Chapter 2

Factors Regulating Neurogenesis in the Adult Dentate Gyrus

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Abstract

The dentate gyrus (DG), an important part of the hippocampus, plays a critical role in consolidation of information from short-term to long-term memory, and also in spatial navigation. Neural stem/progenitor cells (NSPCs) exist throughout life in the subgranular zone (SGZ) of the DG, where they develop into granular cells and establish synaptic connections with nearby cells. Granular cells of the DG sprout axons targeting neurons in the cornu ammonis 3 (CA3) area of the hippocampus, forming a neural trisynaptic circuit, an important part of the neural network in the hippocampus. Thus, the DG and the neurogenic cells it contains are of importance in controlling formation of memories, learned behaviors, and also in the maintenance and restoration of functions of the hippocampus. According to reports, both *in vivo* and *in vitro* neurogenesis in the DG are regulated by a variety of endogenous and exogenous factors at different stages. Therefore, a better understanding of the factors in NSPC niches and the intracellular molecules regulating/directing adult DG neurogenesis is needed to fully realize the potential of NSPCs in the treatment of hippocampal-related disorders. This chapter systematically summarizes the factors reported in regulating adult DG neurogenesis in mammals. Specifically, neurotransmitters, hormones, trophic factors, and others will be discussed.

Keywords: dentate gyrus, hippocampus, neurogenesis, neural stem and progenitor cell, regulation

1. Introduction

The dentate gyrus (DG) is an important structure within the hippocampus and plays critical roles in consolidation of information from short-term memory to long-term memory, as well as spatial navigation. Neural stem/progenitor cells (NSPCs), which undergo neurogenesis,

are present throughout life in the subgranular zone (SGZ) of the DG. Approximately 700 newborn granular neurons are formed every day in the adult human DG [1]. NSPCs in the SGZ, which differentiate into granular cells, are anchored within the granular layer of the DG, and following differentiation, establish synaptic connections with neighboring neurons, and maintain the function of the hippocampus. Granular cells in the DG sprout axons targeting neurons in the cornu ammonis 3 (CA3) area of the hippocampus, forming a neural trisynaptic circuit, an important part of the neural network in the hippocampus. Thus, the DG and the neurogenic cells it contains are of importance in controlling the formation of memories and learned behaviors. A better understanding of the factors regulating neurogenesis in the DG is therefore needed to fully understand the mechanisms involved in the differentiation of NSPCs in the hippocampus. Indeed, adult DG neurogenesis is regulated by a variety of endogenous and exogenous factors at different stages of differentiation. This chapter reviews the effect of regulation factors, including chemical cytokines, signals, and also of physiological and pathological factors on the neurogenic potential of NSPCs in the adult DG.

2. Neurotransmitters

Neurotransmitters are specific chemicals that act as a "messenger" in synaptic transmission. As neurobiology has developed, a large number of neurotransmitters have been found in the nervous system. It was shown that the presence of many neurotransmitters influences neurogenic niche.

2.1. Serotonin (5-hydroxytryptamine, 5-HT)

The 5-HT is a monoamine neurotransmitter of the central nervous system (CNS) and is synthesized primarily by the lower midbrain and the raphe nuclei of the medulla oblongata (reviewed in [2]) from the amino acid tryptophan. Fibers of serotonergic neurons project throughout the brain, including afferent to the hippocampus. A role for 5-HT in the enhancement of adult hippocampal neurogenesis was first identified through the use of selective serotonin reuptake inhibitors (SSRIs), which were used as antidepressant drugs [3]. Chronic administration of SSRIs was shown to markedly increase adult neurogenesis [4, 5], but interestingly, was reduced or blocked in aged models [6]; this suggests that actions of SSRIs on neurogenesis may depend on the age of the treated individual and that the therapeutic effects of antidepressants in elderly patients are not mediated by neurogenesis modulation. Furthermore, neurogenesis in the adult hippocampus in aged mice was enhanced when central 5-HT levels were reduced specifically in adulthood (reviewed in [7]). These findings collectively suggested that aging was a key factor affecting adult hippocampal neurogenesis and that this is important in effect of serotonin. With regard to 5-HT receptors, several studies showed that 5-HT1A and 5-HT4 receptor agonists increased adult cell proliferation in the DG [8–12], while 5-HT1A receptor antagonists decreased proliferation and survival of newborn cells in the DG [13, 14]. Interestingly, both receptors have been shown to have putative antidepressant activity [15, 16], possibly partially depending on the receptor mediating hippocampal neurogenesis [12]. These reports also found that brain-derived neurotrophic factor

(BDNF) isoforms may act as a bridge between serotonin and its pro-neurogenic effects in the DG, because BDNF has the ability to enhance neurogenesis and its level can be up-regulated by serotonin ([17]; as reviewed below).

