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REVIEW

Injury-induced neurogenesis in the mammalian forebrain

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Abstract It has been accepted that new neurons are added to the olfactory bulb and the hippocampal dentate gyrus throughout life in the healthy adult mammalian brain. Recent studies have clarified that brain insult raises the proliferation of neural stem cells/neural progenitor cells existing in the subventricular zone and the subgranular zone, which become sources of new neurons for the olfactory bulb and the dentate gyrus, respectively. Interestingly, convincing data has shown that brain insult invokes neurogenesis in various brain regions, such as the hippocampal cornu ammonis region, striatum, and cortex. These reports suggest that neural stem cells/neural progenitor cells, which can be activated by brain injury, might be broadly located in the adult brain or that new neurons may migrate widely from the neurogenic regions. This review focuses on brain insult-induced neurogenesis in the mammalian forebrain, especially in the neocortex.

Keywords Insult · Ischemia · Neurogenesis · Stem cells · Progenitor cell · Proliferation

Abbreviations

BrdU	Bromodeoxyuridine
CA	Cornu ammonis
L1-INP	Layer 1 inhibitory neuron progenitor
MGE	Medial ganglionic eminence
NSC	Neural stem cell
NPC	Neural progenitor cell
SGZ	Subgranular zone
SVZ	Subventricular zone

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Introduction

It has long been believed that almost all neurons in the adult mammalian brain are produced during development and do not regenerate even after injury. "No new neurons after birth" has been a central dogma in the neuroscience field [1–4]. However, recent in vitro and in vivo studies of adult neurogenesis have identified neural stem cells (NSCs) and neural progenitor cells (NPCs) in the adult mammalian brain [3, 4]. This great discovery in the field of neurogenesis has been achieved by innovations in detection methods for neurogenesis, such as molecular cell markers for NSCs, NPCs, and new neurons, DNA replication markers [tritiated thymidine and bromodeoxyuridine (BrdU)], retrovirus, and genetically modified animals [1–7].

In the subventricular zone (SVZ) and the subgranular zone (SGZ), NSCs and NPCs show self-renewal and continue to produce new neurons even under healthy conditions [8, 9]. Besides, new neurons in the olfactory bulb and the hippocampus are needed for olfactory memory [10, 11], and contextual and spatial memory [12–17], respectively. These findings suggest that new neurons play important roles in the neuronal plasticity of the adult brain.

Recently, adult neurogenesis has been reported in various regions of the adult mammalian brain, including the cortex, striatum, and hippocampal cornu ammonis (CA) region. Importantly, neurogenesis in these regions may be induced by brain insults, suggesting that therapeutic innovation for brain insults may be created using endogenous

NSCs and NPCs. However, the mechanism of insult-induced neurogenesis remains to be determined. In this review, we summarize the recent findings of insult-induced, especially ischemia-dependent, neurogenesis in the SVZ and the SGZ. In addition, since neocortical adult neurogenesis under pathological conditions has been a hot subject in the field of adult neurogenesis, we further focus on neocortical adult neurogenesis.

Neurogenesis in the olfactory bulb and the hippocampus of the adult mammal under healthy and ischemic conditions

It is now widely accepted that constitutive neurogenesis in the healthy adult mammalian forebrain occurs in the anterior SVZ and the SGZ [3, 4]. Since NSCs and NPCs in the anterior SVZ and the SGZ were first identified in the adult forebrain [12, 13], research into neurogenesis in these regions has advanced, while research of neurogenesis in other brain regions, such as the neocortex and striatum, has lagged behind. The basic phenomena of adult neurogenesis in the anterior SVZ and the SGZ have been well described (Fig. 1).

In the SVZ, four main cell types exist: A, B, C, and ependymal cells, which are defined by morphological and immunohistochemical characteristics (Fig. 1a) [14]. Type-A cells (neuroblasts) are born throughout the SVZ, migrate in chains toward the olfactory bulb, and differentiate into granule and periglomerular interneurons [15]. The chains of type-A cells are ensheathed by type-B cells (SVZ GFAP-positive cells) [14, 16]. Some of the type-B cells have been reported to work as NSCs. Type-C cells are clusters of rapidly dividing immature cells on the migration pathway physically located between type-B and type-A cells [14]. Altogether, the SVZ neurogenic lineage is type-B cell → type-C cell → type-A cell.

