZ) of the adult mammalian brain, including the human brain. Because some of these new neurons migrate to the injured striatum and differentiate into mature neurons, such new neurons may be able to replace degenerated neurons and improve or repair neurological deficits. To establish a neuroregenerative therapy using this endogenous system, endogenous regulatory mechanisms that can be co-opted for efficient regenerative interventions must be understood, along with any potential drawbacks. Here, we review current knowledge on the generation of new neurons in the adult brain and discuss their potential for use in replacing striatal neurons lost to neurodegenerative diseases, including HD, and to ischemic stroke.

1. Introduction

Huntington’s disease (HD) is an adult-onset autosomal-dominant inherited neurodegenerative disorder with progressive symptoms that include involuntary movements, cognitive deficits, and various psychiatric disturbances [1–3]. HD is caused by an expanded CAG repeat in the huntingtin gene [4–6]. The expanded CAG repeat gives rise to an abnormally long polyglutamine stretch in the mutant huntingtin, which is toxic to neurons in the striatum and frontal cortex [7]. The most striking pathophysiology of HD is the progressive degeneration of projection neurons and heightened gliosis, leading to a marked atrophy of the striatum and cerebral cortex [8]. So far, although potential therapeutic interventions aimed at suppressing the production of the mutant huntingtin protein and reducing its toxicity have been aggressively pursued [9–13], no effective treatment for HD has been developed. Offering hope, however, are findings by recent studies suggesting that the adult brain’s capacity to generate new neurons may be a resource for replacing the affected neurons with newly generated ones.

In the mammalian brain, the subventricular zone (SVZ), which is a thin cell layer in the lateral walls of lateral ventricles, continues to produce new neurons during adulthood. Postmortem analyses have shown that the SVZ in HD patients is thickened by increased cell proliferation [14, 15]. In addition, in an HD transgenic mouse model, R6/2 mice carrying the human HD gene with long CAG repeats [16] generate new neurons in the SVZ that migrate into the affected striatum and differentiate into mature neurons. Unfortunately, although these alterations may reflect protective responses provoked by the progressive degeneration of striatal neurons owing to HD, they are insufficient to compensate for the pathological process. Nonetheless, these observations may signal the possibility of future interventions that promote the production and migration of new neurons to the damaged striatum and improve the neurological impairments of this disease and/or stop its progression. Here, we review current knowledge on the generation of new neurons (neurogenesis) in the adult brain and discuss its potential for replacing neurons damaged by pathological conditions, including HD.
2. Adult Neurogenesis

In the mammalian brain, the production of new neurons in the SVZ and the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus continues during adulthood (Figure 1(a)) [17–21]. Here, we particularly focus on the SVZ because the new neurons generated there have the notable ability to migrate fast and for a long distance in the adult brain.

There are four types of cells in the adult SVZ: neural stem cells, transit-amplifying cells, newly generated immature neurons, and ependymal cells (Figure 1(b)) [22]. The neural
stem cells in the adult SVZ express the astrocyte-specific protein GFAP, and their morphology is not clearly distinguishable from nonneurogenic astrocytes in other brain regions [23, 24]. The SVZ is thought to provide a specific microenvironment, a “stem cell niche,” that supports the neural stem cells’ ability to maintain their self-renewing, multipotent state. The process and regulatory mechanisms of neurogenesis in the adult brain have been studied in detail, particularly in rodents. In the SVZ, the stem cells proliferate slowly and continuously to generate transit-amplifying cells, which proliferate quickly; their progeny become immature new neurons. New neurons in the adult rostral migratory stream (RMS), which leads to the olfactory bulb (OB) at the anterior tip of the telencephalon, are still proliferative during their migration. Interestingly, whereas the Wnt-β-catenin signaling is involved in the proliferation and differentiation of transit-amplifying cells [25], we found that Diversin, a component of the Wnt pathway, is important in the proliferation of the new neurons [26].

It is particularly notable that the new neurons migrating through the RMS move quite quickly, 100 μm/h in rodents. This rapid, directional migration is controlled by signals involved in cytoskeletal modification, directional guidance, and interactions between the new neurons and their microenvironment [27–41].