2.2. Dopamine (DA)

CNS-derived DA is mainly secreted by dopaminergic neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Dopaminergic fibers from the SNc and VTA have been shown to partially target the hippocampal subventricular zone (SVZ) [18, 19]. In addition, ultrastructural evidence showed that highly proliferative precursors in the adult brain express dopamine receptors and receive dopaminergic afferents [20]. Together, these results implicate that DA participated in regulating adult neurogenesis. Moreover, evidence indicated that destruction of DA neurons in SNc and VTA, or deletion of dopamine through neurotoxic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) injection, all reduced proliferation of NSPCs in both the SVZ and SGZ [18, 20]. It has also been demonstrated that pramipexole, a D2-like selective DA agonist, enhanced the proliferation of hippocampal NSPCs and also enhanced the proportion of neuronal differentiation in the DG of adult mice [21]. In contrast, Egeland et al. found that pharmacological or genetic blockade of the D3 receptor increased neurogenesis in the hippocampus of adult mice [22]. Taken together, these studies showed that the DA system plays an important role in adult hippocampus neurogenesis.

2.3. γ-Aminobutyric acid (GABA)

GABA, the major inhibitory neurotransmitter in the adult brain, exerts its roles via two main receptor types, GABA-A and GABA-B [23]. GABAergic signaling modulates the spatially and temporally regulated network activities underling hippocampus-dependent memory [24]. The previous studies have shown that the GABA-A receptor is expressed in NSPCs *in vitro* [25, 26]. In addition to findings that GABA influences postnatal neurogenesis in the SVZ and striatum [27, 28], a role in hippocampal neurogenesis has also been suggested. Deletion of distinct GABA-A receptor subunits, $\gamma 2$ and $\alpha 4$, reduced adult hippocampal neurogenesis [29, 30]. In contrast, pharmacological inhibition of the GABA-B receptor stimulated NSPC proliferation, and genetic deletion of the GABA-B receptor increased NSPC proliferation and also differentiation of neuroblasts *in vivo* [23]. These findings propose that the GABAergic system is an important regulator of adult neurogenesis in the DG, and that different GABA receptor subtypes provide different or opposing effects on neurogenesis and neuronal maturation in the adult hippocampus.

2.4. Acetylcholine (ACh)

ACh is an important transmitter in the basal forebrain cholinergic system, located primarily in the medial septum, nucleus basalis of Meynert, vertical limbs of the diagonal band of Broca, and substantia innominate, which project their fibers to the hippocampus, thalamus, olfactory bulb, and cortical regions (reviewed in [31]). In particular, the septo-hippocampal pathway from the medial septal nucleus and diagonal band to the hippocampus plays a significant role in both learning and in cognitive deficits that are associated with aging and Alzheimer's disease

(AD) [32]. Neurons in the DG and olfactory bulb abundantly express nicotinic acetylcholine receptors (nAChRs) and metabotropic muscarinic acetylcholine receptors [33, 34]. It was shown that cholinergic fibers innervated and synapsed on immature neurons in the DG [35]. Thus, it is possible that cholinergic afferent fibers in the DG contribute to the control of neurogenesis as well as neuronal activity. Previous studies reported that deletion of forebrain cholinergic input using the selective neurotoxic, 192 IgG-saporin, reduced DG neurogenesis, whereas administration of physostigmine, the cholinergic agonist, increased DG neurogenesis in adult and aged rodents [36, 37]. Furthermore, deletion of the β-2 subunit of nAChRs reduced cell proliferation by ~43% in the DG, and was accompanied by a significant decrease in both DG area and granule cell layer length [38]. Similarly, stimulation of α-7nAChRs promoted hippocampal neurogenesis, including neuronal differentiation, maturation, integration, and survival [39, 40]. ACh released in synapses is usually removed through hydrolysis by acetylcholinesterase (AChE) and both pharmacological inhibition of AChE activities and transgenic deletion of AChE increased proliferating cells and the survival of newborn neurons in the DG, while increased AChE levels induced apoptosis [41]. Interestingly, pharmacological activation of muscarinic receptors reversed the deficits in hippocampal neurogenesis following cholinergic denervation [42]. These data suggested that in the cholinergic system, the levels of ACh and its interactions with AChRs are important in controlling adult neurogenesis in the hippocampus.