In the adult hippocampus NSCs, NPCs, and postmitotic granule cells are each distributed in a distinctive location (Fig. 1c) [17–19]. NSCs (type-1 cells) exist near the border between the hilus and the dentate granule cell layer. Neuroblasts (type-3 cells) produced from transient multiplying cells (type-2 cells) in the SGZ migrate radially a short distance into the granule cell layer. Then, neuroblasts are integrated into the deepest portion of the granule cell layer, where they differentiate into granule cells, extending dendrites and axons and receive synaptic inputs [20].

The above description of persistent adult neurogenesis in the SVZ and the SGZ is based on evidence under healthy conditions. In addition, recent studies have been gradually clarifying that adult neurogenesis can be regulated by various factors, for example, exercise, environmental enrichment, pregnancy, and ischemia up-regulate neurogenesis, while

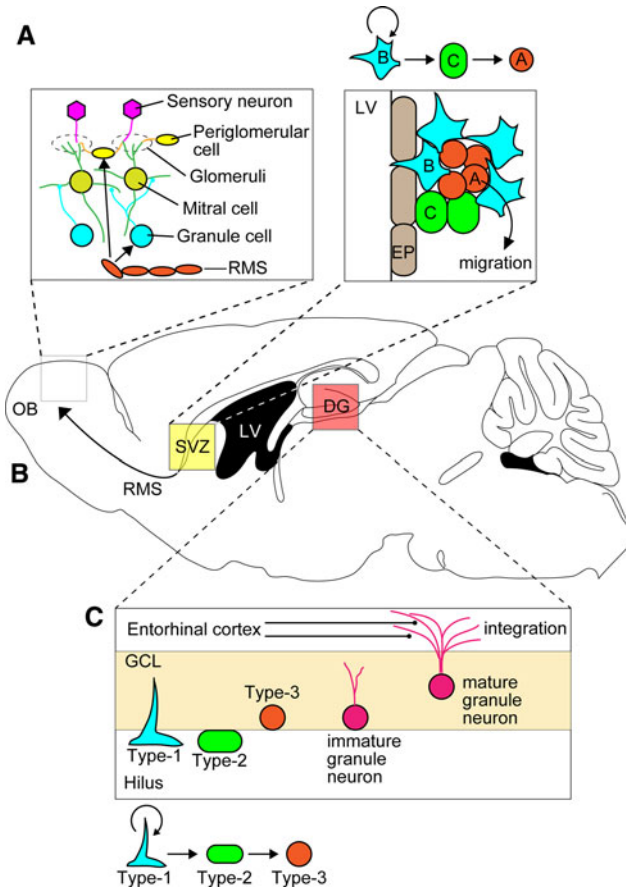

Fig. 1 Schematic representation of adult neurogenesis in the SVZ and the SGZ. **a** In the SVZ-olfactory bulb (OB) system, the NSCs (type-B cells, *cyan*) give rise to neuroblast cells (type-A cells, *red*) via transient intermediate cells (type-C cells, *green*). Type-A cells migrate to the OB through the rostral migration stream (RMS) and differentiate to granule cells and periglomerular cells. **b** The sagittal section of the adult mouse brain after drowning. Two well-known neurogenic regions, the SVZ (*yellow*) and the DG (*red*), are indicated with the *colored boxes*. **c** The NSCs (type-1 cells, *cyan*), which exist in the SGZ, the thin lamina between the hilus and granule cell layer (GCL), produce transient progenitor cells (type-2 cells, *green*). The neuroblast cells (type-3 cells, *red*) derived from type-2 cells migrate shortly to the GCL and differentiate to granule cells. Newly generated granule cells are integrated into the existing neural network. *EP* ependymal cell, *LV* lateral ventricle

stress and aging down-regulate it [4]. Among them, ischemia is one of the most widely used methods in adult neurogenesis research.

Here, we focus on the effects of brain ischemia on adult neurogenesis in the SVZ and the SGZ. Brain ischemia is defined as the condition by which a stroke, such as cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage, brain injury, or transient cardiorespiratory arrest critically decreases or completely interrupts the blood flow of the whole brain or a certain region of the brain [21, 22]. Brain ischemia is mainly divided into two types, focal brain ischemia and global brain ischemia. The

former reduces blood flow to a specific brain region because a blood clot occludes a cerebral vessel, whereas the latter is a drastic reduction of blood flow in the whole brain caused by events such as cardiac arrest [21]. The most common experimental model of focal cerebral ischemia is induced by transient middle cerebral artery occlusion (MCAO). Global ischemia occurs when the aorta or vena cava is occluded.

