We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 2

Factors Regulating Neurogenesis in the Adult Dentate Gyrus

Lei Zhang and Xinhua Zhang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75631

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,

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

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.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (31171038), Jiangsu Natural Science Foundation (BK2011385), Jiangsu “333” program funding (BRA2016450), and a project funded by the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions.

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

Author details

Lei Zhang and Xinhua Zhang*

*Address all correspondence to: zhangxinhua@ntu.edu.cn

Department of Anatomy, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China

References

[1] Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Bostrom E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisen J. Dynamics of hippocampal neurogenesis in adult humans. Cell. 2013;**153**(6):1219-1227. DOI: 10.1016/j.cell.2013.05.002

[2] Gaspar P, Cases O, Maroteaux L. The developmental role of serotonin: News from mouse molecular genetics. Nature Reviews. Neuroscience. 2003;**4**:1002-1012, 1012. DOI: 10.1038/nrn1256

[3] Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nature Neuroscience. 2007;**10**(9):1110-1115. DOI: 10.1038/nn1969

[4] Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. The Journal of Neuroscience. 2008;**28**(6):1374-1384. DOI: 10.1523/JNEUROSCI.3632-07.2008

[5] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. The Journal of Neuroscience. 2000;**20**(24):9104-9110

[6] Couillard-Despres S, Wuertinger C, Kandasamy M, Caioni M, Stadler K, Aigner R, Bogdahn U, Aigner L. Ageing abolishes the effects of fluoxetine on neurogenesis. Molecular Psychiatry. 2009;**14**(9):856-864. DOI: 10.1038/mp.2008.147

[7] Song NN, Huang Y, Yu X, Lang B, Ding YQ, Zhang L. Divergent roles of central serotonin in adult hippocampal neurogenesis. Frontiers in Cellular Neuroscience. 2017;**11**:185. DOI: 10.3389/fncel.2017.00185

[8] Klempin F, Babu H, De Pietri Tonelli D, Alarcon E, Fabel K, Kempermann G. Oppositional effects of serotonin receptors 5-HT1a, 2, and 2c in the regulation of adult hippocampal neurogenesis. Frontiers in Molecular Neuroscience. 2010;**3**:1-11. DOI: 10.3389/fnmol.2010.00014

[9] Banasr M, Hery M, Printemps R, Daszuta A. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology. 2004;**29**(3):450-460. DOI: 10.1038/sj.npp.1300320

[10] Arnold SA, Hagg T. Serotonin 1A receptor agonist increases species- and region-selective adult CNS proliferation, but not through CNTF. Neuropharmacology. 2012;**63**(7):1238-1247. DOI: 10.1016/j.neuropharm.2012.07.047

[11] Alenina N, Klempin F. The role of serotonin in adult hippocampal neurogenesis. Behavioural Brain Research. 2015;**277**:49-57. DOI: 10.1016/j.bbr.2014.07.038

[12] Segi-Nishida E. The effect of serotonin-targeting antidepressants on neurogenesis and neuronal maturation of the hippocampus mediated via 5-HT1A and 5-HT4 receptors. Frontiers in Cellular Neuroscience. 2017;**11**:142. DOI: 10.3389/fncel.2017.00142

[13] Radley JJ, Jacobs BL. 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Research. 2002;**955**(1-2):264-267

[14] Zhang J, Cai CY, Wu HY, Zhu LJ, Luo CX, Zhu DY. CREB-mediated synaptogenesis and neurogenesis is crucial for the role of 5-HT1a receptors in modulating anxiety behaviors. Scientific Reports. 2016;**6**:29551. DOI: 10.1038/srep29551

[15] Lucas G, Rymar VV, Du J, Mnie-Filali O, Bisgaard C, Manta S, Lambas-Senas L, Wiborg O, Haddjeri N, Pineyro G, Sadikot AF, Debonnel G. Serotonin(4) (5-HT(4)) receptor agonists are putative antidepressants with a rapid onset of action. Neuron. 2007;**55**(5):712-725. DOI: 10.1016/j.neuron.2007.07.041

[16] Pascual-Brazo J, Castro E, Diaz A, Valdizan EM, Pilar-Cuellar F, Vidal R, Treceno B, Pazos A. Modulation of neuroplasticity pathways and antidepressant-like behavioural responses following the short-term (3 and 7 days) administration of the 5-HT(4) receptor agonist RS67333. The International Journal of Neuropsychopharmacology. 2012;**15**(5):631-643. DOI: 10.1017/S1461145711000782

[17] Foltran RB, Diaz SL. BDNF isoforms: A round trip ticket between neurogenesis and serotonin? Journal of Neurochemistry. 2016;**138**(2):204-221. DOI: 10.1111/jnc.13658

[18] Baker SA, Baker KA, Hagg T. Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone. The European Journal of Neuroscience. 2004;**20**(2):575-579. DOI: 10.1111/j.1460-9568.2004.03486.x

[19] Gasbarri A, Sulli A, Packard MG. The dopaminergic mesencephalic projections to the hippocampal formation in the rat. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 1997;**21**(1):1-22

[20] Hoglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nature Neuroscience. 2004;**7**(7):726-735. DOI: 10.1038/nn1265

[21] Salvi R, Steigleder T, Schlachetzki JC, Waldmann E, Schwab S, Winner B, Winkler J, Kohl Z. Distinct effects of chronic dopaminergic stimulation on hippocampal neurogenesis and striatal doublecortin expression in adult mice. Frontiers in Neuroscience. 2016;**10**:77. DOI: 10.3389/fnins.2016.00077

[22] Egeland M, Zhang X, Millan MJ, Mocaer E, Svenningsson P. Pharmacological or genetic blockade of the dopamine D3 receptor increases cell proliferation in the hippocampus of adult mice. Journal of Neurochemistry. 2012;**123**(5):811-823. DOI: 10.1111/jnc.12011

[23] Giachino C, Barz M, Tchorz JS, Tome M, Gassmann M, Bischofberger J, Bettler B, Taylor V. GABA suppresses neurogenesis in the adult hippocampus through GABAB receptors. Development. 2014;**141**(1):83-90. DOI: 10.1242/dev.102608

[24] Paulsen O, Moser EI. A model of hippocampal memory encoding and retrieval: GABAergic control of synaptic plasticity. Trends in Neurosciences. 1998;**21**(7):273-278

[25] Farrant M, Nusser Z. Variations on an inhibitory theme: Phasic and tonic activation of GABA(A) receptors. Nature Reviews. Neuroscience. 2005;**6**(3):215-229. DOI: 10.1038/nrn1625

[26] Ge S, Pradhan DA, Ming GL, Song H. GABA sets the tempo for activity-dependent adult neurogenesis. Trends in Neurosciences. 2007;**30**(1):1-8. DOI: 10.1016/j.tins.2006.11.001

[27] Liu X, Wang Q, Haydar TF, Bordey A. Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors. Nature Neuroscience. 2005;**8**(9):1179-1187. DOI: 10.1038/nn1522

[28] Nguyen L, Malgrange B, Breuskin I, Bettendorff L, Moonen G, Belachew S, Rigo JM. Autocrine/paracrine activation of the GABA(A) receptor inhibits the proliferation of neurogenic polysialylated neural cell adhesion molecule-positive (PSA-NCAM+) precursor cells from postnatal striatum. The Journal of Neuroscience. 2003;**23**(8):3278-3294

