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REVIEW

NEUROGENESIS IN THE ADULT BRAIN[1]

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Neurogenesis is a process that involves cell proliferation, migration and differentiation. Adult neurogenesis has been discovered by Altman in the mid 1960s. It is known now that neurogenesis occurs in two main neurogenic areas of the adult mammalian brain: the olfactory bulb and the hippocampal dentate gyrus, although other brain regions, such as cortex or substantia nigra cannot be excluded. The rate of neurogenesis can be regulated in a positive and negative manner by several factors like, age, growth factors, hormones, environmental or pharmacological stimuli. Functional significance of adult neurogenesis is still under investigation, however, several evidences suggest involvement of newly generated neurons in cognitive processes. There are also several findings indicating that the impairment of adult neurogenesis may be involved in the pathophysiology of some brain diseases, like depression, epilepsy, ischemia or neurodegenerative disorders. It appears that alterations in the rate of neurogenesis may have important functional and therapeutic implications.

Key words*: adult neurogenesis, BrdU, hippocampus, olfactory bulb*

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Abbreviations: Aβ – *β*-amyloid peptide, APP – *amyloid precursor protein*, BDNF – *brain-derived neurotrophic factor*, bHLH – *basic helix-loop-helix*, BMP – *bone morphogenetic protein*, BrdU – *bromodeoxyuridine*, DG – *dentate gyrus*, dT – *thymidine*, EGF – *epidermal growth factor*, FGF – *fibroblast growth factor*, GDF – *growth and differentiation factor*, GL – *granular layer*, H – *hilus*, HB-EFG – *heparin-binding epidermal growth factor*, 5-HT – *serotonin*, IGF – *insulin-like growth factor*, IL – *interleukin*, NCS – *neural stem cells*, Ng – *neurogenesin*, Ngn – *neurogenin*, OB – *olfactory bulb*, PCNA – *proliferating cell nuclear antigen*, pHisH3 – *histone H3 phosphorylated at serine 10*, RMS – *rostral migratory stream*, SGZ – *subgranular zone*, SVZ – *subventricular zone*, TGF-β – *transforming growth factor β,* VEGF – *vascular endothelial growth factor*

Introduction

Neurogenesis is a process that involves cell proliferation, migration and differentiation. During proliferation neural stem cells (NSCs) divide asymmetrically and give rise to progenitor cells. They are also capable of proliferating. However, progenitor cells migrate from proliferation area and begin to differentiate. The differentiation process transforms the immature cell to mature neuronal or glial cells [34, 37, 135].

Neurogenesis is primarily a developmental process. First evidence that the adult brain contained some dividing cells differentiating into cells possessing neuron-like morphology was reported by Altman in the mid 1960s [3, 4]. Subsequent investigations provided more evidence in support of the adult neurogenesis [38, 65, 98]. It is clear now that mature neurons cannot divide but rather there is a population of stem cells in the adult brain, which is capable of dividing and differentiating into neurons or glial cells. Adult neurogenesis has been observed in several mammalian species, such as rat [3, 4, 41, 65], rabbit [47], cat [144], mouse [70], non-human primates [44, 45, 72] and also in the human brain [33].

Neurogenesis labeling methods

The investigation of neurogenesis requires methods detecting cell proliferation, the initial phase of neurogenesis, and subsequently should be capable of determining phenotype of the newly born cell using cell class specific markers. There are several exogenous and endogenous markers of cell division and also various cellular antigens which can be used to specify the phenotype (neuronal or glial) of the cells. Representative markers of cell proliferation and differentiation are listed in Table 1.

The principal methods of studying neurogenesis utilize exogenous markers of proliferation, thymidine or its analog bromodeoxyuridine (BrdU). The discovery of the adult neurogenesis was possible because of introduction of the autoradiographic method with ^{3}H-thymidine (^{3}H-dT) for detection of cell division. ^{3}H-dT is incorporated into nuclear DNA during S-phase of the cell cycle and the amount of ^{3}H-dT incorporated in a given cell is directly proportional to the number of silver grain overlay [3, 4]. More recently, evidence for neurogenesis has been obtained with the use of BrdU (for our data see Fig. 2, 3), which also incorporates into DNA during S-phase [99]. The advantage of this method is that its immunohistochemical detection can be more easily combined with various cell class specific markers to determine cell phenotype. Other useful feature of BrdU is its long-term retention in the divided cells and its passage to their

Table 1. The list of representative markers expressed by proliferating and differentiating cells in the adult brain