2.5. Glutamate

Another neurotransmitter associated with hippocampal neurogenesis is glutamate, an important excitatory neurotransmitter. Previous studies indicated that glutamate can regulate adult neurogenesis in the DG [43, 44]. Among the eight metabotropic glutamate receptors (mGluRs), mGluR5 is highly expressed in NSPCs [45, 46]. The mGluR5-induced neurogenesis may contribute to the markedly ameliorated cognitive impairment through stimulating mGluR5 receptors, but not mGluR2/3 [47]. Although the mechanism of these pro-cognitive effects of mGluR5 was not elucidated, mGluR5 activation most likely partially contributed to the increased neurogenesis found in these studies.

3. Hormones

3.1. Ghrelin

Ghrelin, a unique 28-amino acid peptide hormone synthesized primarily in the stomach, has various physiological actions such as stimulating growth hormone release and regulating the function of the gastrointestinal tract [48–51]. Recent studies have shown that the ghrelin receptor mRNA is widely expressed in the brain, including the CA2 and CA3 areas of the hippocampus, as well as in the DG [52–54]. Furthermore, researchers found that exogenous ghrelin passes through the blood-brain barrier and binds to neurons located in areas of the hippocampus [55] where NSPCs expressed ghrelin receptors [56]. Interestingly, hippocampal neurogenesis was shown to be enhanced in adult rodents treated with systemic delivery of ghrelin [57–59]. Furthermore, ghrelin knockout decreased the number of NSPCs in the DG of mice [60]. Of more

significance was the discovery that ghrelin restored impaired hippocampal neurogenesis in an AD animal model, 5× FAD mice [61], indicating that it is a potential candidate for treatment of AD. However, unlike systemic administration that exerted positive neurogenic effects, local intra-hippocampus ghrelin infusion showed no effects on adult neurogenesis, and even impaired spatial memory formation [58]. Although causes for this phenomenon remain unclear, it is proposed that systemic administration of ghrelin is more like the physiological condition; therefore, the effect of ghrelin may be mediated by different mechanisms compared to local administration.

3.2. Thyroid hormone

Thyroid hormone is synthesized by the follicular cells of thyroid gland and is released into blood as the precursor thyroxine (3,30,5,50-tetraiodothyronine; T4), and also as the active form of thyroid hormone (3,30,5-triiodothyronine; T3) [62, 63]. The process of transporting thyroid hormones into the brain is regulated by the transporters, monocarboxylate transporter-8 and transthyretin, among others [64–67]. Reports indicated that thyroid hormone perturbations resulted in decreased hippocampal progenitor proliferation and survival, while the adult hippocampal progenitors exhibited enhancement of proliferation, survival in response to thyroid hormone in adult rat [68–70]. The thyroid hormone receptors (TRs), TRα and TRβ comprise distinct isoforms, TRα1 and TRα2, TRβ1, and TRβ2 [71]. Research has indicated that TRs also influence adult hippocampal neurogenesis. TRα1 receptors are involved in regulating survival and differentiation of post-mitotic progenitors in adult hippocampus [72], while loss of TRβ may contribute to the increased progenitor proliferation and differentiation in adult hippocampus [73]. These data suggested that the thyroid hormone system plays a role in the regulation of adult hippocampal neurogenesis.

3.3. Sex hormones

Several studies have shown that there are differences in hippocampal neurogenesis in adult rodents depending on sex. For example, adult female rodents had higher levels of cell proliferation than males in the DG [74, 75]. These sex differences in hippocampal neurogenesis may be dependent on the natural fluctuations of gonadal hormones.