[29] Duveau V, Laustela S, Barth L, Gianolini F, Vogt KE, Keist R, Chandra D, Homanics GE, Rudolph U, Fritschy JM. Spatiotemporal specificity of GABAA receptor-mediated regulation of adult hippocampal neurogenesis. The European Journal of Neuroscience. 2011;**34**(3):362-373. DOI: 10.1111/j.1460-9568.2011.07782.x

[30] Earnheart JC, Schweizer C, Crestani F, Iwasato T, Itohara S, Mohler H, Luscher B. GABAergic control of adult hippocampal neurogenesis in relation to behavior indicative of trait anxiety and depression states. The Journal of Neuroscience. 2007;**27**(14):3845-3854. DOI: 10.1523/JNEUROSCI.3609-06.2007

[31] Paul S, Jeon WK, Bizon JL, Han JS. Interaction of basal forebrain cholinergic neurons with the glucocorticoid system in stress regulation and cognitive impairment. Frontiers in Aging Neuroscience. 2015;**7**:43. DOI: 10.3389/fnagi.2015.00043

[32] Winkler J, Thal LJ, Gage FH, Fisher LJ. Cholinergic strategies for Alzheimer's disease. Journal of Molecular Medicine (Berlin, Germany). 1998;**76**(8):555-567

[33] Quik M, Polonskaya Y, Gillespie A, Jakowec M, Lloyd GK, Langston JW. Localization of nicotinic receptor subunit mRNAs in monkey brain by in situ hybridization. The Journal of Comparative Neurology. 2000;**425**(1):58-69

[34] Levey AI, Edmunds SM, Koliatsos V, Wiley RG, Heilman CJ. Expression of m1-m4 muscarinic acetylcholine receptor proteins in rat hippocampus and regulation by cholinergic innervation. The Journal of Neuroscience. 1995;**15**(5 Pt 2):4077-4092

[35] Kaneko N, Okano H, Sawamoto K. Role of the cholinergic system in regulating survival of newborn neurons in the adult mouse dentate gyrus and olfactory bulb. Genes to Cells. 2006;**11**(10):1145-1159. DOI: 10.1111/j.1365-2443.2006.01010.x

[36] Mohapel P, Leanza G, Kokaia M, Lindvall O. Forebrain acetylcholine regulates adult hippocampal neurogenesis and learning. Neurobiology of Aging. 2005;**26**(6):939-946. DOI: 10.1016/j.neurobiolaging.2004.07.015

[37] Itou Y, Nochi R, Kuribayashi H, Saito Y, Hisatsune T. Cholinergic activation of hippocampal neural stem cells in aged dentate gyrus. Hippocampus. 2011;**21**(4):446-459. DOI: 10.1002/hipo.20761

[38] Harrist A, Beech RD, King SL, Zanardi A, Cleary MA, Caldarone BJ, Eisch A, Zoli M, Picciotto MR. Alteration of hippocampal cell proliferation in mice lacking the beta 2

subunit of the neuronal nicotinic acetylcholine receptor. Synapse. 2004;**54**(4):200-206. DOI: 10.1002/syn.20081

[39] Cui W, Cui GZ, Li W, Zhang Z, Hu S, Mak S, Zhang H, Carlier PR, Choi CL, Wong YT, Lee SM, Han Y. Bis(12)-hupyridone, a novel multifunctional dimer, promotes neuronal differentiation more potently than its monomeric natural analog huperzine A possibly through alpha7 nAChR. Brain Research. 2011;**1401**:10-17. DOI: 10.1016/j.brainres.2011.05.042

[40] Campbell NR, Fernandes CC, Halff AW, Berg DK. Endogenous signaling through alpha7-containing nicotinic receptors promotes maturation and integration of adult-born neurons in the hippocampus. The Journal of Neuroscience. 2010;**30**(26):8734-8744. DOI: 10.1523/JNEUROSCI.0931-10.2010

[41] Cohen JE, Zimmerman G, Melamed-Book N, Friedman A, Dori A, Soreq H. Transgenic inactivation of acetylcholinesterase impairs homeostasis in mouse hippocampal granule cells. Hippocampus. 2008;**18**(2):182-192. DOI: 10.1002/hipo.20381

[42] Van Kampen JM, Eckman CB. Agonist-induced restoration of hippocampal neurogenesis and cognitive improvement in a model of cholinergic denervation. Neuropharmacology. 2010;**58**(6):921-929. DOI: 10.1016/j.neuropharm.2009.12.005

[43] Ge S, Yang CH, Hsu KS, Ming GL, Song H. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron. 2007;**54**(4):559-566. DOI: 10.1016/j.neuron.2007.05.002

[44] Laplagne DA, Esposito MS, Piatti VC, Morgenstern NA, Zhao C, van Praag H, Gage FH, Schinder AF. Functional convergence of neurons generated in the developing and adult hippocampus. PLoS Biology. 2006;**4**(12):e409. DOI: 10.1371/journal.pbio.0040409

[45] Di Giorgi Gerevini VD, Caruso A, Cappuccio I, Ricci Vitiani L, Romeo S, Della Rocca C, Gradini R, Melchiorri D, Nicoletti F. The mGlu5 metabotropic glutamate receptor is expressed in zones of active neurogenesis of the embryonic and postnatal brain. Brain Research. Developmental Brain Research. 2004;**150**(1):17-22. DOI: 10.1016/j.devbrainres.2004.02.003

[46] Melchiorri D, Cappuccio I, Ciceroni C, Spinsanti P, Mosillo P, Sarichelou I, Sale P, Nicoletti F. Metabotropic glutamate receptors in stem/progenitor cells. Neuropharmacology. 2007;**53**(4):473-480. DOI: 10.1016/j.neuropharm.2007.05.031

[47] Vales K, Svoboda J, Benkovicova K, Bubenikova-Valesova V, Stuchlik A. The difference in effect of mGlu2/3 and mGlu5 receptor agonists on cognitive impairment induced by MK-801. European Journal of Pharmacology. 2010;**639**(1-3):91-98. DOI: 10.1016/j.ejphar.2009.11.067

[48] Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology. 2000;**141**(11):4255-4261. DOI: 10.1210/endo.141.11.7757

[49] Kojima M, Kangawa K. Ghrelin: Structure and function. Physiological Reviews. 2005;**85**(2):495-522. DOI: 10.1152/physrev.00012.2004

[50] van der Lely AJ, Tschop M, Heiman ML, Ghigo E. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocrine Reviews. 2004;**25**(3):426-457. DOI: 10.1210/er.2002-0029

[51] Ghigo E, Broglio F, Arvat E, Maccario M, Papotti M, Muccioli G. Ghrelin: More than a natural GH secretagogue and/or an orexigenic factor. Clinical Endocrinology. 2005;**62**(1):1-17. DOI: 10.1111/j.1365-2265.2004.02160.x

[52] Furness JB, Hunne B, Matsuda N, Yin L, Russo D, Kato I, Fujimiya M, Patterson M, McLeod J, Andrews ZB, Bron R. Investigation of the presence of ghrelin in the central nervous system of the rat and mouse. Neuroscience. 2011;**193**:1-9. DOI: 10.1016/j.neuroscience.2011.07.063

[53] Mani BK, Walker AK, Lopez Soto EJ, Raingo J, Lee CE, Perello M, Andrews ZB, Zigman JM. Neuroanatomical characterization of a growth hormone secretagogue receptor-green fluorescent protein reporter mouse. The Journal of Comparative Neurology. 2014;**522**(16):3644-3666. DOI: 10.1002/cne.23627

