Behavioural Brain Research 317 (2017) 332–339

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Physical exercise induces hippocampal neurogenesis and prevents cognitive decline

Chun-Lian Ma[a,b], Xiao-Tang Ma[c], Jin-Ju Wang[d], Hua Liu[e], Yan-Fang Chen[d], Yi Yang (M.D, Ph.D) (Professor)[e,*]

[a] Graduate School, Wuhan Sports University, Wuhan 430079, China
[b] School of Sports Science and Technology, Wuhan Sports University, Wuhan, 430205,China
[c] Guangdong Key Laboratory of Age-Related Cardiac and Cerebral Diseases, Institute of Neurological Diseases, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong,524001, China
[d] Department of Pharmacology and Toxicology, Boonshoft School of Medicine, Wright State University, Dayton, OH 45435, USA
[e] College of Health Science, Wuhan Sports University, Wuhan, 430079, China

HIGHLIGHTS

- Hippocampal neurogenesis reduction accompanied with cognitive decline happens in aging-related neurodegenerative diseases.
- We review the integration of new born neurons and the roles of physical exercise induces hippocampal neurogenesis in humans and rodents.
- Physical exercise has emerged as an effective, low-cost, and low-tech way for prevention or slowdown of cognitive decline.

ARTICLE INFO

Article history:
Received 14 August 2016
Received in revised form
24 September 2016
Accepted 30 September 2016
Available online 1 October 2016

Keywords:
Neurogenesis
Exercise
Cognition
Brain plasticity
Neurodegenerative disease
Aging

ABSTRACT

Accumulating evidence from animal and human research indicate that adult hippocampal neurogenesis plays a key role in cognition. Meanwhile, cognitive decline is well known to associate with ageing-related neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Therefore, prevention of hippocampal neurogenesis reduction should be critical for these diseases. Physical exercise, a potent enhancer of adult hippocampal neurogenesis, has emerged as a potential therapy or an adjunctive therapeutic strategy for cognitive decline. In this review, we discuss the recent findings on hippocampal neurogenesis and the incorporation of new born neurons into the neuronal network in humans and in rodents. By focusing on hippocampal neurogenesis, we illustrate the role and possible mechanisms of physical exercise in cognition preservation.

Contents

* Corresponding Author: College of Health Science, Wuhan Sports University, Wuhan 430079, China.
E-mail address: yangyi999999@yahoo.com (Y. Yang).

http://dx.doi.org/10.1016/j.bbr.2016.09.067
0166-4328/

1. Introduction

Neurogenesis, the production of neural cell-types from neural stem cells (NSCs) or neural progenitor cells (NPCs) occurs throughout life [1]. This new conception overturns the long-held dogma that the adult brain has no capacity for generating new neurons. Adult neurogenesis has been consistently observed in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus under normal conditions [2]. Neurons born in the SGZ can incorporate into the existing neural network of granule cells in the dentate gyrus [3,4]. Furthermore, new born adult dentate granule cells (DGCs) are believed to contribute to hippocampus-dependent functions such as learning and memory [5,6] and in particular pattern separation, defined as the ability to transform a set of similar input patterns into a less-similar set of output patterns in information processing [7,8].

Hippocampal neurogenesis reduction happens in aging-related neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD),which are accompanied with cognitive decline [9–11]. Hence, promotion of the hippocampal neurogenesis has become a new insight to cure these diseases and to delay or halt brain aging. How to enhance hippocampal neurogenesis has captured the attention of many neuroscientists. Adult neurogenesis in the mammalian brain has been suggested as a dynamic process which is regulated by numerous intrinsic and extrinsic factors [12]. Hippocampal neurogenesis represents the regenerative capacity of adult mammalian brain and a striking form of brain plasticity. Interestingly, recent studies indicate that physical exercise regulates the proliferation, differentiation, survival and maturation of NPCs, and support the positive correlation between exercise-induced hippocampal neurogenesis and cognition improvement [13–18].