Marker	Name
Mitosis	dT (thymidine)
	BrdU (bromodeoxyuridine)
	PCNA (proliferating cell nuclear antigen)
	Ki-67
	pHisH3 (phosphorylated histone H3)
Neuronal cell differentiation	Tuj1 (neuron-specific β-tubulin protein)
	NeuroD
	PSA-NCAM (polysialylated neural cell adhesion molecule)
	CRMP-4 (collapsing response mediator protein-4)
	DCX (doublecortin)
	NeuN (neuronal nuclear protein)
	NSE (neuron-specific enolase)
	calbindin
Glial (astrocyte) cell differentiation	GFAP (glial fibrillary acidic protein)
	S-100β

References [3, 23, 34, 66, 67, 99, 110, 111, 124, 133]

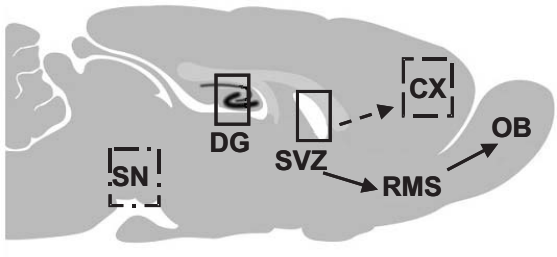

Fig. 1. Schematic representation of the neurogenic areas of the adult rat brain. DG – the dentate gyrus, SVZ – the subventricular zone of the lateral ventricle, RMS – rostral migratory stream, OB – olfactory bulb, CX – cortex, SN – substantia nigra

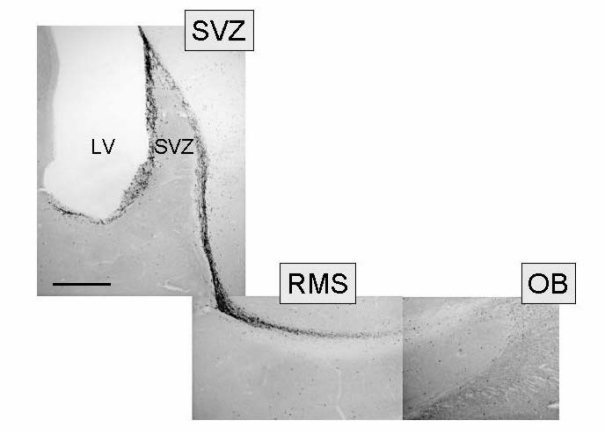

Fig. 2. Photomontage of sagittal section immunostained for BrdU showing migration of proliferating cells from the subventricular zone (SVZ) of the lateral ventricle (LV) *via* rostral migratory stream (RMS) to the olfactory bulb (OB). Scale bar 100 μm

daughter cells. This feature can be used to trace the cell lineage and cell survival.

An alternative approach is to monitor endogenous, cell cycle phase-specific proteins, such as proliferating cell nuclear antigen (PCNA), nuclear protein Ki-67 or histone H3 phosphorylated at serine 10 (pHis H3) [23, 66, 67, 133]. PCNA, a component of the DNA polymerase δ complex, which is expressed most abundantly during late G1 phase and early S phase, and is present at detectable levels during G2 and mitosis (M) [66, 133]. Ki-67 is expressed in all phases of the cell cycle except for the resting phase (Go) [67]. In contrast, pHisH3 expression is most abundant in early G2 till the end of M phase of the cell cycle [23]. For the technical consideration and limitation of neurogenesis labeling methods see [42, 67, 110].

Areas of neurogenesis in the adult brain

Neurogenesis has been shown to occur in two main neurogenic areas of the adult mammalian brain: the olfactory bulb (OB) and the dentate gyrus (DG) of the hippocampus (Fig. 1, 2, 3). Previous studies have revealed that neurogenesis occurs in the OB of adult rodents [3, 4, 85, 86], and non-human primates [73]. The new neuronal cells in the OB are generated from neural progenitor cells (type C cells) [27] in the anterior part of the subventricular zone (SVZ) [86]. The SVZ is a narrow zone of tissue within the wall of the lateral ventricle in the forebrain. The neural progenitor cells of the SVZ migrate to the OB *via* the rostral migratory stream (RMS) (Type A cells) [27], where they differentiate into interneurons of the OB: granule cells and periglomerular cells [85, 86] (Fig. 1, 2).

Neurogenesis in the adult DG of the hippocampus has been observed in the brain of rodents [3, 4, 19, 124], non-human primates [44, 72] and humans [33]. The neuronal progenitor cells are generated in the subgranular zone (SGZ) of the DG and migrate from the SGZ into the granule cell layer (GL) of the DG and differentiate into neuronal and glial cells [19] (Fig. 1, 3). Retrograde tracing studies have shown that the newly generated neuronal cells extend their axons into the CA3 region of the hippocampus [50, 91, 131] as soon as 4–10 days after mitosis [50]. They receive synaptic input [91] and establish functional connections *in vitro* [130] and *in vivo* with the CA3 region [140].