[54] Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK. Expression of ghrelin receptor mRNA in the rat and the mouse brain. The Journal of Comparative Neurology. 2006;**494**(3):528-548. DOI: 10.1002/cne.20823

[55] Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, Gaskin FS, Nonaka N, Jaeger LB, Banks WA, Morley JE, Pinto S, Sherwin RS, Xu L, Yamada KA, Sleeman MW, Tschop MH, Horvath TL. Ghrelin controls hippocampal spine synapse density and memory performance. Nature Neuroscience. 2006;**9**(3):381-388. DOI: 10.1038/nn1656

[56] Hafkenscheid A. Psychometric evaluation of a standardized and expanded Brief Psychiatric Rating Scale. Acta Psychiatrica Scandinavica. 1991;**84**(3):294-300

[57] Moon M, Kim S, Hwang L, Park S. Ghrelin regulates hippocampal neurogenesis in adult mice. Endocrine Journal. 2009;**56**(3):525-531

[58] Zhao Z, Liu H, Xiao K, Yu M, Cui L, Zhu Q, Zhao R, Li GD, Zhou Y. Ghrelin administration enhances neurogenesis but impairs spatial learning and memory in adult mice. Neuroscience. 2014;**257**:175-185. DOI: 10.1016/j.neuroscience.2013.10.063

[59] Kent BA, Beynon AL, Hornsby AK, Bekinschtein P, Bussey TJ, Davies JS, Saksida LM. The orexigenic hormone acyl-ghrelin increases adult hippocampal neurogenesis and enhances pattern separation. Psychoneuroendocrinology. 2015;**51**:431-439. DOI: 10.1016/j.psyneuen.2014.10.015

[60] Li E, Chung H, Kim Y, Kim DH, Ryu JH, Sato T, Kojima M, Park S. Ghrelin directly stimulates adult hippocampal neurogenesis: Implications for learning and memory. Endocrine Journal. 2013;**60**(6):781-789

[61] Moon M, Cha MY, Mook-Jung I. Impaired hippocampal neurogenesis and its enhancement with ghrelin in 5XFAD mice. Journal of Alzheimer's Disease. 2014;**41**(1):233-241. DOI: 10.3233/JAD-132417

[62] Palha JA. Transthyretin as a thyroid hormone carrier: Function revisited. Clinical Chemistry and Laboratory Medicine. 2002;**40**(12):1292-1300. DOI: 10.1515/CCLM.2002.223

[63] Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. Journal of Neuroendocrinology. 2008;**20**(6):784-794. DOI: 10.1111/j.1365-2826.2008.01733.x

[64] Tohyama K, Kusuhara H, Sugiyama Y. Involvement of multispecific organic anion transporter, Oatp14 (Slc21a14), in the transport of thyroxine across the blood-brain barrier. Endocrinology. 2004;**145**(9):4384-4391. DOI: 10.1210/en.2004-0058

[65] Jansen J, Friesema EC, Milici C, Visser TJ. Thyroid hormone transporters in health and disease. Thyroid. 2005;**15**(8):757-768. DOI: 10.1089/thy.2005.15.757

[66] Schweizer U, Kohrle J. Function of thyroid hormone transporters in the central nervous system. Biochimica et Biophysica Acta. 2013;**1830**(7):3965-3973. DOI: 10.1016/j.bbagen.2012.07.015

[67] Wirth EK, Schweizer U, Kohrle J. Transport of thyroid hormone in brain. Frontiers in Endocrinology (Lausanne). 2014;**5**:98. DOI: 10.3389/fendo.2014.00098

[68] Desouza LA, Ladiwala U, Daniel SM, Agashe S, Vaidya RA, Vaidya VA. Thyroid hormone regulates hippocampal neurogenesis in the adult rat brain. Molecular and Cellular Neurosciences. 2005;**29**(3):414-426. DOI: 10.1016/j.mcn.2005.03.010

[69] Ambrogini P, Cuppini R, Ferri P, Mancini C, Ciaroni S, Voci A, Gerdoni E, Gallo G. Thyroid hormones affect neurogenesis in the dentate gyrus of adult rat. Neuroendocrinology. 2005;**81**(4):244-253. DOI: 10.1159/000087648

[70] Montero-Pedrazuela A, Venero C, Lavado-Autric R, Fernandez-Lamo I, Garcia-Verdugo JM, Bernal J, Guadano-Ferraz A. Modulation of adult hippocampal neurogenesis by thyroid hormones: Implications in depressive-like behavior. Molecular Psychiatry. 2006;**11**(4):361-371. DOI: 10.1038/sj.mp.4001802

[71] Yen PM. Physiological and molecular basis of thyroid hormone action. Physiological Reviews. 2001;**81**(3):1097-1142

[72] Kapoor R, van Hogerlinden M, Wallis K, Ghosh H, Nordstrom K, Vennstrom B, Vaidya VA. Unliganded thyroid hormone receptor alpha1 impairs adult hippocampal neurogenesis. The FASEB Journal. 2010;**24**(12):4793-4805. DOI: 10.1096/fj.10-161802

[73] Kapoor R, Ghosh H, Nordstrom K, Vennstrom B, Vaidya VA. Loss of thyroid hormone receptor beta is associated with increased progenitor proliferation and NeuroD positive cell number in the adult hippocampus. Neuroscience Letters. 2011;**487**(2):199-203. DOI: 10.1016/j.neulet.2010.10.022

[74] Galea LA, McEwen BS. Sex and seasonal differences in the rate of cell proliferation in the dentate gyrus of adult wild meadow voles. Neuroscience. 1999;**89**(3):955-964

[75] Tanapat P, Hastings NB, Reeves AJ, Gould E. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. The Journal of Neuroscience. 1999;**19**(14):5792-5801

[76] Heinlein CA, Chang C. The roles of androgen receptors and androgen-binding proteins in nongenomic androgen actions. Molecular Endocrinology. 2002;**16**(10):2181-2187. DOI: 10.1210/me.2002-0070

[77] Bennett NC, Gardiner RA, Hooper JD, Johnson DW, Gobe GC. Molecular cell biology of androgen receptor signalling. The International Journal of Biochemistry & Cell Biology. 2010;**42**(6):813-827. DOI: 10.1016/j.biocel.2009.11.013

[78] Xiao L, Jordan CL. Sex differences, laterality, and hormonal regulation of androgen receptor immunoreactivity in rat hippocampus. Hormones and Behavior. 2002;**42**(3):327-336

[79] Tabori NE, Stewart LS, Znamensky V, Romeo RD, Alves SE, McEwen BS, Milner TA. Ultrastructural evidence that androgen receptors are located at extranuclear sites in the rat hippocampal formation. Neuroscience. 2005;**130**(1):151-163. DOI: 10.1016/j.neuroscience.2004.08.048

[80] Hamson DK, Roes MM, Galea LA. Sex hormones and cognition: Neuroendocrine influences on memory and learning. Comprehensive Physiology. 2016;**6**(3):1295-1337. DOI: 10.1002/cphy.c150031

[81] Galea LA, Wainwright SR, Roes MM, Duarte-Guterman P, Chow C, Hamson DK. Sex, hormones and neurogenesis in the hippocampus: Hormonal modulation of neurogenesis and potential functional implications. Journal of Neuroendocrinology. 2013;**25**(11):1039-1061. DOI: 10.1111/jne.12070