Historically, adult neurogenesis in the SVZ and SGZ was established in the late 1990s [3–5]. Then, in the next decade from the late 1990s, adult neurogenesis research moved to examine whether new neurons from NSCs and NPCs can replace dying cells or lost ones, which would be the starting point of regenerative medicine for brain injury with endogenous NSCs and NPCs [23–26]. The first researchers used brain ischemia [23]. If neurogenesis is up-regulated by brain ischemia, endogenous NSCs and NPCs may be useful for therapy of brain insults. Using brain ischemia as an experimental method, almost all studies in the recent decade have reported that brain ischemia potently stimulates adult neurogenesis in the SVZ and the SGZ (Table 1) [23–54]. Proliferating cells in the SVZ and the SGZ are significantly increased by ischemia, and increases in the number of new neurons could be detected. In addition, it is important that NPCs in the SVZ have been found to migrate to ischemic regions and appear to form proper neuronal subtypes to replace damaged neurons in the striatum and cortex [29, 41, 43, 55–60]. These ectopic migrations have not been found under healthy conditions. Thus, brain ischemic stimulation might evoke a molecular

Table 1 A list of experimental studies that examine whether adult neurogenesis in the SVZ and the SGZ is promoted by ischemia

Species	Regions	Treatment	Effect	Reference
Gerbil	SGZ	Global ischemia for 2–10 min	Up-regulated	[23]
Gerbil	SGZ	Global ischemia for 10 min	Up-regulated	[24]
SD rat	aSVZ, SGZ	Focal ischemia for 90 min	Up-regulated	[25]
Wistar rat	aSVZ, SGZ	Focal ischemia until killing	Up-regulated	[26]
Wistar rat	SGZ	Global ischemia for 10 min	Up-regulated	[27]
Wistar rat	SGZ	Focal ischemia for 30 min or 2 h	Up-regulated	[28]
Wistar rat	aSVZ	Focal ischemia until killing	Up-regulated	[29]
Wistar rat	SGZ	Focal ischemia until killing	Up-regulated	[30]
Gerbil	SGZ	Global ischemia for 5 min	Up-regulated	[31]
Wistar rat	aSVZ	Focal ischemia for 2 h	Up-regulated	[32]
SD rat	aSVZ	Focal ischemia for 90 min	Up-regulated	[33]
SD rat	SGZ	Focal ischemia for 90 min	Up-regulated	[34]
Macaque monkey	aSVZ, SGZ	Global ischemia for 20 min	Up-regulated	[35]
SD rat	aSVZ	Focal ischemia for 90 min	Up-regulated	[36]
Wistar rat	aSVZ	Focal ischemia until killing	Up-regulated	[37]
Wistar rat	SGZ	Global ischemia for 15 min	Up-regulated	[38]
SD rat	SGZ	Focal ischemia for 90 min	Up-regulated	[39]
Hypertensive rat	aSVZ	Focal ischemia until killing	Up-regulated	[40]
Wistar rat	SGZ	Focal ischemia until killing	Up-regulated	[41]
Hypertensive rat	aSVZ	Focal ischemia for 60 min or 2 h	Up-regulated	[42]
Wistar rat	aSVZ	Focal ischemia for 2 h	Up-regulated	[43]
Macaque monkey	aSVZ, SGZ	Focal ischemia until killing	Up-regulated	[44]
Human	aSVZ	Ischemic brain autopsy	Up-regulated	[45]
Hypertensive rat	aSVZ	Focal ischemia until killing	Up-regulated	[46]
C57BL mouse	aSVZ	Focal ischemia for 15 min	Up-regulated	[47]
C57BL mouse	aSVZ	Focal ischemia until killing	Up-regulated	[48]
C57BL mouse	aSVZ	Focal ischemia until killing	Up-regulated	[49]
Macaque monkey	SGZ	Global ischemia for 20 min	Up-regulated	[50]
Wistar rat	aSVZ	Focal ischemia until killing	Up-regulated	[51]
SD rat	aSVZ	Focal ischemia for 90 min	Up-regulated	[52]
SD rat	aSVZ	Global ischemia for 10 min	Up-regulated	[53]
Human	aSVZ	Ischemic brain autopsy	Up-regulated	[54]

aSVZ anterior subventricular zone, *SGZ* subgranular zone

mechanism of migration for damaged regions, such as various attractive and repulsive humoral factors and extracellular matrices that have not yet been identified.