2. Adult hippocampal neurogenesis in humans and rodents

The existence of adult NSCs in the rodent brain was reported in the 1960s, while the first direct evidence supporting the notion of human adult neurogenesis was discovered in hippocampus in 1998 by using bromodeoxyuridine (BrdU) labeling technique [19]. However, due to safety concerns, it has been difficult to study neurogenesis in humans by BrdU technique. Thus, the current methods employed to study adult human neurogenesis rely on immunostaining of postmortem brain tissues with endogenous markers, such as glial fibrillary acidic protein (GFAP), for astroglia, and NeuN, calbindin, doublecortin (DCX), Ki67 and, Nestin for neurons [19,20] or culturing human NPCs isolated from tissue biopsies [21,22]. A new technique using the natural ^{14}C abundance in genomic DNA has been developed to determine the neuronal age, which has been integrated into some mathematical models to calculate dynamics of neurogenesis in adult human postmortem hippocampus [23]. Nevertheless, these ex vivo measurements could not provide further information on the possible role of adult neurogenesis. Notably, magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) techniques are thought to be available methods to assess hippocampal neurogenesis in living person [24,25]. The former detects the neurogenesis by identifying a NPC-specific metabolic biomarker [24], and the latter tests neurogenesis based on the positive correlation between MRI measurements of cerebral blood volume and neurogenesis because of their coupling [25], but the validity and accuracy remain to be determined. Technological limitations halt the analysis of the functional role of adult hippocampal neurogenesis in humans. To date, it is still difficult to study hippocampal neurogenesis directly in living person and a huge amount of studies mainly come from rodent experiments.

The findings of several studies indicate the same location and similar regulation of adult hippocampal neurogenesis between humans and other mammals. Firstly, Eriksson et al. [19] provided solid evidence that adult neurogenesis in humans occurs in the SGZ of dentate gyrus, the same region in which new neurons reside in rodents and monkeys [20,23,26]. Secondly, the number of new born neurons in human dentate gyrus shows a steadily reduction with aging [20,23]. This parallels with the age-related decrease seen in non-human mammals [27,28] which provides evidence that the regulation of adult hippocampal neurogenesis in humans could be similar to that in other mammalian species.

Given few relevant human studies, it is difficult to compare the number of new adult DGCs between humans and non-human mammals. Snyder and Cameron speculated that the true number of new adult born DGCs might be significantly higher in humans than in rats, with the reasons that the dosage of BrdU conversed from a very small dose used in humans failed to detectably label 40–90% of S-phase cells in rodents and that the human subjects were terminally ill and, advanced in age with likely reduced neurogenesis [26]. In addition, the turnover rate of DGCs could be higher in humans than in mouse, with 35% in humans compared to 10% in mouse [23,29]. Furthermore, the maturation period of the new adult born neurons deviate in different species. The maturation period of DGCs in adult macaque monkeys is 6 times longer than that in adult rodents [30]. The maturation time might be even longer in humans because of that the total length of the embryonic neurogenic period is 100d in humans, 60d in monkeys and, 6d in mice, and that the cell cycle of human NPCs is 5 times longer compared with that of other mammals suggesting that NPCs in dentate gyrus divide at a slow rate in humans [30].

In the adult brain, the hippocampus is a critical structure for the formation of certain types of memory [31–33] and mood regulation [34]. A fundamental question has been raised that whether the continuously generated neurons have some specific functions? It is well known that immediate early gene (IEG), such as Arc, Fos, and Egr1 (also known as Zif268), are the indicators of recently activated neurons [35–37]. Therefore, immunofluorescence double labeling of IEG and BrdU has been used to confirm the adult new born neurons contributing to process the hippocampus-dependent information [37,38]. Furthermore, irradiation and anti-mitotic drugs have been used to assess the contribution of adult new born neurons to animal behaviors and the results revealed that ablation or reduction of adult hippocampal neurogenesis results in functional deficit [39,40]. A recent study has shown that increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors [41]. Collectively, these studies demonstrate that new adult neurons contribute to hippocampus-dependent functions.