Recently, Gould et al. [45] presented data showing that neurogenesis also occurred in the adult primate frontal cortex. They suggested that in adult macaques, the cells derived from the SVZ migrated through the white matter to specific cortical regions of the neocortex [45] (Fig. 1). It has also been reported that the number of the newly generated cells in the rat prefrontal cortex increases after treatment with antipsychotic drugs [141]. However, the results of other authors do not substantiate the claim of neurogenesis in normal adult primate cortex [73]. It appears that neurogenesis in the adult neocortex awaits confirmation.

It has also been found that new neurons are generated under physiological conditions in the rat substantia nigra pars compacta [147] (Fig. 1). However, the number of newly born cells in the

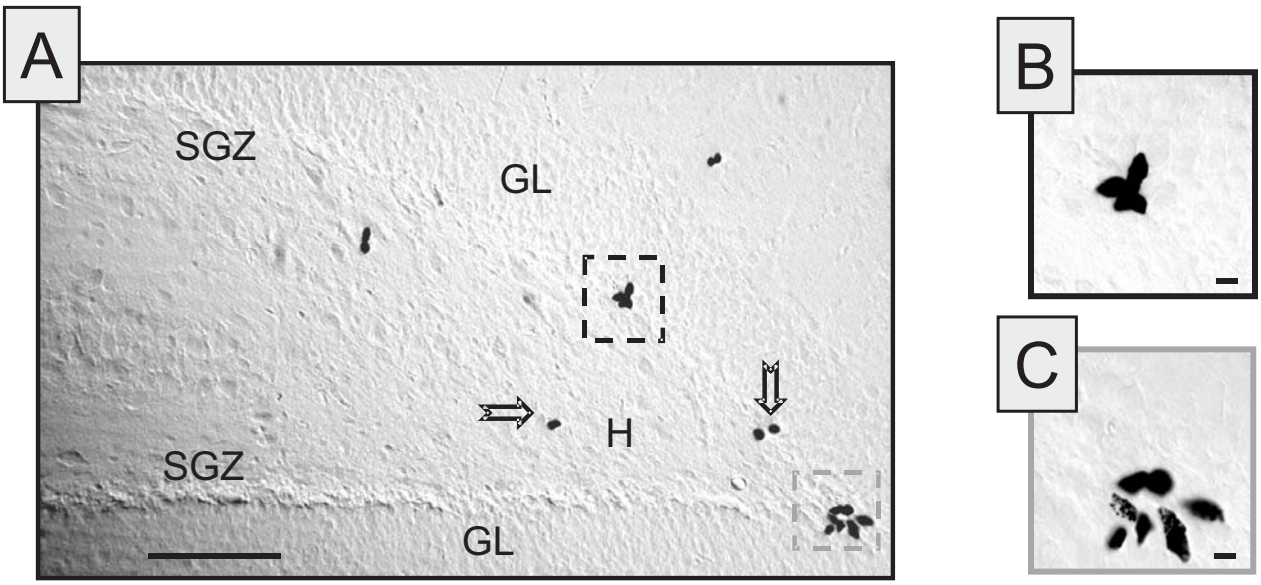

Fig. 3. Examples of BrdU immunostaining in the dentate gyrus (DG) of the adult hippocampus. A – microphotograph showing BrdU immunopositive nuclei (arrowheads) in the subgranular zone (SGZ) and hilus (H) of the DG. B, C represent enlarged fragments framed in A. GL – granular layer. Scale bar 50 μm (A) and 10 μm (B, C)

substantia nigra is several orders of magnitude smaller than in the DG of the hippocampus [147]. These data indicate that neurogenesis in the adult brain is more widespread than previously thought.

Neural stem cells

NSCs are distinguished by their two functional properties: a seemingly unlimited capacity for self-renewal by symmetric division and the ability to generate multiple mature NSC types (multipotent). Switch from a pattern of symmetric to asymmetric division generates a progenitor cell. A single NCS is capable of generating various kinds of cells within the central nervous system, including neurons and glial cells (astrocytes, oligodendrocytes). In contrast, progenitors of neurons and glial cells are the cells capable of proliferation but possessing a limited capacity for self-renewal and are often unipotent [35, 100, 101, 108, 123, 135]. Endogenous NSCs are present at neurogenic (the SVZ of the lateral ventricle, the hippocampal DG) but also at non-neurogenic sites of the adult brain (septum, striatum, cerebral cortex, corpus callosum) [102], and in the adult spinal cord [142].

The problem of which population of cells corresponds to the NSCs in the SVZ of the lateral ventricle is a matter of controversy [21]. One view is that these cells are the ependymal cells facing the ventricle [64], whereas an alternative view identifies cells having characteristics of the SVZ astrocytes as the NSCs [26] (type B cells) [27].