During their migration in the RMS, the new neurons exhibit a highly polarized morphology with an extended leading and trailing process, and they form elongated cell aggregates called “chains,” within which they move over and past one another (Figure 1(c)). Polysialic acid-neural cell adhesion molecule (PSA-NCAM) and β1-integrin expressed on the surface of the new neurons and intracellular Cdk5 signaling are involved in this chain migration [28, 31, 32, 39]. These chains of new neurons move inside tunnels formed by astrocytic processes, termed “glial tubes” (Figure 1(c)) [33, 35, 36], which assist the migration of the new neurons. We recently demonstrated that the relationship between the neurons and glia appears to be interdependent. The tunnel-like arrangement of astrocytes depends on a diffusible protein, Slit1, secreted by the new neurons migrating inside them. (Figure 1(c)) [34]. The neuron-glia interaction may be particularly important for neuronal migration in the adult brain, since it includes a large glial population. In addition, matrix metalloproteases produced by the new neurons, and extracellular matrix molecules including tenasin-C, proteoglycans, and the laminins are all involved in the migration of new neurons in the RMS [28, 33, 37].

New neurons are guided by extracellular cues to migrate toward the OB, and we found that the directional flow of cerebrospinal fluid (CSF) in the lateral ventricle plays a critical role in their rostral migration [41]. CSF flow is created by the coordinated beating of the multiple ependymal cell cilia, and generates concentration gradients of diffusible proteins, including chemorepellents, secreted into the lateral ventricle. The concentration gradients guide new neurons rostrally toward the OB. In addition, new neurons are guided to the OB by a number of secreted proteins that are produced in the OB, including prokineticin 2 [38], glial cell-line-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF) [29, 40].

New neurons that reach the OB detach from the chain, and the individual cells migrate radially into the granule cell layer and the glomerular layer, where they differentiate into granule cells and periglomerular cells, respectively (Figures 1(d) and 1(e)). The granule cells and periglomerular cells are GABAergic interneurons, which include a small number of periglomerular dopaminergic interneurons. Although the functional significance of these new neurons remains unclear, the neurogenic capacity of the adult rodent brain encourages the hope that this ability might be harnessed to replace neurons destroyed by injury or disease.

The human SVZ and DG also retain some ability to generate neurons in adulthood [21, 42], but it is difficult to evaluate human neurogenesis quantitatively, because the experimental procedures are limited. Studies using non-human primates and postmortem or surgically dissected human brain tissues indicate that neurogenesis is much less active in the human SVZ than in that of rodents [43–45]. However, new neurons in the human SVZ exhibit a migratory-like polarized morphology and are distributed between the SVZ and OB. These morphological and histological characteristics suggest that new neurons might migrate for long distances in the adult human brain, but this possibility is still controversial [45–49]. In any case, some of the mechanisms that regulate neurogenesis are likely to be common in humans and rodents.

3. Alteration of Adult Neurogenesis under Pathological Conditions

Neurogenesis in the adult brain is affected by various brain insults. Following the loss of neurons caused by pathological conditions including stroke and neurodegenerative diseases, newly generated neurons appear in and around the damaged areas.

Studies of grade 3 HD patients reported that the SVZ becomes 2.8-fold thicker, with a 2.6-fold increase in the production of new neurons [49, 50]. Although the numbers of transit-amplifying cells and new neurons in the patients’ SVZ had increased moderately, the most prominent increase observed was of neural stem cells. In addition, the SVZ of R6/2 mice, a transgenic model for HD, becomes thicker, with a marked increase in the proportion and proliferation of neural stem cells. The self-renewal ability of neural stem cells dissociated from the R6/2 mouse SVZ gradually increases in parallel with disease progression. The rostral migration of new neurons from the SVZ toward the OB is significantly suppressed in these mice; instead, a large population of new neurons migrates laterally into the affected striatum where they differentiate into mature neurons (Figure 2(a)) [16]. The precise mechanism that leads these changes remains to be elucidated; however, the stem cells in the SVZ may function to replace degenerated striatal neurons with new ones, at least in the rodent HD model. In addition, the SVZ-associated neuroregenerative response observed in HD takes place in other pathologies, including ischemic stroke and Parkinson’s disease (PD) [35].
Table 1: Factors promoting the regeneration of neurons in the striatum. This table lists examples of interventions that could increase the proliferation of neural stem/progenitor cells in the SVZ, enhance the migration of new neurons into the striatum, and promote their differentiation/maturation and survival, which could be promising strategies for replacing degenerated neurons with new ones derived from endogenous neural stem cells of the adult SVZ. SVZ, subventricular zone; RMS, rostral migratory stream; OB, olfactory bulb; TH, tyrosine hydroxylase; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 2; TGF-α, transforming growth factor α; GDNF, glial cell-derived neurotrophic factor; SDF-1α, stromal cell-derived factor 1α; BDNF, brain-derived neurotrophic factor; aCSF artificial cerebrospinal fluid; HI, hypoxic-ischemic cerebral injury; MCAO, middle cerebral artery occlusion; 6-OHDA, 6-hydrodopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydroxydropyridine; hNSCs, human neural stem cells; ESCs, embryonic stem cells.