3.3.1. Androgens

Androgens, the predominant gonadal hormones in males, include testosterone, and rostenedione, and 5a-dihydrotestosterone (DHT). They are primarily produced in the testes Leydig cells and carried elsewhere through the blood system. Androgen receptors (ARs) are expressed throughout the male and female rat brain, including the hippocampus [76–78]. Within the rat hippocampus, ARs are expressed primarily in the pyramidal cell layer of CA1 and stratum lucidum of CA3, but not in the adult DG [78–80]. Several studies have shown that androgens influence DG neurogenesis. Long-term exposure to androgens increased neurogenesis in the DG of adult male rodents [81], whereas removal of testicular hormones resulted in the reduction of newly generated neurons in the DG [80, 82, 83]. Androgenic regulation of neurogenesis in the DG may be associated with the activation of ARs in rodents. Administration of testosterone metabolite DHT with higher affinity for ARs than testosterone, resulted in increased neurogenesis, which was subsequently blocked by the AR antagonist, flutamide. Moreover,

testosterone treatment did not enhance neurogenesis in rats with a mutation in the AR gene [80]. Mahmoud et al. speculated that androgens binding with ARs in the CA3 region may induce retrograde signaling of survival factors from CA3 and promote neurogenesis in the adult DG [84].

3.3.2. Estrogen

Estrogen is secreted primarily by follicular cells of the ovary (but also from the testis, placenta, and adrenal gland), and promotes the development of primary and secondary sexual organs in women and maintains normal sexual and reproductive functions. Three forms of estrogens exist, estradiol, estrone, and estriol, with estradiol being the most abundant. Reports have confirmed that estrogen, especially estradiol, regulates adult neurogenesis in the hippocampus [81, 85]. Estradiol carries out its physiological effects by binding to the classical estrogen receptors (ER), ERα and ERβ, and the G protein-coupled estrogen receptor (GPER) [86–88]. The fact that ERα and ERβ receptors are both expressed in the hippocampus [89–91] indicates that hippocampus is the important target of estrogens. Treatment with the ERα- or ERβ-selective agonists resulted in an increase of cell proliferation in the hippocampus of adult ovariectomized female rats, while it was shown that estrogen receptor antagonists reversed estradiol-induced increase in cell proliferation [92, 93]. Interestingly, treatment with a GPER agonist G1 and antagonist G15, respectively, decreased and increased cell proliferation in adult ovariectomized rats [94], indicating the estradiol independent role of GPER on hippocampal neurogenesis. Taken together, these studies suggested that the estrogen system participates in the process of neurogenesis in the adult hippocampus.

4. Trophic factors

4.1. BDNF

It has been reported that BDNF modulates neuronal development in the hippocampus and participates in the maturation of GABAergic inhibitory networks in the cortex [95–97]. In adult macaque brains, the highest levels of BDNF were shown to be in the hippocampus [98]. Further studies found that neurogenesis was attenuated by BDNF knockdown in the adult DG [99], but was increased in response to exogenous BDNF injection [100]. Dendritic growth in adult hippocampal neurons was also decreased by BDNF deletion and increased by BDNF overexpression [101]. Increases in proliferation were reported in heterozygous BDNF knockout mice [102, 103]. Specifically, it was shown that proliferation of SGZ NSPCs increased in mice with BDNF conditional knockout in hippocampal neurons [104]. These conflicting results have not yet been fully reconciled, although it was suggested that developmental and/or behavioral differences between the strains used in these studies may have contributed to the divergent findings [105].

4.2. Neurotrophic growth factor (NGF)

Early studies confirmed that NGF is crucial for neuronal survival and growth [106], especially for cholinergic neurons and neurotransmission in both CNS and peripheral nervous system [107, 108]. Recent reports indicated that continuous NGF infusion promotes proliferation and synaptogenesis in the hippocampus and enhanced survival of new neurons in the DG granule

cell layer of young adult rats [109, 110]. Neurogenic conditions in the hippocampus may be enhanced by the synergistic interactions of NGF and its receptor, TrkA, as well as by NGF-mediated cholinergic regulation. Finally, intracerebroventricular NGF infusion rescued hippocampal neurogenesis deficiencies in a transgenic mouse model of Huntington's disease [111], suggesting that NGF may be a valuable therapy in treatment of this disease.