3. Integration of adult new born neurons into the existing network

In the past several years, it has become clear that adult generated neurons can form synaptic connections with the existing circuit. In rodents, there are two precursor pools of the dentate gyrus, type 1 (quiescent) and type 2 (latent) NPCs in the SGZ [42,43]. Type1 NPCs have a radial process and express endogenous progenitor markers of nestin, GFAP, Sox2 [42,44]. Although type 1 NPCs express the astrocyte marker GFAP, they are morphologically and functionally different from mature astrocytes [45]. The type 2 NPCs have only short horizontal processes and express Sox2 [45]. Type 2 progenitors give rise to astrocytes and granule cells in the dentate gyrus, which could play an important role in early AD process. It has been suggested that dysfunctional neurogenesis exacerbates neuronal vulnerability to AD characterized by deposition of amyloid-β (A β), a kind of neurotoxicity protein, whereas enhanced neurogenesis represents an endogenous brain repair mechanism of AD by

providing more new neurons to replace the dead or impaired ones [42,45].

The new adult born DGCs bear little resemblance to their mature counterparts and must undergo a lengthy process of morphological and physiological maturation [13]. As maturation, the new cells receive afferent inputs from local interneurons [4,46] and entorhinal cortex by perforant path [2,13], while, their efferent outputs project to hilus and CA3 pyramidal neurons by mossy fibres [2,47]. During the second week after birth, the formation of synapses connecting local interneurons and the new granule cells occurs [2]. Initially, these synapses are depolarized by gamma-aminobutyric acid (GABA) and are therefore less likely to be inhibited by the strong GABAergic inhibition in the dentate gyrus, however, become indistinct as the neurons maturating [4]. The efferent projections of newborn neurons to the CA3 area also occur at this time [13]. It is worth noting that GABA in the dentate gyrus plays a key role in adult hippocampal neurogenesis through dual regulation of both stem cell activation and neuroblast survival at this time window [46,48].

Consistent with the formation of dendritic spines, afferent input from entorhinal cortex is lack in these new neurons until after 2 weeks of birth [2]. Originally, the majority of spines on the new granule cells are liable to target axon boutons that already synapse with other existing spines [49]. Furthermore, the mossy fibre boutons of new granule cells initially form synapses with CA3 pyramidal neurons either near existing thorny excrescences or directly with thorny excrescences [47,50]. It is suggested that both afferent and efferent synapses formation of new adult born granule cells are influenced by synaptic activity. Moreover, approximately half of all neurons die during the first 4 weeks of birth [51,52] and the basic physiological and morphological properties of the survivors are indistinguishable from their mature counterparts at 8 weeks of age [2,53]. Nevertheless, the structural modifications of dendritic spines and axonal boutons continue to occur as the adult born granule cells become older. Fully maturation of newborn neurons will take months [13], suggesting that synaptic plasticity of the new neurons will take quite a long period of time.

Interestingly, accumulating evidence indicates that immature granule cells in the adult dentate gyrus have specific electrophysiological properties different from their mature counterparts. In the period between 4 and 6 weeks of age, adult born neurons exhibit enhanced long-term potential (LTP) showing a higher potential amplitude and a lower induction threshold [54]. In addition, immature neurons are more easily to be recruited into the neural circuits than their mature counterparts [47,55,56]. The aforementioned findings reveal that young neurons appear to be more excitable than mature neurons and may differ from their mature counterparts in firing patterns. Increased neurogenesis which induces more new neurons taking part in the neuronal network may consequently affect the functions of hippocampus because of the higher activity.

Despite of limited techniques in humans and the deviates between species, there is compelling evidence on adult hippocampal neurogenesis and integration of the new born neurons (Fig. 1). From the synaptic perspective, the formation of new synapses enhances the plasticity of the pre-synaptic and post-synaptic neurons. From the neuronal network perspective, the formation of new synapses reflects the formation of a new neuronal network. A higher excitability of the new neurons makes the neuronal network even more sensitive to the stimulus, which maybe at least in part accounts for the increase of efficiency in processing information, thereby contributes to the improvement of hippocampus-dependent functions.

4. Physical exercise improves cognition via inducing hippocampal neurogenesis

There is growing evidence suggest that physical exercise enhances not only the physical health of individuals but also cognition and other brain functions. Physical exercise improves fitness, memory, attention and reading, thereby benefits academic achievement in children [57,58]. A large scale studies substantiate that cardiovascular fitness positively associated with intelligence [59,60]. Moreover, cardiovascular fitness during early adulthood predicts socioeconomic status and educational attainment later in life [60]. A meta-analysis study has shown that 1 to 12 months of exercise in healthy adults brings behavioral benefits in memory, attention, processing speed and executive function [61]. In addition, both acute and long-term physical exercise leads to improvement in physical performance, executive function and global cognition in healthy older adults and older adults with cognitive impairment [62,63].