Neurogenesis in the neocortex of the adult mammal both under healthy and pathological conditions

Adult neocortical neurogenesis has been an interesting subject since the last century. In the 1890–1900s, a few studies identified cell proliferation in all parts of the CNS of newborn animals and infants [42]. Identifying cell proliferation in the adult neocortex was first reported at 1912. Using tritiated thymidine, a marker of DNA synthesis, Altman [65] rediscovered the addition of new neurons in the neocortex of adult rats. However, as these findings were based on chemical stain or radioautography, it was not clear whether or not the new cells were neurons. Then, using a combination of autoradiography and serial thin sectioning electron microscopy, Kaplan [66] showed that in the adult rat neocortex, the new cells containing tritiated thymidine are stellate cells that have an axonal hillock, initial segment, and synapses on the dendrites and cell bodies. On the contrary, using the same tritiated thymidine and primates as experimental animals, Rakic [2, 67–69] provided convincing evidence beginning in the late 1970s that neurogenesis occurs during early embryo development. Thereafter, several studies on neocortical neurogenesis have been reported, but there is a major conflict regarding neurogenesis in the adult neocortex of healthy mammals, from rodents to primates. This discrepancy might be caused by the experimental methods and animals' conditions, i.e., housing conditions, histories, genetic background, and technical considerations [4]. One reliable reason why adult neocortical neurogenesis is highly controversial is that the new neurons are generated at very low levels in healthy animals [70]. Even in the reports that show positive data for neocortical adult neurogenesis, the percentages of new neurons to total neurons are in the range of only 0.005–0.03% of all existing neurons [71–75]. In addition, if new neurons in the neocortex are inhibitory interneurons, the newly generated cell bodies may be rather small. Thus, it is not hard to suppose that we cannot efficiently detect new neurons in the adult neocortex. Furthermore, animals' breeding conditions may be more important. In particular, non-human primates, such as macaque monkeys, have the ability for higher cognition and complicated emotions at almost the same level with humans, so that the dominant-subordinate status among monkeys in the breeding room is not negligible [76]. In an experimental condition where each monkey is housed in a separate cage and animals cannot see one another, but auditory and olfactory exposure are not prevented, subordinate animals might experience mental stress [76]. Stress has been reported to be one of the repressors of adult neurogenesis [4]. In fact, hippocampal neurogenesis in adult rats is reduced by the dominant-subordinate status [77]. Thus, methods that are devised to reduce stress to experimental animals may be needed. Although it is not clear whether the neocortical neurogenesis is decreased by stress, it would be more difficult to detect neocortical neurogenesis under stressful conditions. Other factors that have not been identified at present might also make the detection of neocortical neurogenesis difficult.

Are there any factors that invoke or enhance adult neocortical neurogenesis? Recent studies have reported the production or addition of new neurons in the adult mammalian neocortex under various pathological conditions, such as focal and global ischemia, chromophore-targeted neuronal degeneration, aspiration lesion, chemical-induced spreading depression, and electrolytic lesions of the thalamus (Table 2). In fact, although the stimulus intensities of these pathological conditions cannot be compared, the production of new neurons in the adult neocortex is up-regulated by a factor of 0.06–1% of total neurons [80, 83, 88, 99]. Almost all studies that employed a combination of the double-staining of BrdU and neuronal markers and three-dimensional confocal microscopy to resolve closely apposed cells clearly identified neocortical neurogenesis [46, 57, 71, 72, 74, 75, 80–91, 93–99].

Where are the neocortical NSCs and NPCs?

One of the reasons why neocortical neurogenesis has remained unclear for such a long time is that NSCs and NPCs of the adult neocortex were not found. The above studies also suggest that NSCs and NPCs, which can be up-regulated by brain injury or stroke, may be maintained within or around the neocortex. Recent studies have gradually clarified NSCs and NPCs of the adult neocortex. Currently, there seem to be neocortical NSCs and NPCs mainly in four regions, the SVZ [57, 71, 80, 85, 90], white matter [87, 96], gray matter [75], and marginal zone [96, 97, 99] (Fig. 2).