4.3. Vascular endothelial growth factor (VEGF)

VEGF is an angiogenesis factor with neurotrophic and neuroprotective effects [112–115]. Additionally, it is increasingly clear that VEGF plays a crucial role in neurogenesis in the adult hippocampus. Jin et al. found that intracerebroventricular administration of VEGF into adult rat brains increased proliferation and neuronal differentiation in the SVZ and SGZ [114]. In addition, adult hippocampal NSPCs are known to secrete large quantities of VEGF, which functionally maintains the neurogenic niche [116]. Specific loss of VEGF in NSPC resulted in impairment of stem cell maintenance although VEGF produced from other cell types was still present [116]. Evidence from knockout mice indicated that hippocampal neurogenesis was impaired in VEGF B-KO mice, whereas intraventricular administration of VEGF B restored neurogenesis to control levels [117]. Moreover, delivery of VEGF via VEGF-secreted cells in microcapsules or VEGF-loaded poly (lactic co-glycolic acid) nanospheres increased the proliferation of neuronal progenitors [118, 119]. These findings suggested that VEGF is involved in neurogenesis in the adult hippocampus. Indeed, increasing evidence has shown that VEGF acts as a molecular mediator for adult hippocampal neurogenesis and is upregulated by antidepressant treatments including drugs, electroconvulsive seizure [120, 121], exercise, and enriched environments [122, 123], indicating that VEGF is a promising target for treatment of neural disorders.

4.4. Fibroblast growth factor-2 (FGF-2)

In the adult CNS, FGF-2 and its receptors (FGFR) are expressed by astrocytes and neurons located in the SVZ and SGZ, although their expression is also found in many other brain regions [124, 125]. After birth, FGF-2 is concentrated primarily in the hippocampal subfields CA1-3, and in neurons of the medial septum and the vertical limb of the diagonal band nuclei. The adult pattern of neuronal FGF-2 is restricted to particular populations, such as those in the cingulate cortex and hippocampus. Within the mature hippocampus, the CA2 region is the primary area of neuron-derived FGF-2 expression [126], suggesting that FGF-2 may play a role in the development and function of the adult hippocampus. In particular, use of FGF-2 knockout mice showed that loss of FGF-2 caused decreases in adult hippocampal neurogenesis and that these defects could not be rescued by exogenous FGF-2 [127]. Yoshimura et al. reported that hippocampal neurogenesis increased in normal adult mice after brain injury, but this phenomenon did not appear in FGF-2 knockout adult mice [128]. These results indicated that endogenous FGF-2 is necessary and sufficient to stimulate NSPC proliferation and differentiation in the adult hippocampus. In the adult rat CNS, FGF-2 receptors, FGFR1 and FGFR4, were shown to be predominantly expressed on neurons, whereas FGFR2 and FGFR3 were more highly expressed on oligodendrocytes and astrocytes, respectively [129, 130]. Genetic deletion of FGFR1 resulted in reduced proliferation of hippocampal NSPCs and reduced hippocampal volume during embryonic and postnatal development [131]. These studies suggested that the functions of the FGF-2/FGFR system may promote neurogenesis in the adult hippocampus.

5. Signaling pathways

5.1. Wingless (Wnt)

The Wnt pathway is one of the principal developmental pathways and is involved in body axis specification, morphogenesis, and stem cell proliferation, and differentiation [132]. To date, 19 Wnt proteins have been confirmed in mammals. Studies by Lie et al. showed that Wnt signaling components and their respective receptors have been shown to be expressed in the adult hippocampus. When Wnt3 was overexpressed, neurogenesis was increased, while blockade of Wnt signaling was reduced [133]. Evidence also suggested that β-catenin plays an important role in the dendritic development of adult hippocampal neurons [134]. These data suggested that Wnt signaling may be a regulator of adult hippocampal neurogenesis.