In rodents, voluntary running exercise significantly increases proliferation of NPCs in the dentate gyrus [14,64] and also benefits spatial memory [16]. Moreover, treadmill running (forced exercise) can regulate hippocampal neurogenesis through an intensity-dependent manner. It was demonstrated that supra-lactate threshold treadmill exercise can significantly increase hippocampal neurogenesis [65], while treadmill running below the lactate threshold improves survival and maturation of new born neurons as well as benefits spatial memory [15]. Furthermore, wheel running increases spine motility and the mushroom spine density as well as enhances spine growth during early maturational stages, thereby, regulates the maturation and integration of newborn neurons into the hippocampal circuit [13]. It is strikingly that exercise heightens the amplitude of LTP in the dentate gyrus and improves learning characterized by faster acquisition and better retention tested in Morris water maze [64,66]. Thus, physical exercise is involved in the regulation of adult hippocampal neurogenesis including proliferation, differentiation, survival, maturation and function.

Collectively, above studies demonstrate that exercise benefits cognition in humans as well as in animals and increases neurogenesis in the dentate gyrus in rodents. However, whether exercise-induced hippocampal neurogenesis is the underpinning of beneficial effects that physical exercise brings to cognition? Studies using neurogenesis inhibition and IEG labeling techniques provide us with valuable information to cut through the fog. Focal irradiation to inhibit hippocampal neurogenesis results in cognitive deficits, whereas, 3 weeks wheel running ameliorates the impairment [67]. Another study using a lentiviral approach to block neurogenesis of dentate gyrus showed that blocking hippocampal neurogenesis impairs cognition in a level-dependent manner, and resulted in spatial memory decrease and even object recognition impairment [6]. Furthermore, IEG studies confirmed that new DGCs may be preferentially recruited into circuits, which mediate spatial information processing and memory formation [5,38,68].

However, other studies draw a different conclusion. It is suggested that ablation of hippocampal neurogenesis by focal irradiation impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus, but has no effect on spatial learning tested in Morris water maze and Y maze [40]. Swimming in the water maze with or without platform can both increase hippocampal neurogenesis, but young neurons are activated only by platform location training [68]. To some degree, these conflicting conclusions are interpreTable Spatial processing depends on the dorsal hippocampus, whereas anxiety-related behavior relies more on the ventral hippocampus [68]. Different irradiation regions and degrees of irradiation among the studies could be responsible for the deviation results in cognition [6,68]. It is also possible that there exist