The localization of the stem cells in the adult mammalian hippocampus is still discussed [123]. It has been shown that the NSCs are resident in the hippocampal SGZ [103]. Other localization of the NSCs (to the ventricular supendyma) and neuronal progenitors (to the hippocampal SGZ) [122] provides insight into the mechanism of neuron generation in this region. The newborn adult neurons in the DG could have developed from the neuron-specific progenitors present therein, as well as from the NSCs that exist peripherally in the ventricular supendyma around the hippocampus. These stem cells might generate progenitor cells that migrate into the DG [123].

It is known that the adult NSCs have remarkable plasticity [35]. However, active neurogenesis is limited to discrete regions of the adult brains. Local environment seems to dictate further fate of adult stem cells. Adult spinal cord-derived NSCs are able to produce neurons *in vitro* and when transplanted into neurogenic sites, such as the hippocampal DG [125]. However, *in situ* these cells proliferate and differentiate into astrocytes, but not into neurons, even after spinal cord injury [96, 101]. In the case, when the NSCs are obtained from

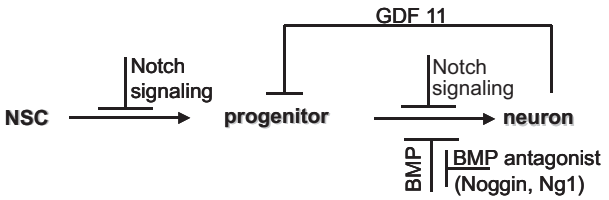

Fig. 4. Scheme of the regulation of the neural cell differentiation in the neurogenic areas of the adult brain. NSC – neural stem cell, BMP – bone morphogenetic protein, GDF11 – growth and differentiation factor 11

the adult hippocampus and implanted back into the hippocampus, they can generate new neurons and glia, similar to the the cells normally generated in the adult DG. Moreover, these cells can produce OB neurons when implanted into the RMS [36, 132]. However, when implanted into regions that do not normally generate neurons in the adult brain, the stem cells are able to make again glial cells, but not neurons [36, 132]. The above results raise the possibility of therapeutic neuron replacement, but more complete understanding of the cellular and molecular events that control differentiation and maturation of newly generated cells, is a prerequisite for the use of this strategy for therapy.

Molecular mechanisms controlling neurogenesis

As mentioned above, NSCs can generate neuronal lineage only in neurogenic areas of the adult brain. It seems that some signals capable of maintaining stem cell in an undifferentiated state and promoting the differentiation of progenitor cells must be present in these regions. At present, Notch receptor signaling and bone morphogenetic proteins (BMP) have been described as two potential regulatory factors controlling decision making process on NSC fate [21] (Fig. 4).

Notch signaling depends on Notch receptors, their ligands (Delta, LAG-2, APX-1) and downstream modulators. The proteins downstream of Notch include a large number of molecules called basic helix-loop-helix (bHLH) proteins. Signals exchanged between neighboring cells through the Notch receptor can amplify and consolidate molecular differences, which may dictate cell fates (for more details see [5]). In the nervous system, activation of the Notch1 receptor has been shown to inhibit neurogenesis (Fig. 4) [5, 81]. One of the suggested mechanisms consists in maintaining of NSCs in their undifferentiated state by Notch signaling, potentially by promoting symmetrical division and self-renewal [55]. It has also been described that activation of the Notch pathway usually inhibits the expression and activity of proteins belonging to the proneuronal bHLH transcription factor families [5]. It is known that neuronal commitment or differentiation during neurogenesis process is controlled by the neuronal bHLH transcription factors including Mash1, Neurogenins (Ngn1 and Ngn2), NeuroD and Math family [74, 101].

BMP group is a member of the transforming growth factor-β (TGF-β) superfamily, a large group of secreted proteins with widespread roles in development and tissue homeostasis [49]. BMPs and their cognate receptors (BMPRs) are widely expressed throughout development, playing important roles in cell lineage determination. Depending on the context, BMP can act either as strong instructive neurogenic factors [82] or potent inhibitors of neurogenesis [46, 128]. In adulthood, BMP and BMPR expression is observed in limited neurogenic areas of the brain, i.e. the SVZ and the hippocampal DG [84, 118, 136]. It appears that BMP alters the fate of NSC from neurogenesis to gliogenesis, probably by a mechanism involving degradation of proneuronal transcription factors (Mash1) [128] or by up-regulating the expression of antineurogenic bHLH factors (Id1, Id3 or Hes5) [46, 145]. On the other hand, it is known that the endogenous BMP antagonists (Noggin, Neurogenesin-1 [Ng1]) are potential molecules that control neural commitment of NSC and can provide neurogenic cues for NSC (Fig. 4). To date the BMP-binding protein Noggin has been shown to be expressed by ependymal cells of the SVZ, and appears to support neurogenesis by binding to endogenous BMP and consequently preventing activation of BMPRs which would otherwise induce gliogenesis [84]. BMPs and their receptors are expressed throughout the SVZ, while antagonistic Noggin expression is limited only to ependymal (astrocyte) cells of the SVZ [84]. Similar mechanisms supporting neurogenesis by inhibiting BMP has been observed in the DG of the hippocampus. It has been shown that hippocampal astrocytes secrete Ng1 which antagonizes BMP-4 [136]. It is likely that astrocytes can control the fate of adult NSCs, by creating the local environment of the hippocampus or the SVZ [129].