5.2. Notch

Studies have shown that Notch molecules (four in mammals) and their associated signaling pathway are crucial for the maintenance, proliferation, and differentiation of stem cells [135]. In adult mice, overexpression of Notch1 increases hippocampal cell proliferation and maintenance of GFAP-expressing NSPCs [136]. Abrogation of Notch signaling leads to a decrease in cell proliferation and a shift in differentiation of newly born cells toward a neuronal lineage [137]. This evidence suggested that, in particular, Notch1 signaling is required to maintain a reservoir of undifferentiated cells and ensure continuity of adult hippocampal neurogenesis. In addition, Notch1 signaling modulates the dendritic morphology of newborn granule cells by increasing dendritic arborization [137]. Furthermore, the expression of Notch1 signaling components (including Jag1, NICD, Hes1, and Hes5) are increased in parallel with hippocampal neurogenesis in adult rats after chronic fluoxetine (antidepressant) administration [138]. These findings suggested that Notch1 signaling is involved in adult hippocampal neurogenesis.

5.3. Bone morphogenetic protein (BMP)

BMP, an extracellular signaling molecule, regulates cell proliferation and fate commitment throughout development and in the postnatal SVZ and SGZ neurogenic niches [139, 140]. It has been shown that BMP signaling inhibits neurogenesis and promotes NSPC glial differentiation in the adult SVZ [140]. However, in the adult hippocampus, BMP signaling inhibits NSPC proliferation and promotes their maintenance in an undifferentiated and quiescent state [141]. Specifically, Gobeske et al. found that exercise reduced levels of BMP signaling in hippocampus, and that blockade of BMP signaling reproduced the effects of exercise on learning and neurogenesis in adult mice [142]. These studies showed that BMP decreases adult neurogenesis and that inhibition of BMP can partially rescue neurogenesis in the adult hippocampus.

5.4. Sonic hedgehog (Shh)

Shh is crucial for the expansion and establishment of postnatal hippocampal progenitors [143]. The Shh receptors, patched (Ptc) and smoothened (Smo), were detected in the DG, including

the neurogenic niche of the SGZ and NSPCs derived from adult hippocampus [144, 145]. In adult rats, overexpression of Shh in the DG increased cell proliferation and survival [145]. However, inhibition of Shh signaling with the inhibitor, cyclopamine, reduced cell proliferation [145, 146]. In addition, the loss of Shh signaling results in SVZ cells undergoing programmed cell death [147]. These studies emphasized the importance of the Shh signaling pathway in adult neurogenesis. Furthermore, in electroconvulsive seizure-mediated adult rat hippocampal neurogenesis, the Shh signaling cascade was found to be activated [146].

5.5. PI3K-Akt

The PI3K-Akt signaling pathway is a downstream pathway of neurotrophic and growth factor receptors, as well as monoamine receptors [148]. It has been potentially implicated in a number of different functions and is especially associated with cell survival through inhibition of the activation of proapoptotic proteins and transcription factors [149]. It was shown that Akt1 and Akt2 (two members of the Akt protein kinase family) knockout mice had lower levels of hippocampal cell proliferation compared to wild-type animals, but only Akt2 knockout mice had impaired survival of adult born hippocampal progenitors [150]. Reports also showed that PI3K/Akt participated in the enhancement of adult hippocampal neurogenesis via activation by other factors [151], VEGF [152] and intermittent hypoxia after ischemia [153].

5.6. Reelin

Reelin is an extracellular matrix glycoprotein and aides in neural migration and brain development [154–156]. It is preferentially secreted by GABAergic interneurons located in the cortex and hippocampus of the mammalian brain [157]. Gain and loss of function studies indicated that the reelin pathway regulated adult hippocampal neurogenesis and dendritic maturation orientation [158]. In addition, using retroviral tracing and 3D-EM, it was shown that the reelin/Dab1 pathway controlled adult granular cell spinogenesis and synaptogenesis [159]. Recent studies suggested that changes in reelin expression contribute to the pathogenesis of several neurological diseases that display abnormalities in granule cell neurogenesis and organization [160–162]. These studies indicated that reelin signaling participates not only in the development of the embryonic brain, but also in multiple processes of adult hippocampal neurogenesis, and enhanced cognitive ability [163].