[82] Spritzer MD, Galea LA. Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. Developmental Neurobiology. 2007;**67**(10):1321-1333. DOI: 10.1002/dneu.20457

[83] Wainwright SR, Lieblich SE, Galea LA. Hypogonadism predisposes males to the development of behavioural and neuroplastic depressive phenotypes. Psychoneuroendocrinology. 2011;**36**(9):1327-1341. DOI: 10.1016/j.psyneuen.2011.03.004

[84] Mahmoud R, Wainwright SR, Galea LA. Sex hormones and adult hippocampal neurogenesis: Regulation, implications, and potential mechanisms. Frontiers in Neuroendocrinology. 2016;**41**:129-152. DOI: 10.1016/j.yfrne.2016.03.002

[85] Pawluski JL, Brummelte S, Barha CK, Crozier TM, Galea LA. Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. Frontiers in Neuroendocrinology. 2009;**30**(3):343-357. DOI: 10.1016/j.yfrne.2009.03.007

[86] McEwen BS, Akama KT, Spencer-Segal JL, Milner TA, Waters EM. Estrogen effects on the brain: Actions beyond the hypothalamus via novel mechanisms. Behavioral Neuroscience. 2012;**126**(1):4-16. DOI: 10.1037/a0026708

[87] Vasudevan N, Pfaff DW. Non-genomic actions of estrogens and their interaction with genomic actions in the brain. Frontiers in Neuroendocrinology. 2008;**29**(2):238-257. DOI: 10.1016/j.yfrne.2007.08.003

[88] Prossnitz ER, Oprea TI, Sklar LA, Arterburn JB. The ins and outs of GPR30: A transmembrane estrogen receptor. The Journal of Steroid Biochemistry and Molecular Biology. 2008;**109**(3-5):350-353. DOI: 10.1016/j.jsbmb.2008.03.006

[89] Brailoiu E, Dun SL, Brailoiu GC, Mizuo K, Sklar LA, Oprea TI, Prossnitz ER, Dun NJ. Distribution and characterization of estrogen receptor G protein-coupled receptor 30 in the rat central nervous system. The Journal of Endocrinology. 2007;**193**(2):311-321. DOI: 10.1677/JOE-07-0017

[90] Hazell GG, Yao ST, Roper JA, Prossnitz ER, O'Carroll AM, Lolait SJ. Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. The Journal of Endocrinology. 2009;**202**(2):223-236. DOI: 10.1677/JOE-09-0066

[91] Towart LA, Alves SE, Znamensky V, Hayashi S, McEwen BS, Milner TA. Subcellular relationships between cholinergic terminals and estrogen receptor-alpha in the dorsal hippocampus. The Journal of Comparative Neurology. 2003;**463**(4):390-401. DOI: 10.1002/cne.10753

[92] Mazzucco CA, Lieblich SE, Bingham BI, Williamson MA, Viau V, Galea LA. Both estrogen receptor alpha and estrogen receptor beta agonists enhance cell proliferation in the dentate gyrus of adult female rats. Neuroscience. 2006;**141**(4):1793-1800. DOI: 10.1016/j.neuroscience.2006.05.032

[93] Nagy AI, Ormerod BK, Mazzucco C, Galea LAM. Estradiol-induced enhancement in cell proliferation is mediated through estrogen receptors in the dentate gyrus of adult female rats. Drug Development Research. 2005;**66**:142-149

[94] Duarte-Guterman P, Lieblich SE, Chow C, Galea LA. Estradiol and GPER activation differentially affect cell proliferation but not GPER expression in the hippocampus of adult female rats. PLoS One. 2015;**10**(6):e0129880. DOI: 10.1371/journal.pone.0129880

[95] Huang EJ, Reichardt LF. Neurotrophins: Roles in neuronal development and function. Annual Review of Neuroscience. 2001;**24**:677-736. DOI: 10.1146/annurev.neuro.24.1.677

[96] Waterhouse EG, Xu B. New insights into the role of brain-derived neurotrophic factor in synaptic plasticity. Molecular and Cellular Neurosciences. 2009;**42**(2):81-89. DOI: 10.1016/j.mcn.2009.06.009

[97] Hong EJ, McCord AE, Greenberg ME. A biological function for the neuronal activity-dependent component of Bdnf transcription in the development of cortical inhibition. Neuron. 2008;**60**(4):610-624. DOI: 10.1016/j.neuron.2008.09.024

[98] Mori T, Shimizu K, Hayashi M. Differential expression patterns of TrkB ligands in the macaque monkey brain. Neuroreport. 2004;**15**(16):2507-2511

[99] Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Molecular Psychiatry. 2010;**15**(1):80-92. DOI: 10.1038/mp.2009.67

[100] Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Experimental Neurology. 2005;**192**(2):348-356. DOI: 10.1016/j.expneurol.2004.11.016

[101] Wang L, Chang X, She L, Xu D, Huang W, Poo MM. Autocrine action of BDNF on dendrite development of adult-born hippocampal neurons. The Journal of Neuroscience. 2015;**35**(22):8384-8393. DOI: 10.1523/JNEUROSCI.4682-14.2015

[102] Sairanen M, Lucas G, Ernfors P, Castren M, Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. The Journal of Neuroscience. 2005;**25**(5):1089-1094. DOI: 10.1523/JNEUROSCI.3741-04.2005

[103] Lee J, Duan W, Mattson MP. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. Journal of Neurochemistry. 2002;**82**(6):1367-1375

[104] Chan JP, Cordeira J, Calderon GA, Iyer LK, Rios M. Depletion of central BDNF in mice impedes terminal differentiation of new granule neurons in the adult hippocampus. Molecular and Cellular Neurosciences. 2008;**39**(3):372-383. DOI: 10.1016/j.mcn.2008.07.017

[105] Vilar M, Mira H. Regulation of neurogenesis by neurotrophins during adulthood: Expected and unexpected roles. Frontiers in Neuroscience. 2016;**10**:26. DOI: 10.3389/fnins.2016.00026

[106] Levi-Montalcini R, Hamburger V. Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. The Journal of Experimental Zoology. 1951;**116**(2):321-361

[107] Moises HC, Womble MD, Washburn MS, Williams LR. Nerve growth factor facilitates cholinergic neurotransmission between nucleus basalis and the amygdala in rat: An electrophysiological analysis. The Journal of Neuroscience. 1995;**15**(12):8131-8142

[108] Cooper JD, Salehi A, Delcroix JD, Howe CL, Belichenko PV, Chua-Couzens J, Kilbridge JF, Carlson EJ, Epstein CJ, Mobley WC. Failed retrograde transport of NGF in a mouse model of Down's syndrome: Reversal of cholinergic neurodegenerative phenotypes following NGF infusion. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**(18):10439-10444. DOI: 10.1073/pnas.181219298

[109] Frielingsdorf H, Simpson DR, Thal LJ, Pizzo DP. Nerve growth factor promotes survival of new neurons in the adult hippocampus. Neurobiology of Disease. 2007;**26**(1):47-55. DOI: 10.1016/j.nbd.2006.11.015

[110] Birch AM, Kelly AM. Chronic intracerebroventricular infusion of nerve growth factor improves recognition memory in the rat. Neuropharmacology. 2013;**75**:255-261. DOI: 10.1016/j.neuropharm.2013.07.023