It has also been shown that another member of TGF-β family, growth and differentiation factor 11

(GDF 11) is capable of inhibiting neurogenesis in the olfactory epithelium (Fig. 4) [143]. However, GDF 11 is secreted by neurons themselves or their immediate progenitors [51, 143]. *In vitro* study showed that GDF 11 inhibited neurogenesis reversibly arresting the division of the progenitor cells by up-regulating the expression of cyclin-dependent kinase inhibitor $p27^{Kip}$ [143]. Mice lacking functional GDF 11 have more progenitors and neurons in the olfactory epithelium, whereas mice lacking follistatin, a GDF 11 antagonist, show decreased neurogenesis [143].

The above data indicate that adult neurogenesis can be regulated at NSC level by local environment (Notch receptor signaling pathway or BMP proteins) which determines neural fate of progenitor cells (Fig. 4). Moreover, neurons themselves could be the endogenous source of factors, like for example GDF 11, inhibiting neurogenesis (Fig. 4).

Factors regulating adult neurogenesis

Recent studies indicate that the rate of neurogenesis can be regulated by several factors. It is also known that neurogenesis can be controlled in both a positive and negative manner by internal (genetics, age, growth factors, hormones, neurotransmitters) and external factors (environmental or pharmacological stimuli) (see [29]). The focus of this chapter is to describe briefly factors which may influence the rate of neurogenesis.

Genetics

The recent report [70] indicates that genetic background plays an important role in the regulation of adult neurogenesis. Different strains (C57BL/6, BalB/c, CD1 and 129/SVJ) of mice have been examined to determine the rate of neurogenesis in the adult hippocampus. Proliferation has been found to be the highest in C57BL/6 mice, although the number of newly generated neurons was the highest in the CD1 strain [70]. Moreover, exposure to an enriched environment has different effects on two of these strains of mice. In C57BL/6 mice enrichment of environment promotes the survival of progenitor cells but does not affect proliferation, whereas the increase in proliferation and neurogenesis has been observed in 129/SVJ mice [68]. Thus, strain differences not only influence the baseline rate of adult hippocampal neurogenesis, but also determine vulnerability of neurogenesis to environmental challenge.

Growth factors

There are a few reports showing the role of growth factors in the regulation of adult neurogenesis. It has been shown that intraventricular administration of brain-derived neurotrophic factor (BDNF) increases neurogenesis in the adult OB [148]. Moreover, BDNF is also required for basal neurogenesis in the adult mice hippocampus [79]. In addition, peripheral infusion of insulin-like growth factor-I (IGF-I) enhances neurogenesis in the adult rat hippocampus [1]. Another study has shown that fibroblast growth factor (FGF-2) and epidermal growth factor (EGF) have differential and site-specific effects on progenitor cells *in vivo* [77]. Intracerebroventricular (*icv*) infusion of FGF-2 into the lateral ventricle resulted in the increased numbers of new neurons in the OB, while EGF infusion reduced the number of neurons reaching the OB, but substantially increased generation of astrocytes in the OB [77]. In contrast, Craig et al. [22] found the enhanced SVZ neurogenesis following the EGF and FGF-2 infusion. It has also been observed that there is an increase in the SVZ and in the DG neurogenesis after *icv* administration of heparin-binding epidermal growth factor (HB-EGF) [58] and vascular endothelial growth factor (VEGF) [63]. In general, it seems that growth factors have a stimulatory effect on the adult neurogenesis.

Neurotransmitters

The involvement of several neurotransmitters, such as glutamate, endocannabinoids or monoamines (serotonin [5-HT], norepinephrine, dopamine), in the regulation of adult neurogenesis has been examined.

Glutamate, the major excitatory neurotransmitter in the brain, has been shown to regulate neurogenesis in the adult hippocampus. Most studies to date have focused on NMDA glutamate receptor subtype. It has been reported that proliferation of cells in the adult hippocampus is decreased by administration of NMDA and increased by NMDA receptor antagonist (MK-801, CGP 43487) [16, 18, 95]. In addition, lesion of the entorhinal cortex, which provides a major glutamatergic input to the hippocampus, increases hippocampal cell proliferation [16]. Recent reports have also shown that other glutamate receptors, such as AMPA receptor [9] or metabotropic receptors [146] can be involved in the regulation of cell proliferation in the hippocampus.