6. Physiological and pathological factors

6.1. Exercise

Exercise exerts many effects on brain functions, including enhancement of adult hippocampal neurogenesis [164]. Increased blood flow due to exercises most likely facilitates delivery of trophic factors to the neurogenic niche. Furthermore, running has been shown to influence all aspects of hippocampal neurogenesis, including cell proliferation, survival, differentiation, and recruitment in the DG [165–167]. Studies suggested that exercise increases peripheral and central levels of BDNF and FGF-2 [168–171], which were both reported to be involved in neurogenesis

in the developing and adult brain [170, 172]. Peripheral VEGF produced by skeletal muscles after exercise may also play an important role in exercise-induced adult hippocampal neurogenesis, because the increased number of newborn neuronal precursor cells in the hippocampus were not present in adult conditional skeletal myofiber-specific VEGF gene-ablated mice [173, 174], suggesting that VEGF expressed by skeletal myofibers may directly or indirectly regulate hippocampal neurogenesis, as well as blood flow.

6.2. Enriched environment (EE)

Running and exposure to an enriched environment (EE) are two of the most common ways to increase adult neurogenesis, which provide sensory, social, and motor stimulation. Researchers discovered that there was no effect on cell proliferation in mice exposed to EE, but these mice showed significantly higher numbers of total granule neurons in hippocampus compared with controls [175]. In order to determine the long-term effects of EE, 10-month-old mice were housed in an EE for 10 months (roughly half of their life) [176] and consistent with the above results, neuronal differentiation of newborn cells significantly increased in these mice, but not proliferating cells. More recently, several reports suggested that the notable EE-induced increase in adult neurogenesis was attributed to physical activity associated with exercise [177, 178].

6.3. Aging

Aging is a natural process associated with cognitive decline and functional and social impairments, and is also very closely associated with changes to hippocampal formation. Indeed, the number of newborn neurons in the SGZ declines with age [179–181]. During the aging process, reduction of hippocampal volume [182], degeneration of hippocampal vessels, [183] and decrease in hippocampal blood flow [184] may all contribute to the reduced neurogenesis seen in the aged hippocampus. In addition, increase in microglial activation with age was observed in the hippocampus of both rats and humans [185, 186]. This microglia-mediated neuroinflammation and subsequent neuronal damage also likely contribute to decline neurogenesis with age. Furthermore, several neurotrophic factors such as FGF-2 [187], BDNF [188, 189], VEGF [187, 190], and NGF [191] exhibit considerable decline with age, all of which play an important role in hippocampal neurogenesis (as reviewed above). Therefore, an overall reduction of these factors may also contribute to deficits in hippocampal neurogenesis with age. Interestingly, although hippocampal neurogenesis declines with age, it persists in certain pathological conditions. Darsalia et al. reported that hippocampal neurogenesis was observed in aged rats with stroke, but maturation and survival of these newborn neurons in the DG were approximately one-third less compared to the young DG [192]. As the decline of hippocampal neurogenesis with age cannot be explained by only one factor, there is likely a complex regulation of different factors associated with this decline.

6.4. Stress

Stress is a threat-induced response associated with the homeostasis of an organism and subsequent physiological and behavioral responses. Individuals experiencing this phenomenon exhibit differential responses to various stress-inducing factors (stressors). Increasing evidence

suggested that exposure to stress at different life stages leads to distinct alterations in hippocampal neurogenesis. Studies have shown that chronic and acute stressors reduce cell proliferation, survival, and neuronal differentiation in the adult DG [193–196]. Yet, the correlation between stress and reduced neurogenesis is more complex. Changes induced by prenatal stress may depend upon genetic background [197, 198]. Susceptibility and resilience to stress highlight that gene-environment interactions may modulate adult stress-altered hippocampal neurogenesis. Using animals with different genetic backgrounds, it was shown that they could be segregated into subgroups of stress-susceptible animals that showed depression-like behaviors, stress behaviors, and stress-resilient behaviors that showed no or little response to stressors [199]. Interestingly, this difference in the stress response has been linked to hippocampal volume. Hippocampal volume increased in resilient animals after stress, while susceptible animals exhibited a decrease in volume [200]. Whether adult hippocampal neurogenesis occurred specifically in animals that were more resilient or more susceptible to stress remains unclear, but susceptible behaviors were reversed by increased hippocampal neurogenesis [201, 202]. It will be important to carefully examine how adult hippocampal neurogenesis contributes to stress resilience or susceptibility and to the process of developing effective treatments for stress-related psychiatric disorders according to individual genetic backgrounds.