[111] Zhang H, Petit GH, Gaughwin PM, Hansen C, Ranganathan S, Zuo X, Smith R, Roybon L, Brundin P, Mobley WC, Li JY. NGF rescues hippocampal cholinergic neuronal markers, restores neurogenesis, and improves the spatial working memory in a mouse model of Huntington's Disease. Journal of Huntington's Disease. 2013;**2**(1):69-82. DOI: 10.3233/JHD-120026

[112] Sondell M, Lundborg G, Kanje M. Vascular endothelial growth factor has neurotrophic activity and stimulates axonal outgrowth, enhancing cell survival and Schwann cell proliferation in the peripheral nervous system. The Journal of Neuroscience. 1999;**19** (14):5731-5740

[113] Jin KL, Mao XO, Greenberg DA. Vascular endothelial growth factor: Direct neuroprotective effect in in vitro ischemia. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**(18):10242-10247

[114] Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**(18):11946-11950. DOI: 10.1073/pnas.182296499

[115] Matsuzaki H, Tamatani M, Yamaguchi A, Namikawa K, Kiyama H, Vitek MP, Mitsuda N, Tohyama M. Vascular endothelial growth factor rescues hippocampal neurons from glutamate-induced toxicity: Signal transduction cascades. The FASEB Journal. 2001;**15**(7):1218-1220

[116] Kirby ED, Kuwahara AA, Messer RL, Wyss-Coray T. Adult hippocampal neural stem and progenitor cells regulate the neurogenic niche by secreting VEGF. Proceedings of the National Academy of Sciences of the United States of America. 2015;**112**(13):4128-4133. DOI: 10.1073/pnas.1422448112

[117] Sun Y, Jin K, Childs JT, Xie L, Mao XO, Greenberg DA. Vascular endothelial growth factor-B (VEGFB) stimulates neurogenesis: Evidence from knockout mice and growth factor administration. Developmental Biology. 2006;**289**(2):329-335. DOI: 10.1016/j.ydbio.2005.10.016

[118] Antequera D, Portero A, Bolos M, Orive G, Hernandez RM, Pedraz JL, Carro E. Encapsulated VEGF-secreting cells enhance proliferation of neuronal progenitors in the hippocampus of AbetaPP/Ps1 mice. Journal of Alzheimer's Disease. 2012;**29**(1):187-200. DOI: 10.3233/JAD-2011-111646

[119] Herran E, Perez-Gonzalez R, Igartua M, Pedraz JL, Carro E, Hernandez RM. Enhanced hippocampal neurogenesis in APP/Ps1 mouse model of Alzheimer's disease after implantation of VEGF-loaded PLGA nanospheres. Current Alzheimer Research. 2015; **12**(10):932-940

[120] Segi-Nishida E, Warner-Schmidt JL, Duman RS. Electroconvulsive seizure and VEGF increase the proliferation of neural stem-like cells in rat hippocampus. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(32):11352-11357. DOI: 10.1073/pnas.0710858105

[121] Fournier NM, Duman RS. Role of vascular endothelial growth factor in adult hippocampal neurogenesis: Implications for the pathophysiology and treatment of depression. Behavioural Brain Research. 2012;**227**(2):440-449. DOI: 10.1016/j.bbr.2011.04.022

[122] Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. The European Journal of Neuroscience. 2003;**18**(10):2803-2812

[123] Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, Young D, During MJ. VEGF links hippocampal activity with neurogenesis, learning and memory. Nature Genetics. 2004;**36**(8):827-835. DOI: 10.1038/ng1395

[124] Chadashvili T, Peterson DA. Cytoarchitecture of fibroblast growth factor receptor 2 (FGFR-2) immunoreactivity in astrocytes of neurogenic and non-neurogenic regions of the young adult and aged rat brain. The Journal of Comparative Neurology. 2006;**498**(1):1-15. DOI: 10.1002/cne.21009

[125] Weickert CS, Kittell DA, Saunders RC, Herman MM, Horlick RA, Kleinman JE, Hyde TM. Basic fibroblast growth factor and fibroblast growth factor receptor-1 in the human hippocampal formation. Neuroscience. 2005;**131**(1):219-233. DOI: 10.1016/j.neuroscience.2004.09.070

[126] Gomez-Pinilla F, Lee JW, Cotman CW. Distribution of basic fibroblast growth factor in the developing rat brain. Neuroscience. 1994;**61**(4):911-923

[127] Werner S, Unsicker K, von Bohlen und Halbach O. Fibroblast growth factor-2 deficiency causes defects in adult hippocampal neurogenesis, which are not rescued by exogenous fibroblast growth factor-2. Journal of Neuroscience Research. 2011;**89**(10):1605-1617. DOI: 10.1002/jnr.22680

[128] Yoshimura S, Takagi Y, Harada J, Teramoto T, Thomas SS, Waeber C, Bakowska JC, Breakefield XO, Moskowitz MA. FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**(10):5874-5879. DOI: 10.1073/pnas.101034998

[129] Asai T, Wanaka A, Kato H, Masana Y, Seo M, Tohyama M. Differential expression of two members of FGF receptor gene family, FGFR-1 and FGFR-2 mRNA, in the adult rat central nervous system. Brain Research. Molecular Brain Research. 1993;**17**(1-2):174-178

[130] Miyake A, Hattori Y, Ohta M, Itoh N. Rat oligodendrocytes and astrocytes preferentially express fibroblast growth factor receptor-2 and -3 mRNAs. Journal of Neuroscience Research. 1996;**45**(5):534-541. DOI: 10.1002/(SICI)1097-4547(19960901)45:5<534::AID-JNR3>3.0.CO;2-D

[131] Ohkubo Y, Uchida AO, Shin D, Partanen J, Vaccarino FM. Fibroblast growth factor receptor 1 is required for the proliferation of hippocampal progenitor cells and for hippocampal growth in mouse. The Journal of Neuroscience. 2004;**24**(27):6057-6069. DOI: 10.1523/JNEUROSCI.1140-04.2004

[132] van Amerongen R, Nusse R. Towards an integrated view of Wnt signaling in development. Development. 2009;**136**(19):3205-3214. DOI: 10.1242/dev.033910

[133] Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A, Lein ES, Jessberger S, Lansford H, Dearie AR, Gage FH. Wnt signalling regulates adult hippocampal neurogenesis. Nature. 2005;**437**(7063):1370-1375. DOI: 10.1038/nature04108

[134] Gao X, Arlotta P, Macklis JD, Chen J. Conditional knock-out of beta-catenin in postnatal-born dentate gyrus granule neurons results in dendritic malformation. The Journal of Neuroscience. 2007;**27**(52):14317-14325. DOI: 10.1523/JNEUROSCI.3206-07.2007

[135] Mason HA, Rakowiecki SM, Gridley T, Fishell G. Loss of notch activity in the developing central nervous system leads to increased cell death. Developmental Neuroscience. 2006;**28**(1-2):49-57. DOI: 10.1159/000090752

[136] Ables JL, Decarolis NA, Johnson MA, Rivera PD, Gao Z, Cooper DC, Radtke F, Hsieh J, Eisch AJ. Notch1 is required for maintenance of the reservoir of adult hippocampal stem cells. The Journal of Neuroscience. 2010;**30**(31):10484-10492. DOI: 10.1523/JNEUROSCI.4721-09.2010

[137] Breunig JJ, Silbereis J, Vaccarino FM, Sestan N, Rakic P. Notch regulates cell fate and dendrite morphology of newborn neurons in the postnatal dentate gyrus. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(51):20558-20563. DOI: 10.1073/pnas.0710156104