| Protein | Model | Technique | Function in neurogenesis | References |
|---------|-------|-----------|--------------------------|------------|
| EGF     | Intact| Infusion into the lateral ventricle using an osmotic pump | Proliferation of SVZ progenitors (18-fold increase compared with saline infusion group) | [69] |
|         | Intact| Infusion into the lateral ventricle using an osmotic pump | Proliferation of SVZ progenitors (9.5-fold increase compared with aCSF infusion group) | [70] |
|         | MCAO  | Overexpression in the SVZ | Proliferation of SVZ progenitors (1.7-fold increase compared with control vector treatment group) | [64] |
| FGF-2   | Intact| Infusion into the lateral ventricle using an osmotic pump | Proliferation of SVZ progenitors (2.4-fold increase compared with serum albumin infusion group) | [69] |
|         | Intact| Infusion into the lateral ventricle using an osmotic pump | Proliferation of SVZ progenitors (3.3-fold increase compared with aCSF infusion group) | [70] |
|         | MCAO  | Infusion into the cisterna magna | Proliferation of SVZ progenitors (increase compared with vehicle treatment group) | [65] |
| Angiopoietin 2 | 6-OHDA | Infusion into the lateral ventricle | Proliferation of SVZ progenitors (increase compared with BSA treatment group) | [71] |
| TGF-α   | Intact| Infusion into the lateral ventricle using an osmotic pump | Proliferation of SVZ progenitors (14-fold increase compared with albumin infusion group) | [69] |
|         | 6-OHDA| Infusion into the striatum using an osmotic pump | Proliferation of SVZ progenitors (increase compared with PBS infusion group) | [72] |
|         | 6-OHDA| Infusion into the striatum using an osmotic pump | Generation of neurons in the striatum (immature neuron, 1.86-fold; mature neuron, 1.2-fold, increase compared with PBS treatment group) | [73] |
| GDNF    | MCAO  | Infusion into the striatum using an osmotic pump | Generation of neurons in the striatum (immature neuron, 1.86-fold; mature neuron, 1.2-fold, increase compared with PBS treatment group) | [66] |
| SDF-1α  | HI    | Migration of implanted hNSCs toward the injured area in ischemic brain slice (increase) | Migration of implanted hNSCs toward the injured area in ischemic brain slice (increase) | [57] |
| Tenascin-R | Intact| Tenascin-R expressing cell implantation into the striatum | Migration of SVZ new neurons toward the striatum (4-fold increase compared with the Tenascin nonexpression cell implanted group) | [74] |
|         | Quinolic acid | TNR-expressing ESCs implantation into the striatum | Migration of SVZ new neurons into the striatum (increase compared with TNR-nonexpression ESCs implanted group) | [75] |
| BDNF    | Intact| Infusion into the lateral ventricle using an osmotic pump | Generation of neurons in the OB (increase compared with PBS infusion group) | [76] |
|         | Intact| Infusion into the lateral ventricle using an osmotic pump | Generation of neurons in the striatum (increase compared with PBS infusion group) | [77] |
|         | R6/2  | Overexpression in the SVZ | Generation of neurons in the striatum (21-fold increase compared with saline group) | [68] |
Cerebral ischemia is the most commonly studied model of neuronal regeneration after extensive neuronal death (Figure 2(b)). In patients after ischemic stroke, cell proliferation and the production of new neurons in the SVZ are increased, and immature new neurons appear in the cortex close to injured areas and in the striatum close to the SVZ [51–53]. The mechanism and functional significance of the ischemia-induced neurogenesis have mostly been studied using rodent models of transient middle cerebral artery occlusion (MCAO), an experimental model of focal brain ischemia that causes infarction of the ipsilateral striatum and adjacent neocortex [54]. The new neurons generated in the SVZ have a migratory morphology that is directed toward the infarct area, and frequently form chain-like aggregates similar to those observed in the RMS (Figure 2(c)). Our lineage-specific tracing study revealed that the SVZ is almost
the sole source of migrating new neurons in the striatum [55]. We also found that new neurons in the striatum are closely associated with astrocytic processes and migrate along blood vessels (Figures 2(d) and 2(e)) [55, 56]. Several proteins produced by the glia and endothelial cells around the infarct area are implicated in this migration, as are their receptors and the MMPs expressed by the new neurons [57–60]. After the migration, most of the new neurons die before they mature, but some survive to differentiate into functional neurons with synaptic contacts.