A role of 5-HT neurotransmitter system has been demonstrated using several different approaches [39]. Lesion of the 5-HT system or inhibition of 5-HT synthesis has been shown to decrease the proliferation in the hippocampus and in the SVZ [12, 13]. Moreover, administration of d-fenfluramine, an agent releasing 5-HT, increases the number of BrdU-positive cells in the hippocampus, and this effect is blocked by pretreatment with WAY 100635, a 5-HT_{1A} antagonist [57]. In addition, administration of a 5-HT_{1A} agonist, 8-hydroxy-2-dipropylaminotetralin, also increases the number of BrdU-labeled cells [57]. The recent data indicate the involvement of 5-HT_{1A} receptor in the regulation of the adult neurogenesis. However, 5-HT may also regulate neurogenesis acting through other 5-HT receptor subtypes, such as 5-HT_{2A} or 5-HT_7 [29].

Recent data indicate that noradrenergic system can also regulate adult neurogenesis. It has been shown that depletion of norepinephrine decreases the proliferation, but does not affect differentiation or survival of hippocampal cells [78]. In contrast, the blockade of α_2-adrenergic receptor in the rat OB system by systemic administration of an antagonist dexefaroxan, does not alter the number of newborn BrdU-positive cells in the SVZ, but increases neuron survival in the OB, putatively as a result of reducing the apoptotic fate of telencephalic stem cell progenies [11].

The recent studies indicate the involvement of dopamine in the regulation of adult neurogenesis. It has been reported that depletion of dopamine in rodents decreases precursor cell proliferation in both the SVZ and the SGZ [56]. Moreover, proliferation is restored by an agonist of D_2-like receptors [56]. In addition, stimulation of D_3 receptors enhances proliferation in the SVZ [138]. It appears that dopamine acting through D_2-like receptors may enhance adult neurogenesis.

Some evidences suggest the role of endocannabinoids in the regulation of adult neurogenesis. However, the results are not clear. Nevertheless, CB_1R–knockout mice show reduction in the number of BrdU-labeled cells in the DG and in the SVZ suggesting that activation of CB_1 cannabinoid receptors promotes neurogenesis [62]. On the other hand, activation of CB_1 receptor by endocannabinoid, anandamide, decreases adult neurogenesis in the DG [115]. However, in both cases an antagonist of CB_1 receptor, SR141716A, increases the number of BrdU-labeled cells [62, 115]. To date, SR 141716A is thought to act by other than CB_1 receptors, for example VR_1 vanilloid receptor, and its effect on the adult neurogenesis may be independent of endocannabinoid system [62].

Hormones

Studies conducted over the past several years have identified steroid hormones (adrenal steroids, estrogen) or peptide hormones (prolactin) that are potential regulators of adult neurogenesis.

Recent findings indicate that adrenal steroids naturally suppress production of new neurons. Experimentally evoked enhancement of the levels of adrenal steroids resulted in decreases in the rate of adult neurogenesis in the hippocampus [15]. In contrast, removal of adrenal steroids stimulates proliferation of the hippocampal cells [41, 94, 113]. Considerable evidence indicates that adrenal steroids suppress the rate of adult neurogenesis by acting through an NMDA receptor-mediated pathway [18]. The latter observation is in line with data showing that NMDA receptor may also be involved in the regulation of the adult neurogenesis (see above).

In contrast to adrenal steroids, estrogen increases cell proliferation in the hippocampal SGZ [134]. Removal of circulating estrogen by ovariectomy results in significant decrease in the proliferation of hippocampal granule cell precursors [134]. Whether the effects of estrogen on cell proliferation in the SGZ are exerted directly or indirectly through another receptor system is unclear but serotonin seems to be involved in the estrogen-dependent proliferative effect [10].

Estrogen's effect on proliferation has been observed in the hippocampus, but not in the SVZ. In contrast, prolactin stimulates the production of neuronal progenitors in the SVZ [126]. The increase in olfactory neurons associated with pregnancy may implicate the heightened sense of smell observed in pregnant women [80].

Age

It is known that advanced age seems to be very important factor declining adult neurogenesis. The decrease in the number of BrdU-positive cells has been observed in the DG in aging rats [76] and monkeys [44]. The reduction has not been observed in the SVZ of aging rats [76], although the decrease in the population of NSCs in the SVZ of aging

mice has been found [92]. It appears that the observed reduction of cell proliferation in the aged hippocampus is related to the elevated levels of circulating glucocorticoids [117]. Removal of adrenal steroids by adrenalectomy increases cell proliferation in the SGZ of both aged and young adult rats [17]. Thus, adrenal steroids are an important factor regulating neurogenesis also in aging animals. Besides hormones, it has been shown that growth factors (IGF-I) can stimulate neurogenesis in the aged rodent brain [83]. It is likely that the rate of neurogenesis in the hippocampal DG is more responsive to age-induced changes in the levels of hormones or growth factors than in the SVZ.