[138] Sui Y, Zhang Z, Guo Y, Sun Y, Zhang X, Xie C, Li Y, Xi G. The function of Notch1 signaling was increased in parallel with neurogenesis in rat hippocampus after chronic fluoxetine administration. Biological & Pharmaceutical Bulletin. 2009;**32**(10):1776-1782

[139] Bonaguidi MA, Peng CY, McGuire T, Falciglia G, Gobeske KT, Czeisler C, Kessler JA. Noggin expands neural stem cells in the adult hippocampus. The Journal of Neuroscience. 2008;**28**(37):9194-9204. DOI: 10.1523/JNEUROSCI.3314-07.2008

[140] Lim DA, Tramontin AD, Trevejo JM, Herrera DG, Garcia-Verdugo JM, Alvarez-Buylla A. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. Neuron. 2000;**28**(3):713-726

[141] Mira H, Andreu Z, Suh H, Lie DC, Jessberger S, Consiglio A, San Emeterio J, Hortiguela R, Marques-Torrejon MA, Nakashima K, Colak D, Gotz M, Farinas I, Gage FH. Signaling through BMPR-IA regulates quiescence and long-term activity of neural stem cells in the adult hippocampus. Cell Stem Cell. 2010;**7**(1):78-89. DOI: 10.1016/j.stem.2010.04.016

[142] Gobeske KT, Das S, Bonaguidi MA, Weiss C, Radulovic J, Disterhoft JF, Kessler JA. BMP signaling mediates effects of exercise on hippocampal neurogenesis and cognition in mice. PLoS One. 2009;**4**(10):e7506. DOI: 10.1371/journal.pone.0007506

[143] Palma V, Lim DA, Dahmane N, Sanchez P, Brionne TC, Herzberg CD, Gitton Y, Carleton A, Alvarez-Buylla A, Ruiz i Altaba A. Sonic hedgehog controls stem cell behavior in the postnatal and adult brain. Development. 2005;**132**(2):335-344. DOI: 10.1242/dev.01567

[144] Traiffort E, Charytoniuk DA, Faure H, Ruat M. Regional distribution of Sonic Hedgehog, patched, and smoothened mRNA in the adult rat brain. Journal of Neurochemistry. 1998;**70**(3):1327-1330

[145] Lai K, Kaspar BK, Gage FH, Schaffer DV. Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. Nature Neuroscience. 2003;**6**(1):21-27. DOI: 10.1038/nn983

[146] Banerjee SB, Rajendran R, Dias BG, Ladiwala U, Tole S, Vaidya VA. Recruitment of the Sonic hedgehog signalling cascade in electroconvulsive seizure-mediated regulation of adult rat hippocampal neurogenesis. The European Journal of Neuroscience. 2005;**22**(7):1570-1580. DOI: 10.1111/j.1460-9568.2005.04317.x

[147] Machold R, Hayashi S, Rutlin M, Muzumdar MD, Nery S, Corbin JG, Gritli-Linde A, Dellovade T, Porter JA, Rubin LL, Dudek H, McMahon AP, Fishell G. Sonic hedgehog is required for progenitor cell maintenance in telencephalic stem cell niches. Neuron. 2003;**39**(6):937-950

[148] Datta SR, Brunet A, Greenberg ME. Cellular survival: A play in three Akts. Genes & Development. 1999;**13**(22):2905-2927

[149] Aberg MA, Aberg ND, Palmer TD, Alborn AM, Carlsson-Skwirut C, Bang P, Rosengren LE, Olsson T, Gage FH, Eriksson PS. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. Molecular and Cellular Neurosciences. 2003;**24**(1):23-40

[150] Balu DT, Easton RM, Birnbaum MJ, Lucki I. Deletion of Akt Isoforms Reduce Hippocampal Neurogenesis. Washington, DC: Fear Conditioning and Antidepressant Behavioral Responses, in Society for Neuroscience; 2008

[151] Bruel-Jungerman E, Veyrac A, Dufour F, Horwood J, Laroche S, Davis S. Inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the dentate gyrus. PLoS One. 2009;**4**(11):e7901. DOI: 10.1371/journal.pone.0007901

[152] Tsai YW, Yang YR, Sun SH, Liang KC, Wang RY. Post ischemia intermittent hypoxia induces hippocampal neurogenesis and synaptic alterations and alleviates long-term memory impairment. Journal of Cerebral Blood Flow and Metabolism. 2013;**33**(5):764-773. DOI: 10.1038/jcbfm.2013.15

[153] Fournier NM, Lee B, Banasr M, Elsayed M, Duman RS. Vascular endothelial growth factor regulates adult hippocampal cell proliferation through MEK/ERK- and PI3K/Akt-dependent signaling. Neuropharmacology. 2012;**63**(4):642-652. DOI: 10.1016/j.neuropharm.2012.04.033

[154] D'Arcangelo G, Miao GG, Chen SC, Soares HD, Morgan JI, Curran T. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. Nature. 1995;**374**(6524):719-723. DOI: 10.1038/374719a0

[155] Cooper JA. A mechanism for inside-out lamination in the neocortex. Trends in Neurosciences. 2008;**31**(3):113-119. DOI: 10.1016/j.tins.2007.12.003

[156] Alcantara S, Ruiz M, D'Arcangelo G, Ezan F, de Lecea L, Curran T, Sotelo C, Soriano E. Regional and cellular patterns of reelin mRNA expression in the forebrain of the developing and adult mouse. The Journal of Neuroscience. 1998;**18**(19):7779-7799

[157] Pesold C, Impagnatiello F, Pisu MG, Uzunov DP, Costa E, Guidotti A, Caruncho HJ. Reelin is preferentially expressed in neurons synthesizing gamma-aminobutyric acid in cortex and hippocampus of adult rats. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**(6):3221-3226

[158] Teixeira CM, Kron MM, Masachs N, Zhang H, Lagace DC, Martinez A, Reillo I, Duan X, Bosch C, Pujadas L, Brunso L, Song H, Eisch AJ, Borrell V, Howell BW, Parent JM, Soriano E. Cell-autonomous inactivation of the reelin pathway impairs adult neurogenesis in the hippocampus. The Journal of Neuroscience. 2012;**32**(35):12051-12065. DOI: 10.1523/JNEUROSCI.1857-12.2012

[159] Bosch C, Masachs N, Exposito-Alonso D, Martinez A, Teixeira CM, Fernaud I, Pujadas L, Ulloa F, Comella JX, DeFelipe J, Merchan-Perez A, Soriano E. Reelin regulates the maturation of dendritic spines, synaptogenesis and glial ensheathment of newborn granule cells. Cerebral Cortex. 2016;**26**(11):4282-4298. DOI: 10.1093/cercor/bhw216

[160] Heinrich C, Nitta N, Flubacher A, Muller M, Fahrner A, Kirsch M, Freiman T, Suzuki F, Depaulis A, Frotscher M, Haas CA. Reelin deficiency and displacement of mature neurons, but not neurogenesis, underlie the formation of granule cell dispersion in the epileptic hippocampus. The Journal of Neuroscience. 2006;**26**(17):4701-4713. DOI: 10.1523/JNEUROSCI.5516-05.2006

[161] Gong C, Wang TW, Huang HS, Parent JM. Reelin regulates neuronal progenitor migration in intact and epileptic hippocampus. The Journal of Neuroscience. 2007;**27**(8):1803-1811. DOI: 10.1523/JNEUROSCI.3111-06.2007