The SVZ is historically the oldest putative source of neocortical new neurons. Migrating neuroblasts from the SVZ have been observed, even if the neocortex is in healthy condition [71, 85], although the number of new neurons is quite small in these studies. In contrast, pathological treatments, such as ischemia, seem to increase in the new neurons from the SVZ. After 90 min of focal cerebral ischemia in adult rats, neuroblasts, which express doublecortin, a migrating neuron marker, have been observed to migrate from the anterior SVZ, to the lateral cortical stream along the corpus callosum, and finally to the ischemic

Table 2 A list of experimental studies that examined neurogenesis in the adult neocortex

Species/age	Condition	Evaluation of neurogenesis/proliferation	Positive of negative	Reference
Albino rat/1 day–2 years	Healthy	Histological analysis of mitotic cells by thionine	Positive	[64]
Long evans rat/young adult	Lesion of LGN	Autoradiography with tritiated thymidine	Positive	[78]
Long evans rat/4 months	Healthy	Autoradiography with tritiated thymidine	Positive	[65]
Cats/2,500 g	Healthy	Autoradiography with tritiated thymidine	Positive	[65]
Long evans rat/1–60 day	Healthy	Autoradiography with tritiated thymidine	Positive	[79]
Rat/90 day	Healthy	Electron microscopy/autoradiography with tritiated thymidine	Positive	[66]
Macaque monkey/5–16 years	Healthy	IF with BrdU, NeuN, NSE, MAP-2, TOAD-64	Positive	[71]
C57BL mouse/over 6 weeks	Chromophore-targeted degeneration	IF with BrdU, NeuN, DCX, HuCD/axon elongation with FluoroGold	Positive	[80]
Wistar rat/12 weeks	Photothrombotic stroke for 2 min	IF with BrdU, MAP-2, NeuN	Positive	[81]
Macaque monkey/over 5 years	Healthy	IF with BrdU, NeuN, TuJ1	Negative	[82]
Macaque monkey/5–5.7 years	Healthy	IF with BrdU, NeuN, TuJ1	Positive	[72]
Wistar rat/9–10 weeks	Focal ischemia for 2 h	IF with BrdU, NeuN, TuJ1, MAP-2	Positive	[83]
Wistar rat/300–350 g	Focal ischemia until killing (7–42 day)	IF with BrdU, PSA-NCAM, NeuN, MAP-2	Negative	[84]
Macaque monkey/6–12 years	Healthy	IF with BrdU, NeuN, MAP-2, TuJ1, TUC-4	Positive	[85]
Squirrel monkey/3–6 years	Healthy	IF with BrdU, NeuN, MAP-2, TuJ1, TUC-4	Positive	[85]
C57BL mouse/2 months	Healthy after run and enrichment	IF with BrdU, NeuN	Negative	[86]
Macaque monkey/2–5 years	Healthy	IF with BrdU, NeuN, DCX	Positive	[74]
SD rat/280–310 g	Focal ischemia for 90 min	IF with BrdU, nestin, TuJ1, NeuroD, ENCAM, DCX, NeuN	Positive	[57]
Human white matter/1–69 years		In vitro neurosphere assay/IF with TuJ1, GAD67	Positive	[87]
C57BL mouse/?	Chromophore-targeted degeneration	IF with BrdU, NeuN, DCX/axon elongation with FluoroGold	Positive	[88]
Macaque monkey/5–11 years	Whole brain ischemia for 20 min	IF with BrdU, Ki67, phospho-histone H3, musashi1, nestin, NeuN, TuJ1, DCX, GAD65/67	Positive	[89]
Mouse/12 weeks	Aspiration lesion	IF with BrdU, DCX	Positive	[90]
Wistar rat/11–12 weeks	Healthy	IF with BrdU, nestin, vimentin, phospho-histone H3, DCX, NeuN, TuJ1, HuC/D, Pax6	Positive	[91]

Table 2 continued

Species/age	Condition	Evaluation of neurogenesis/proliferation	Positive of negative	Reference
SD rat/9–10 weeks	Healthy	IF with BrdU, NeuN, NSE, HuC/D, GABA, GAD67, calbindin, calretinin, parvalbumin, EAAC-1	Positive	[75]
Human/33–73 years	Healthy	^{14}C in DNA/IF with BrdU, NeuN, neurofilament	Negative	[92]
Human/25–48 years	Stroke	IF with Ki67, PCNA, DCX, TUC-4, ENCAM, TuJ1	Positive	[93]
Wistar rat/250–350 g	Healthy	IF with BrdU, Ki67, DCX, NeuN, PSA-NCAM	Positive	[94]
Hypertensive rat/?	Focal ischemia for 7–90 day/bFGF AAV injection	IF with BrdU, NeuN, SOX2, nestin, Pax6, Mash1	Positive	[46]
129S2/Sv mouse/2.5–3 months	Focal ischemia for 10 min/whisker stimulation	IF with BrdU, NeuN, DCX	Positive	[95]
Wistar rat/?	Laser-induced lesion	Neurosphere assay/IF with nestin, vimentin, 473HD, DCX	Positive	[96]
SD rat/8–9 weeks	Spreading depression	IF with BrdU, PCNA, vimentin, nestin, DCX, TuJ1	Positive	[97]
Human/34–84 years	Stroke	IF with nestin, musashi-1, TuJ1	Positive	[98]
Wistar rat/6 months	Global forebrain ischemia for 10 min	Retrovirus/IF with BrdU, TuJ1, HuC/D, GABA, GAD67, calretinin, neuropeptide Y, somatostatin, choline acetyltransferase, sodium channel	Positive	[99]