Environmental factors

Enriched environment

Several reports demonstrate that exposure to environmental factors, including enriched environment, exercise, learning and memory training influences the rate of neurogenesis and the survival of newborn neurons. However, it has been shown that enriched environment or physical activity stimulates hippocampal but not OB neurogenesis [14]. Thus, it has been found that mice placed in an enriched environment which accelerates social interactions and availability of wheel for voluntary exercise have enhancement of hippocampal neurogenesis in comparison with mice kept in standard cages [68]. Studies of voluntary exercise demonstrate that activity on a running wheel, in the absence of other components of enriched environment, is sufficient to increase proliferation and recruitment of granule cells into the DG [139]. Recent findings also indicate the increase in generation of new neurons in the DG in response to training on associative learning task that requires the hippocampus [40]. In contrast, training on associative learning task that does not require the hippocampus, does not alter the hippocampal neurogenesis [40].

Stress

Another environmental factor that exerts a potent effect on the adult neurogenesis is stress. Stress decreases the rate of neurogenesis. It has been demonstrated that exposure of adult non-human primates to a psychosocial stressor, the resident-intruder paradigm, decreases the rate of granule cell proliferation in the hippocampus [43]. Similar observation has been made in rats, in which acute or chronic restraint stress suppressed neurogenesis in the DG [107]. The decreased neurogenesis appears to result from the stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis, particularly elevation of glucocorticoids.

Psychotropic drugs

Drugs of abuse

Several abused drugs, such as opiates, ethanol, nicotine or cannabinoids have been investigated to determine their influence on adult neurogenesis. It has been found that opiates (morphine, heroin) inhibit neurogenesis in the adult rat hippocampus [30]. Similar decrease in the rate of neurogenesis has been observed after nicotine [2] and ethanol [54, 97] treatment. For cannabinoids see the Neurotransmitters section. In general, it appears that abused drugs diminish adult neurogenesis.

Antidepressants

The influence of antidepressants on hippocampal neurogenesis has been examined. It has been found that repeated antidepressant administration increases the number of BrdU-labeled cells in the hippocampus [90]. In addition, this increase is dependent on long-term antidepressant treatment and occurs in the response to repeated administration of different classes of antidepressant drugs [90]. Moreover, an increase in hippocampal neurogenesis is also induced by electroconvulsive treatment [88, 90] as well as long-term lithium administration [20]. These findings suggest that the increase in hippocampal neurogenesis is a common cellular action of antidepressant treatment (see [29]).

Antipsychotic drugs

There are several studies investigating the effect of antipsychotic drugs on adult neurogenesis. One evidence indicates that repeated treatment with an antipsychotic drug does not influence adult neurogenesis [90]. Other findings show an increase [25, 48], but also a decrease [8] in hippocampal cell proliferation. Recently, the increase in the number of newly generated cells in the rat prefrontal cortex after chronic antipsychotic drug treatment has been observed [141]. It seems that the effect of antipsychotic drug on adult neurogenesis depends on pharmacological profile of antipsychotic drugs, and it will require further investigation.

Adult neurogenesis and brain diseases

Several reports indicate that brain inflammation causes inhibition of basal formation of new neurons in the hippocampal formation [31, 93]. It has been shown that the detrimental action of inflammation on neurogenesis depends on the degree of activation of the brain resident immune cells, microglia [31, 93]. The deleterious effect of the activated microglia on the newly formed neurons is most likely mediated through the actions of cytokines, such as interleukin-6 (IL-6) [137]. Finally, it has been reported that a selective inhibitor of microglia activation, minocycline [31], as well as a common nonsteroidal anti-inflammatory drug, indomethacin [93], restore hippocampal neurogenesis during inflammation. Since neuroinflammation and microglia activation are believed to be involved in the pathogenesis of neurodegenerative disorders, the application of anti-inflammatory drugs may offer a possible novel strategy improving treatment of neurodegenerative disorders.

There are several findings indicating that the impairment of adult neurogenesis may be involved in the pathophysiology of some brain diseases, such as depression, epilepsy, ischemia or neurodegenerative disorders.

Depression

It has been reported that both physical [107] and psychosocial stress [43] produce a decrease in hippocampal cell proliferation and neurogenesis. These findings are of interest because there are a large number of stress-based hypotheses of depression [28]. Conversely, long-term (consistent with the time course for the therapeutic action), but not short-term treatment with different classes of antidepressants increases cell proliferation and neurogenesis [90]. Moreover, it has been found that disruption of antidepressant-induced neurogenesis by using genetic and radiological methods, blocks behavioral response to antidepressants [116]. Taken together, a current hypothesis is that reduced adult hippocampal cell proliferation and neurogenesis may be involved in the pathophysiology of depression and that reversal or prevention of the decrease in neurogenesis may be one way in which the antidepressant drugs exert their effects [69, 89].