[162] Haas CA, Frotscher M. Reelin deficiency causes granule cell dispersion in epilepsy. Experimental Brain Research. 2010;**200**(2):141-149. DOI: 10.1007/s00221-009-1948-5

[163] Rogers JT, Rusiana I, Trotter J, Zhao L, Donaldson E, Pak DT, Babus LW, Peters M, Banko JL, Chavis P, Rebeck GW, Hoe HS, Weeber EJ. Reelin supplementation enhances cognitive ability, synaptic plasticity, and dendritic spine density. Learning & Memory. 2011;**18**(9):558-564. DOI: 10.1101/lm.2153511

[164] Clark PJ, Brzezinska WJ, Puchalski EK, Krone DA, Rhodes JS. Functional analysis of neurovascular adaptations to exercise in the dentate gyrus of young adult mice associated with cognitive gain. Hippocampus. 2009;**19**(10):937-950. DOI: 10.1002/hipo.20543

[165] Speisman RB, Kumar A, Rani A, Foster TC, Ormerod BK. Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. Brain, Behavior, and Immunity. 2013;**28**:25-43. DOI: 10.1016/j.bbi.2012.09.013

[166] van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proceedings of the National Academy of Sciences of the United States of America. 1999;**96**(23):13427-13431

[167] van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nature Neuroscience. 1999;**2**(3):266-270. DOI: 10.1038/6368

[168] Gomez-Pinilla F, Dao L, So V. Physical exercise induces FGF-2 and its mRNA in the hippocampus. Brain Research. 1997;**764**(1-2):1-8

[169] Russo-Neustadt A, Beard RC, Cotman CW. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. Neuropsychopharmacology. 1999;**21**(5):679-682

[170] Ding Q, Ying Z, Gomez-Pinilla F. Exercise influences hippocampal plasticity by modulating brain-derived neurotrophic factor processing. Neuroscience. 2011

[171] Griffin EW, Mulally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. Physiology & Behavior. 2011

[172] Zigova T, Pencea V, Wiegand SJ, Luskin MB. Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb. Molecular and Cellular Neurosciences. 1998;**11**(4):234-245

[173] Rich B, Scadeng M, Yamaguchi M, Wagner PD, Breen EC. Skeletal myofiber vascular endothelial growth factor is required for the exercise training-induced increase in dentate gyrus neuronal precursor cells. The Journal of Physiology. 2017;**595**(17):5931-5943. DOI: 10.1113/JP273994

[174] Ballard HJ. Exercise makes your brain bigger: Skeletal muscle VEGF and hippocampal neurogenesis. The Journal of Physiology. 2017;**595**(17):5721-5722. DOI: 10.1113/JP274658

[175] Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997;**386**(6624):493-495. DOI: 10.1038/386493a0

[176] Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Annals of Neurology. 2002;**52**(2):135-143. DOI: 10.1002/ana.10262

[177] Kobilo T, Liu QR, Gandhi K, Mughal M, Shaham Y, van Praag H. Running is the neurogenic and neurotrophic stimulus in environmental enrichment. Learning & Memory. 2011;**18**(9):605-609. DOI: 10.1101/lm.2283011

[178] Mustroph ML, Chen S, Desai SC, Cay EB, DeYoung EK, Rhodes JS. Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6J mice. Neuroscience. 2012;**219**:62-71. DOI: 10.1016/j.neuroscience.2012.06.007

[179] Rai KS, Hattiangady B, Shetty AK. Enhanced production and dendritic growth of new dentate granule cells in the middle-aged hippocampus following intracerebroventricular FGF-2 infusions. The European Journal of Neuroscience. 2007;**26**(7):1765-1779. DOI: 10.1111/j.1460-9568.2007.05820.x

[180] Olariu A, Cleaver KM, Cameron HA. Decreased neurogenesis in aged rats results from loss of granule cell precursors without lengthening of the cell cycle. The Journal of Comparative Neurology. 2007;**501**(4):659-667. DOI: 10.1002/cne.21268

[181] Hattiangady B, Shetty AK. Aging does not alter the number or phenotype of putative stem/progenitor cells in the neurogenic region of the hippocampus. Neurobiology of Aging. 2008;**29**(1):129-147. DOI: 10.1016/j.neurobiolaging.2006.09.015

[182] Pruessner JC, Collins DL, Pruessner M, Evans AC. Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. The Journal of Neuroscience. 2001;**21**(1):194-200

[183] Zhang R, Kadar T, Sirimanne E, MacGibbon A, Guan J. Age-related memory decline is associated with vascular and microglial degeneration in aged rats. Behavioural Brain Research. 2012;**235**(2):210-217. DOI: 10.1016/j.bbr.2012.08.002

[184] Small SA, Chawla MK, Buonocore M, Rapp PR, Barnes CA. Imaging correlates of brain function in monkeys and rats isolates a hippocampal subregion differentially vulnerable to aging. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(18):7181-7186. DOI: 10.1073/pnas.0400285101

[185] Griffin R, Nally R, Nolan Y, McCartney Y, Linden J, Lynch MA. The age-related attenuation in long-term potentiation is associated with microglial activation. Journal of Neurochemistry. 2006;**99**(4):1263-1272. DOI: 10.1111/j.1471-4159.2006.04165.x

[186] Ogura K, Ogawa M, Yoshida M. Effects of ageing on microglia in the normal rat brain: Immunohistochemical observations. Neuroreport. 1994;**5**(10):1224-1226

[187] Shetty AK, Hattiangady B, Shetty GA. Stem/progenitor cell proliferation factors FGF-2, IGF-1, and VEGF exhibit early decline during the course of aging in the hippocampus: Role of astrocytes. Glia. 2005;**51**(3):173-186. DOI: 10.1002/glia.20187

[188] Calabrese F, Guidotti G, Racagni G, Riva MA. Reduced neuroplasticity in aged rats: A role for the neurotrophin brain-derived neurotrophic factor. Neurobiology of Aging. 2013;**34**(12):2768-2776. DOI: 10.1016/j.neurobiolaging.2013.06.014

[189] Rex CS, Lauterborn JC, Lin CY, Kramar EA, Rogers GA, Gall CM, Lynch G. Restoration of long-term potentiation in middle-aged hippocampus after induction of brain-derived

neurotrophic factor. Journal of Neurophysiology. 2006;**96**(2):677-685. DOI: 10.1152/jn.00336.2006

[190] Bernal GM, Peterson DA. Phenotypic and gene expression modification with normal brain aging in GFAP-positive astrocytes and neural stem cells. Aging Cell. 2011;**10**(3):466-482. DOI: 10.1111/j.1474-9726.2011.00694.x

[191] Larkfors L, Ebendal T, Whittemore SR, Persson H, Hoffer B, Olson L. Decreased level of nerve growth factor (NGF) and its messenger RNA in the aged rat brain. Brain Research. 1987;**427**(1):55-60

[192] Darsalia V, Heldmann U, Lindvall O, Kokaia Z. Stroke-induced neurogenesis in aged brain. Stroke. 2005;**36**(8):1790-1795. DOI: 10.1161/01.STR.0000173151.36031.be

[193] Mirescu C, Gould E. Stress and adult neurogenesis. Hippocampus. 2006;**16**(3):233-238. DOI: 10.1002/hipo.20155

[194] Kirby E, Kaufer D. Stress and adult neurogenesis in the mammalian central nervous system. In: Soreq H, Friedman A, Kaufer D, editors. STRESS: From Molecules to Behavior. Weinheim: Wiley-Blackwell; 2009. pp. 71-91