BrdU bromodeoxyuridine, *DCX* doublecortin, *EAAC1* excitatory amino acid carrier 1, *ENCAM* embryonic neural cell adhesion molecule, *GAD* glutamic acid decarboxylase, *HuC/D* human neuronal protein C and D, *IF* immunofluorescence, *Ki67* MKI67 gene product antibody clone, *LGN* lateral geniculate nucleus, *MAP-2* microtubule-associated protein 2, *Mash1* mammalian Achaete-Schute Homolog 1, *NeuN* neuronal nuclei, *NSE* neuron-specific enolase, *PSA-NCAM* polysialylated neural cell adhesion molecule, *SOX2 SRY* (sex determining region Y)-box 2, *TOAD-64* turned on after division 64 kDa (Synonyms TUC-4, TOAD/ulip/crmp-4), *TuJ1* anti-neuron-specific class III beta-tubulin clone TuJ1

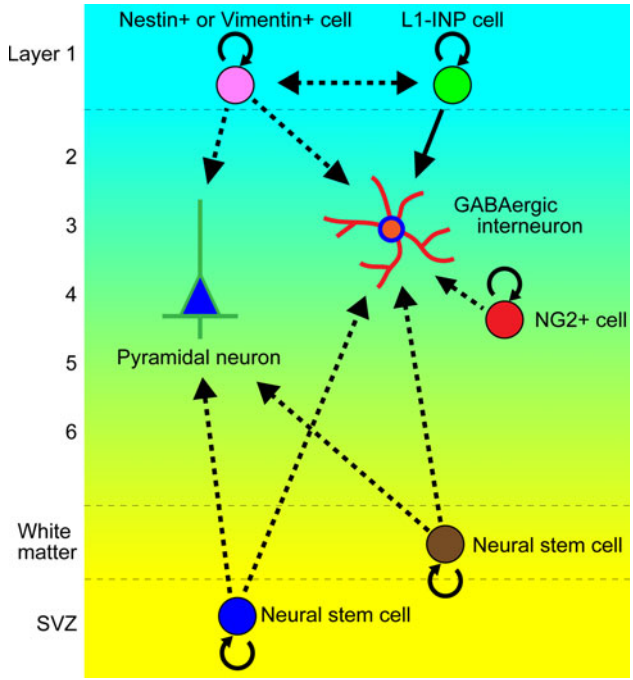

Fig. 2 Neurogenesis in the adult neocortex. There are four putative subregions in the neocortical parenchyma, where the NSCs/NPCs exist, the SVZ, *white* matter, *gray* matter, and layer 1. *Bold lines* and *dotted lines* are based on direct and indirect evidence, respectively

regions of the neocortex [57]. However, in the control rat brains, such migration of neuroblasts has not been found. The same finding is also reported in the aspiration lesion model of the adult mouse neocortex [90]. Since these experiments explored the migrating neurons up to 2 weeks after injuries, the detailed characteristics of neuronal morphology and the chemical features were not clarified. In other words, it remains unclear whether the new neurons are excitatory or inhibitory, and projection neurons or interneurons. These questions are challenged by Magavi et al. [80]. When layer VI corticothalamic projection neurons are killed by chromophore-targeted neuronal degeneration in the mouse anterior neocortex, projection neurons are newly generated, replaced in layer VI, and interestingly establish long-distance connections. The projection neurons seem to be generated in and migrate from the SVZ.

NSCs are isolated from the white matter of the adult human brain [87]. The isolated NSCs generate neurospheres in vitro, which give rise to neurons and glial cells both in vitro and after transplantation to the fetal rat brains. These white matter samples are surgically taken from patients with epilepsy, arterial aneurysm, dysplasia, and traumatic injury, so that these white matter NSCs might be pathology-inducible ones. In fact, the laser-lesions activate endogenous NSCs and NPCs in the white matter of the adult rat visual neocortex and in layer 1 as described in a later paragraph [96].