In a rat MCAO model, the number of new striatal neurons increased 31-fold compared with that in sham-operated animals [54]. Using the immunocytochemical detection of BrdU, a thymidine analog that is incorporated into DNA during cell proliferation, and of NeuN, a neuronal marker, newly generated neurons have been identified in the injured striatum of several MCAO models. When BrdU (50 mg/kg) was administered twice a day for 14 days to post-MCAO rats, the density of BrdU/NeuN-colabeled new neurons in the striatum 6 weeks after MCAO was more than 700 cells/mm³. On the other hand, in a nonhuman primate (common marmoset) MCAO stroke model, BrdU (50 mg/kg) injections once a day for 18 days after MCAO resulted in a density of BrdU/NeuN-colabeled new striatal neurons 45 days after MCAO that was less than 3 cells/mm³, that is, about 50 cells/mm³, considering the thickness of the brain sections [61]. These reports suggest that the efficiency of neuronal regeneration is lower in the primate brain, although a precise comparison is not possible due to the difference in BrdU-treatment procedures. Moreover, even in the rat MCAO model, these new neurons could replace only about 0.2% of the dead striatal neurons [54], suggesting that the spontaneous neuronal regeneration would be insufficient to replace the functions of the lost neurons in human patients.

Because of the low efficiency of neuronal regeneration, interventions that promote this process are now the focus of intense study. Growth factors that promote cell proliferation, differentiation, migration, and/or survival have been reported to act on neural stem cells and/or their progenies to enhance neuronal regeneration [62, 63] (Table 1). In MCAO model animals, epidermal growth factor (EGF) overexpression in the SVZ and the intracisternal administration of fibroblast growth factor 2 (FGF-2) induced increases in the number of proliferating cells in the SVZ [64, 65] whereas infusion of GDNF around the infarct area increased the new neurons in the region by 2-fold [66]. On the other hand, the stromal cell-derived factor-1α (SDF-1α) CXCR4 signal has been reported to be involved in neuronal migration toward the infarct area [57, 59, 67]. Furthermore, in the R6/2 model mice, BDNF overexpression in the SVZ increased the production of new striatal neurons by about 21-fold, which was enhanced by the co-overexpression of Noggin, a soluble inhibitor of the bone morphogenic proteins (BMPs) [68]. Some of these growth factors may thus be effective in reducing the pathology associated with neuronal loss.

Alterations in neurogenesis are also observed in PD, a more common neurodegenerative disease than HD. PD is a motor system disorder characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, a basal ganglion of the midbrain, that project into the striatum. Therefore, treatments that increase the dopaminergic stimulation of the striatum improve neurological symptoms. In animal models of PD, after chemically induced dopaminergic denervation of the striatum, new neurons migrate from the SVZ to the striatum, where they differentiate into dopaminergic neurons [78–80]. However, these reports are controversial because other researchers showed that the new neurons did not efficiently migrate into the denervated striatum, but into the OB, and that the SVZ-derived migrating progenitors that did arrive in the striatum never differentiated into mature dopaminergic neurons [81].

Therefore, even if the SVZ can generate new neurons that migrate to the striatum in pathological conditions, such as HD, these neurons may not replace the functionality of the lost neurons, possibly because they do not mature and differentiate into the needed neuronal types. As mentioned above, new neurons generated in the SVZ become interneurons in the OB. In contrast, more than 90% of striatal neurons are medium-sized spiny projection neurons, and these are the neurons that are mainly injured in HD and cerebral ischemia [82–87]. Although some previous studies reported the regeneration of mature neurons with phenotypes of striatal projection neurons [54, 88], more recent studies demonstrated that, after ischemic stroke, the new neurons that were generated in the SVZ and differentiated in the striatum almost exclusively became calretinin-expressing neurons, a major type of olfactory interneuron [89–91]. These findings suggested that the neurons generated in the SVZ have a limited differentiative capacity for neuronal regeneration. In considering how to attenuate the progression of HD, it is particularly important to learn whether and how we can control the fates of new neurons generated in the adult brain so that they adopt striatal neuronal phenotypes. Further studies are needed to address these points.

4. Conclusion

The spontaneous regeneration response of the adult SVZ to pathological neuronal loss does not lead to the regeneration of the lost neurons, because of limitations in the numbers of neurons generated and the fates they adopt. However, many studies support the idea that interventions to increase the production of new neurons in the SVZ and promote their migration, maturation, and survival in the damaged area could be beneficial for treating a variety of neurological deficits, including HD (Table 1). To develop a new therapeutic strategy for pathological neuronal loss, including in cases of HD and stroke, using this system, it will be critical to develop a more precise and comprehensive understanding of the mechanisms that regulate neurogenesis in both physiological and pathological conditions.

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