[195] Heine VM, Zareno J, Maslam S, Joels M, Lucassen PJ. Chronic stress in the adult dentate gyrus reduces cell proliferation near the vasculature and VEGF and Flk-1 protein expression. The European Journal of Neuroscience. 2005;**21**(5):1304-1314. DOI: 10.1111/j.1460-9568.2005.03951.x

[196] Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. The Journal of Neuroscience. 1997;**17**(7):2492-2498

[197] Lucassen PJ, Bosch OJ, Jousma E, Kromer SA, Andrew R, Seckl JR, Neumann ID. Prenatal stress reduces postnatal neurogenesis in rats selectively bred for high, but not low, anxiety: Possible key role of placental 11beta-hydroxysteroid dehydrogenase type 2. The European Journal of Neuroscience. 2009;**29**(1):97-103. DOI: 10.1111/j.1460-9568.2008.06543.x

[198] Bosch OJ, Kromer SA, Neumann ID. Prenatal stress: Opposite effects on anxiety and hypothalamic expression of vasopressin and corticotropin-releasing hormone in rats selectively bred for high and low anxiety. The European Journal of Neuroscience. 2006;**23**(2):541-551. DOI: 10.1111/j.1460-9568.2005.04576.x

[199] Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell. 2007;**131**(2):391-404. DOI: 10.1016/j.cell.2007.09.018

[200] Tse YC, Montoya I, Wong AS, Mathieu A, Lissemore J, Lagace DC, Wong TP. A longitudinal study of stress-induced hippocampal volume changes in mice that are susceptible

or resilient to chronic social defeat. Hippocampus. 2014;**24**(9):1120-1128. DOI: 10.1002/hipo.22296

[201] Alves ND, Correia JS, Patricio P, Mateus-Pinheiro A, Machado-Santos AR, Loureiro-Campos E, Morais M, Bessa JM, Sousa N, Pinto L. Adult hippocampal neuroplasticity triggers susceptibility to recurrent depression. Translational Psychiatry. 2017;**7**(3):e1058. DOI: 10.1038/tp.2017.29

[202] Levone BR, Cryan JF, O'Leary OF. Role of adult hippocampal neurogenesis in stress resilience. Neurobiol Stress. 2015;**1**:147-155. DOI: 10.1016/j.ynstr.2014.11.003

[203] Liu J, Solway K, Messing RO, Sharp FR. Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. The Journal of Neuroscience. 1998;**18**(19):7768-7778

[204] Yagita Y, Kitagawa K, Ohtsuki T, Takasawa K, Miyata T, Okano H, Hori M, Matsumoto M. Neurogenesis by progenitor cells in the ischemic adult rat hippocampus. Stroke. 2001;**32**(8):1890-1896

[205] Tan YF, Preston E, Wojtowicz JM. Enhanced post-ischemic neurogenesis in aging rats. Frontiers in Neuroscience. 2010;**4**. DOI: 10.3389/fnins.2010.00163

[206] Takagi Y, Nozaki K, Takahashi J, Yodoi J, Ishikawa M, Hashimoto N. Proliferation of neuronal precursor cells in the dentate gyrus is accelerated after transient forebrain ischemia in mice. Brain Research. 1999;**831**(1-2):283-287

[207] Tureyen K, Vemuganti R, Sailor KA, Bowen KK, Dempsey RJ. Transient focal cerebral ischemia-induced neurogenesis in the dentate gyrus of the adult mouse. Journal of Neurosurgery. 2004;**101**(5):799-805. DOI: 10.3171/jns.2004.101.5.0799

[208] Zhou H, Chen L, Gao X, Luo B, Chen J. Moderate traumatic brain injury triggers rapid necrotic death of immature neurons in the hippocampus. Journal of Neuropathology and Experimental Neurology. 2012;**71**(4):348-359. DOI: 10.1097/NEN.0b013e31824ea078

[209] Salmond CH, Sahakian BJ. Cognitive outcome in traumatic brain injury survivors. Current Opinion in Critical Care. 2005;**11**(2):111-116

[210] Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, Miller BL, Guskiewicz KM, Berger MS, Kramer JH, Welsh-Bohmer KA. Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis. Journal of Neurosurgery. 2016;**124**(2):511-526. DOI: 10.3171/2015.2.JNS14503

[211] Ramaswamy S, Goings GE, Soderstrom KE, Szele FG, Kozlowski DA. Cellular proliferation and migration following a controlled cortical impact in the mouse. Brain Research. 2005;**1053**(1-2):38-53. DOI: 10.1016/j.brainres.2005.06.042

[212] Sun D, Colello RJ, Daugherty WP, Kwon TH, McGinn MJ, Harvey HB, Bullock MR. Cell proliferation and neuronal differentiation in the dentate gyrus in juvenile and adult rats following traumatic brain injury. Journal of Neurotrauma. 2005;**22**(1):95-105. DOI: 10.1089/neu.2005.22.95

[213] Zheng W, ZhuGe Q, Zhong M, Chen G, Shao B, Wang H, Mao X, Xie L, Jin K. Neurogenesis in adult human brain after traumatic brain injury. Journal of Neurotrauma. 2013;**30**(22):1872-1880. DOI: 10.1089/neu.2010.1579

[214] Gao X, Chen J. Moderate traumatic brain injury promotes neural precursor proliferation without increasing neurogenesis in the adult hippocampus. Experimental Neurology. 2013;**239**:38-48. DOI: 10.1016/j.expneurol.2012.09.012

[215] Wang X, Gao X, Michalski S, Zhao S, Chen J. Traumatic brain injury severity affects neurogenesis in adult mouse hippocampus. Journal of Neurotrauma. 2016;**33**(8):721-733. DOI: 10.1089/neu.2015.4097

[216] Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, Ellmo W, Kalmar K, Giacino JT, Harley JP, Laatsch L, Morse PA, Catanese J. Evidence-based cognitive rehabilitation: Updated review of the literature from 1998 through 2002. Archives of Physical Medicine and Rehabilitation. 2005;**86**(8):1681-1692. DOI: 10.1016/j.apmr.2005.03.024

[217] Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. The Journal of Neuroscience. 1997;**17**(10):3727-3738

[218] Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**(19):10432-10437

[219] Kralic JE, Ledergerber DA, Fritschy JM. Disruption of the neurogenic potential of the dentate gyrus in a mouse model of temporal lobe epilepsy with focal seizures. The European Journal of Neuroscience. 2005;**22**(8):1916-1927. DOI: 10.1111/j.1460-9568.2005.04386.x

[220] Jessberger S, Romer B, Babu H, Kempermann G. Seizures induce proliferation and dispersion of doublecortin-positive hippocampal progenitor cells. Experimental Neurology. 2005;**196**(2):342-351. DOI: 10.1016/j.expneurol.2005.08.010

[221] Hattiangady B, Rao MS, Shetty AK. Chronic temporal lobe epilepsy is associated with severely declined dentate neurogenesis in the adult hippocampus. Neurobiology of Disease. 2004;**17**(3):473-490. DOI: 10.1016/j.nbd.2004.08.008

[222] Cha BH, Akman C, Silveira DC, Liu X, Holmes GL. Spontaneous recurrent seizure following status epilepticus enhances dentate gyrus neurogenesis. Brain and Development. 2004;**26**(6):394-397. DOI: 10.1016/j.braindev.2003.12.006