Dayer et al. [75] have reported that in the adult rat neocortex in healthy condition, newly generated GABAergic interneurons are found to comprise up to ~0.01% of total neurons. They used the double-staining technique of BrdU and some neural markers. One of the neural markers, doublecortin, is not contained in BrdU/CRMP-4-double-positive immature neurons in the neocortex, whereas in the striatum, doublecortin is expressed in immature neurons that are definitely migrating and their origin may be the SVZ [75]. Furthermore, more than 90% of BrdU-positive cells in the neocortex are immunoreactive for NG2 (neuroglia proteoglycan 2) 2 h after BrdU injection. At 4–5 weeks after BrdU injection, about 30% of BrdU/NeuN (neuronal nuclei)-double-positive cells have faint to moderate NG2 immunoreactivity. Hence, the authors speculate that in the neocortex, new neurons arise from in situ NG2-positive progenitors rather than from the SVZ or the white matter. However, since these data are derived from immunohistological experiments, they do not constitute direct evidence that NG2-positive cells produce new neurons. In fact, there are a few reports that show that NG2-positive proliferating cells do not produce new neurons at all, by using genetically modified mice [100–103]. In contrast, there are a few reports that some NG2-positive cells might function as NSCs in the hippocampus and the SVZ [104–106]. Thus, there is a big conflict in light of NG2-positive proliferating cells. Further studies to examine whether these progenitors generate neurons, glial cells, or both cell types are needed.

Recently, three groups have independently reported on NSCs and NPCs in the neocortical layer 1. The focal laser-lesion of the rat visual cortex newly induces NSCs/NPCs in layer 1 and white matter of the ipsilateral side, the cells which are detected by the molecular markers of NSCs/NPCs, including nestin, vimentin, and the 473HD epitope [96]. Similar NSCs/NPCs are induced in layer 1 by spreading depression treatment [97]. The NSCs/NPCs are defined as the vimentin- or nestin-positive cells. However, the two reports described above cannot provide direct evidence that new neurons are produced from the vimentin- or nestin-positive NSCs/NPCs, because these data are based on immunohistological data. The direct labeling method of progenitor cells with GFP-expressing retrovirus vectors has identified NPCs in layer 1 of the adult rat [99, 107]. Generally, when retrovirus vectors are used, the exact location of NSCs/NPCs should be determined before virus injection, as the weak infectivity of retroviruses is operative only at mitosis in the cell cycle, and the injected virus is rapidly diffused in the tissues. The genome of the virus vector is integrated into the genome of host cell, so that it is easy to trace daughter cells from NSCs/NPCs labeled with the virus vector. Interestingly, the layer 1 NPCs produce subclasses of GABAergic interneurons, which express

calretinin, but not calbindin and parvalbumin, among the calcium-binding proteins, and also contain neuropeptide Y, somatostatin, and choline acetyltransferase. At present, although mother cells of the layer 1 NPCs have not been identified, the layer 1 NPCs express the markers of the medial ganglionic eminence (MGE), Nkx2.1 and MafB [108, 109]. In the developing neocortical layer 1, similar NSCs/NPCs have been found [110]. Thus, such NSCs/NPCs that are observed during development might be maintained into adulthood. It is also shown that new neurons seem to form neural networks with existing neighbor neurons. Thus, the layer 1 NPCs are designated as L1-INP cells (layer 1 inhibitory neuron progenitor cell). The difference between L1-INP cells and nestin- or vimentin-positive NSCs/NPCs as described above [96, 97] is that L1-INP cells are found in layer 1 in healthy brains. L1-INP cells also have the potency to be increased by ischemia. Thus, there may be a few types of NSCs/NPCs in the neocortical layer 1. The neocortical layer 1 is composed of neurons from diverse origins such as the neuroepithelium, the olfactory primordium, and the GE [111–113]. In contrast, almost all excitatory neurons in layers 2–6 are generated from the ventricular zone during development [114], and the neocortical GABAergic interneurons are produced in and tangentially migrate from the MGE [115]. The critical difference between L1-INP cells and nestin- or vimentin-positive NSCs/NPCs is that newborn immature neurons from the layer 1 nestin- or vimentin-positive NSCs/NPCs express Pax6 [96], which is essential for proliferation and differentiation of excitatory neocortical neurons, such as pyramidal neurons, but not for acquisition of phenotypes of neocortical GABAergic interneurons from the MGE [116]. In contrast, almost all new neurons produced from L1-INP cells are GABAergic neurons. Although it is not determined whether new neurons from L1-INP cells express Pax6, GABAergic interneurons from the MGE do not contain Pax6 [116]. Thus, the possibility that L1-INP cells are distinct from the layer 1 nestin- or vimentin-positive NSCs/NPCs may be high.