Epilepsy

Recent findings indicate that seizures induced by various experimental manipulations (kindling, pilocarpine, kainic acid) increase neurogenesis in the adult rodent DG [7, 32, 106, 109] as well as in the SVZ-OB pathway [105]. However, the effects of seizure-induced neurogenesis in the epileptic brain, in terms of either a pathological or reparative role, are only beginning to be understood. Following seizures, the newly generated cells are responsible for some abnormal structural plasticity in the epileptic hippocampal formation, e.g. aberrant mossy fiber synaptic reorganization [106]. The second abnormality involves anomalous (ectopic) location of the newly born granule-like neurons in the hilus and inner molecular layer [120]. Ectopic hilar granule cells have some electrophysiological [120, 121] and morphological (persistent basal dendrites and an increase in the number of excitatory synapses on the dendrites) [112] abnormalities. These findings support the hypothesis that new granule cell may not act to ameliorate seizures, and might even contribute to them. Furthermore, cognitive deficits following seizures might be in part due to circuits that develop between new cells and the host brain (see [104, 119]).

Ischemia

It has been shown that focal cerebral ischemia increases neurogenesis both in the SGZ of the DG and in the SVZ [59]. Moreover, the increase in hippocampal neurogenesis following focal ischemic insult is mediated by activation of NMDA receptor [6]. Additionally, newly born neuronal precursors in the SVZ, but not in the DG, migrate into the ischemic penumbra of the adjacent striatum and *via* the RMS and lateral cortical stream, they reach the penumbra of ischemic cortex [61]. The hypothesis has been presented suggesting that ischemia-induced neurogenesis may be an adaptive process that contributes to recovery after stroke [61].

Neurodegenerative disorders

Parkinson's disease

In Parkinson's disease, dopaminergic midbrain neurons degenerate, leading to striatal dopamine depletion. Experimental depletion of dopamine in rodents decreases precursor cell proliferation in both the SVZ and the SGZ, and this process in-

volves D_2-like receptor activation [56]. Consistently, the numbers of proliferating cells in the SVZ and neural precursor cells in the SGZ and the OB are reduced in postmortem brains of individuals with Parkinson's disease [56]. These observations suggest that the generation of neural precursor cells in the DG and in the OB is impaired in Parkinson's disease as a consequence of dopaminergic denervation [56]. On the other hand, recent evidence indicates that new dopaminergic neurons are generated in the substantia nigra pars compacta of adult rodents under physiological conditions [147]. The number of newly born neurons in the substantia nigra is several orders of magnitude smaller than in the DG, but the rate of neurogenesis in the substantia nigra is increased after lesion [147]. The above observation indicates that the rate of neurogenesis can be regulated and understanding of the mechanism controlling neurogenesis may enable the development of strategies to increase the generation of dopaminergic neurons in the adult brain, and potentially offer a new way of Parkinson's disease treatment [147].

Alzheimer's disease

Alzheimer's disease is characterized on the anatomical level by senile plaque containing β-amyloid peptide (Aβ) derived from amyloid precursor protein (APP), and neurofibrillary tangles (NFTs) containing hyperphosphorylated τ-protein. Aβ and phospho-τ-protein may be neurotoxic, leading to progressive neuronal degeneration and death. Recent studies using mouse model of Alzheimer's disease indicate that Aβ disrupts neurogenesis in the SVZ and the hippocampus [52, 53]. In contrast to findings in animal models, the enhancement of neurogenesis has been observed in the hippocampus of patients with Alzheimer's disease [60]. This discrepancy may be explained by fact that molecular stimulus to neurogenesis in Alzheimer's disease is unknown and other factors than Aβ may also influence this process [60].

Huntigton's disease

Huntigton's disease is caused by a mutated form of the huntingtin genes, but the mechanism of cell loss is not fully understood. The striatum and cortex are affected in early stages of the disease and more recent evidence suggests hippocampal dysfuction as well [114]. Current findings have shown the increase in cell proliferation in the SVZ in the postmortem brain of Huntigton's disease patients, although the extent to which these new cells form functional neurons is not known [24].

Conclusions

Recent studies have brought general acceptance to the hypothesis that neurons are indeed born in the adult mammalian brain. Functional significance of adult neurogenesis is still under investigation. However, the information that has been obtained and published so far provides evidence that neurons generated in the adult brain can function and may contribute to cognitive processes [71, 87, 127, 140]. Moreover, the adult neurogenesis is of special interest because of potential therapeutic applications [37, 75]. It appears that neurogenesis is an important process during adulthood.

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