6.5. Ischemia

Ischemia has been noted to produce enhanced neurogenesis in neural proliferative regions of the adult rodent brain. The first description, in 1998, showed that transient global ischemia in adult gerbils increased neurogenesis in the DG [203]. Subsequent findings in adult mouse and rat also proved that transient focal or global ischemia enhanced hippocampal neurogenesis [204–207]. Tsai et al. indicated that post-ischemia intermittent hypoxia in adult rats induced hippocampal neurogenesis and synaptic alterations, and actually alleviated long-term memory impairment, which may be contributed by the increased neurogenesis [152]. All of these studies suggested that neurogenesis may be a compensatory, adaptive mechanism mediating functional recovery after ischemia in adult mammals.

6.6. Traumatic brain injury (TBI)

As the hippocampus is particularly vulnerable to brain trauma, TBI can induce immature neuronal death in the DG and result in learning and memory dysfunctions [208–210]. However, many studies have confirmed that NSPC proliferation is actually increased after TBI in the adult hippocampus of both rodents and humans [211–213], indicating an innate repair may be occurring in the hippocampus [212–215]. As expected, levels of neurogenesis after TBI correlated with injury severity [215]. This innate repair cannot always completely compensate for cell loss, resulting in permanent functional deficits in numerous TBI survivors [216]. Further research is needed to fully understand the mechanisms involved in TBI-related hippocampal neurogenesis.

6.7. Seizures

Seizures are characterized as the periodic and unpredictable occurrences of epilepsy. Studies have shown that acute seizures abnormally increased the amount of hippocampal neurogenesis

and induced aberrant migration of newly born neurons into the DG hilus and molecular layer [217–220]. Furthermore, recurrent spontaneous seizures also led to dramatically reduced neurogenesis [219, 221], which is concurrent with learning and memory impairments and depression in epilepsy patients. However, a modest increase in neurogenesis was observed 2 months post status epilepticus in a lithium-pilocarpine model of epilepsy using postnatal day 20 rats [222]. These data suggested that seizures can not only disrupt both the structure and the function of the hippocampus, but also increase neurogenesis in the hippocampus. These seemingly contradictory results may be related to the type and severity of epileptic seizures.

7. Conclusions

Differentiation of static radial glial cells (RGC) to mature granular cells occurs in a series of morphologically and genetically identifiable stages, including the slowly dividing RGC stage, the rapidly proliferating NSPC stage, commitment to a neuronal fate, immature to mature neuronal progression, and finally, survival and projection of axons to target cells. Findings also indicated that the regulatory effects of different factors are defined at different steps in the overall differentiation process. For example, the transmitter serotonin exerts its effects at the proliferation stage, while GABA and DA are known to induce neuronal commitment, and glutamate and ACh play positive roles in the survival of newborn neurons. With regard to extrinsic factors, exercise may enhance proliferation of NSPCs, although this process is likely inhibited by stress. Learning and EE induce neuronal differentiation and survival. Taken together, a more complete understanding of the intrinsic and extrinsic factors regulating/directing different stages of adult hippocampal neurogenesis will aide in the development of exogenous and endogenous NSPCs as a therapeutic tool in the treatment of neural disorders. In addition, these findings have increased the likelihood of using hippocampal neurogenesis in the treatment of adult mammalian neurological diseases. Although the exact mechanisms involved in adult neurogenesis have not been identified, emerging technology will likely advance our understanding of the processes involved.

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Abbreviations

5-HT	serotonin or 5-hydroxytryptamine
ACh	acetylcholine

AChE	acetylcholinesterase
AD	Alzheimer's disease
BDNF	brain derived neurotrophic factor
BMP	bone morphogenetic protein
CA	cornu ammonis
CNS	central nervous system
DA	dopamine
DG	dentate gyrus
DHT	dihydrotestosterone
ER	estrogen receptor
FGF-2	fibroblast growth factor-2
GABA	γ-aminobutyric acid
GFAP	glial fibrillary acidic protein
GPER	G protein-coupled estrogen receptor
NGF	neurotrophic growth factors
NSPC	neural stem/progenitor cell
SGZ	subgranular zone
Shh	sonic hedgehog
SVZ	subventricular zone
TBI	traumatic brain injury
VEGF	vascular endothelial growth factor
VTA	ventral tegmental area
Wnt	wingless

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