Why do these various NSCs/NPCs exist in the adult neocortex? One possibility may be that damage-induced neurogenesis differs in its origin depending on the degree and the kind of brain damage. For example, in normal circumstances, new neurons are generated at very low levels from NSCs/NPCs in gray matter [75]. After animals are subjected to a mild injury, such as ischemic insult resulting from a 10-min occlusion of both common carotid arteries, layer 1 NSCs/NPCs, including L1-INP cells, generate new neurons. More intense injuries, such as focal cerebral ischemia caused by 90-min or permanent clamp (7–90 days until perfusion) [46, 57], aspiration- [90] or laser-lesion [96] of the neocortex, and chromophore-targeted neuronal degeneration [80, 88], cause the generation of new neurons from the SVZ, gray and white matter, and layer 1. Taken together, it is gradually becoming clear that the NSCs/NPCs exist in the adult neocortex and their neurogenesis can be promoted by brain insults. However, at present, an unshakeable definition of the neocortical NSCs/NPCs, such as their chemical properties and neurogenetic kinetics for insults, remains largely unclear. Furthermore, the functional implications of adult neocortical neurogenesis have not been absolutely understood. These questions are critical issues to be addressed in the future.

Conclusion and perspectives

Adult neurogenesis in the SVZ and the SGZ has been widely accepted by a great number of studies during the past two decades. In contrast, it remains controversial whether adult neurogenesis of the CNS occurs in other regions. Recently, the phenomena of neocortical adult neurogenesis and neocortical NSCs/NPCs have been widely reported, as described above. Neurogenesis in the adult neocortex may be induced or promoted by brain insults, such as ischemia and lesions. It has also been shown that new neurons are present in the striatum, and that, as expected, neurogenesis in the striatum is greatly increased under pathological conditions [41, 43, 55–60, 75, 89, 117–120]. Surprisingly, there have been several results for adult neurogenesis in regions other than the neocortex and the striatum, including the amygdala [71, 85, 117, 120–122], the hippocampal CA region [123], the hypothalamus [117, 120, 122, 124–126], the substantia nigra [127], the cerebellum [128], the spinal cord [129–134], the olfactory tubercle [135], and the piriform cortex [136]. Of course, there is some controversy regarding adult neurogenesis among these regions [82, 86, 92, 137–139]. However, at least in the SVZ, the SGZ, and the neocortical layer 1, endogenous NSCs and NPCs that can be activated by physiological stimuli, such as brain insults, are consistently maintained, suggesting that these NSCs and NPCs might be the basis for endogenous regenerative therapy for brain damage.

Currently, two major strategies for regeneration treatment for CNS injury are postulated. One is cell transplantation to the injured regions. Another is the activation of endogenous NSCs and NPCs. Each method has both advantages and disadvantages. For example, the former depends on a technology to differentiate NSCs and NPCs into mature functional neurons from ES and iPS cells in vitro and in vivo [140–143]. If a cell differentiation technology is established, it may be relatively easy to produce the requirements of cells for the regeneration of a brain that is completely damaged or deleted. However, after ES cells and iPS cells are differentiated into mature

functional neurons in vitro, it is essential to surgically transplant the mature neurons. Elderly persons, and those without physical strength, cannot endure such a surgical operation. On the other hand, if the mechanisms for proliferation of endogenous NSCs and NPCs and differentiation of neurons from the endogenous NSCs and NPCs are clarified, oral preparations that will be developed based on the mechanism may abolish the surgical burdens on patients, although the problem of the drugs' side-effects should be resolved. Development of a drug-delivery system and nanotechnology seem to be important. Furthermore, there is a great advantage in using endogenous NSCs and NPCs, which might have a lower risk for tumorigenesis. However, the existence of both endogenous NSCs and NPCs in damaged tissues must be fundamentally confirmed to realize the regenerative therapy, namely, if there are no stem/progenitor cells, there can be no neurogenesis. Thus, further detailed exploration is necessary to identify endogenous NSCs and NPCs in the whole brain. The advantages and disadvantages of the above two methods, i.e., the activation of endogenous NSCs and NPCs and the transplantation of exogenous cells, may well complement each other.

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