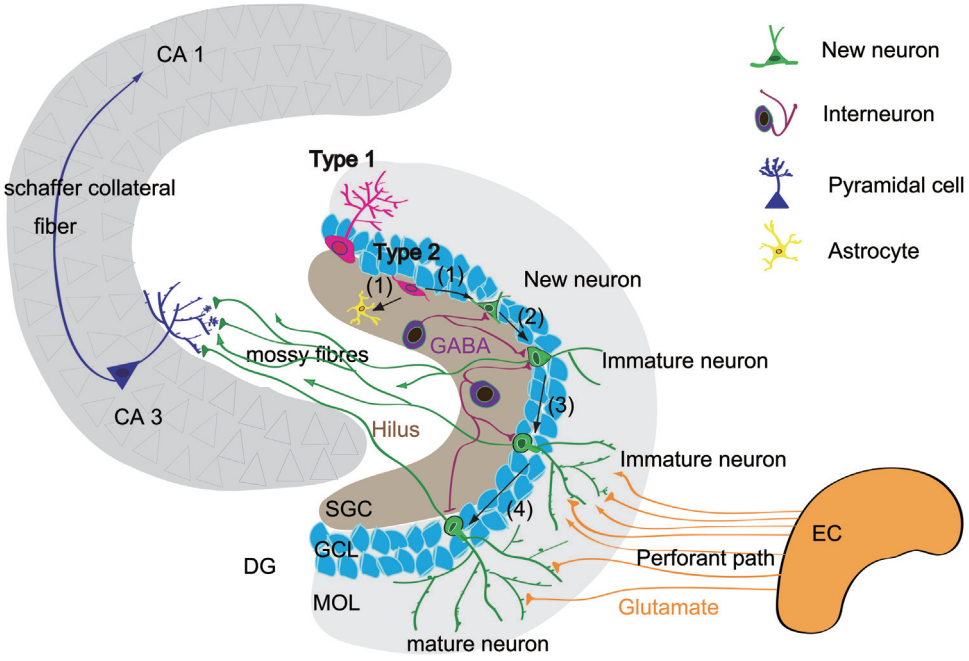

Fig. 1. Adult hippocampal neurogenesis and integration of the new born neurons. (1) Type 2 progenitors give rise to astrocytes and granule neurons. (2) Mainly neurite growth and the axons enter the hilus or CA3 area. (3) Spines formation and target axon boutons of perforant path from EC that already synapse with other spines, and axons of the immature neurons liable to form synapses with or near the thomy excrescences of the pyrimal cells in CA3. (4) Structural modification on neurite and finally the immature neurons become fully maturation. Before maturation the new neurons can be depolarezed by GABA coming from local interneurons, but inhibited by GABA when they maturation. DG, dentate gyrus; SGZ, subgranular zone; GCL, granular cell layer; MOL, molecular layer; EC, entorhinal cortex.

different mechanisms that regulate neurogenesis as well as activate the neurons. Neurogenesis is required for some but not other hippocampus-dependent tasks, and is not required for tasks that do not involve the hippocampus [69,70], therefore, the activation of adult born DGCs is situation-specific [71]. Although swimming is a sensitive stimulus to increase the hippocampal neurogenesis, but it is not the sensitive stimulus to activate these new adult born neurons.

The techniques of retroviral labeling and rabies virus mediated trans-synaptic retrograde tracing which are capable to define and quantify new neuron afferent inputs have paved the way for us to further understand the exercise-induced neurogenesis. Recent studies have demonstrated that wheel running regulates adult born neuron presynaptic connectivity from local interneurons or long-range projection neurons in subcortical regions [56,72], and specifically augments the innervations from entorhinal cortex [72]. Altogether, physical exercise may benefit cognition through increasing adult hippocampal neurogenesis, upregulation innervations between regions and reorganization of neural network, which represents a form of structural and network plasticity in hippocampus and other regions so as to refine neural connections. However, physical exercise-induced neurogenesis is required to contribute to some but not all hippocampus-dependent cognitions [69,73]. Recent evidence reveals that new adult born neurons indirectly encode and store memories by regulating excitation-inhibition balance [74].

5. Mechanisms of physical exercise induced hippocampal neurogenesis

Neurogenic niche, the microenvironments of SGZ and SVZ, may have specific factors that are permissive for the differentiation and incorporation of new neurons [45]. Adult progenitor cells derived from non-neurogenic areas exhibit self-renewal and multipotentiality once transplanted into a neurogenic brain area, and can differentiate in a region-specific context, suggesting that the microenvironment has a crucial role in providing and regulating fate-determining cues in the adult brain [75]. What makes the SGZ special in supporting the proliferation and differentiation of multipotent neural progenitors has attracted the interest of scientists. In addition to progenitors, there are mature neurons, astrocytes, oligodendrocytes, and endothelial cells [76], which may provide some of the components in the neurogenic niche contribute to the regulation of physical exercise-induced hippocampal neurogenesis. Fig. 2 highlights the mechanisms of physical exercise in promoting hippocampal neurogenesis.

Astrocytes, the most abundant cell type in the mammalian brain, make connections with neurons by tripartite synapses [77]. Astrocytes also surround blood vessels by the endfeet, which makes the astrocytes, neurons and blood vessels working together as functional units [78]. Therefore, astrocytes serve as bridges, relaying information and transporting substances between blood vessels and neurons. It is suggested that astrocytes play a key role in promoting the neuronal differentiation of adult hippocampal NPGs and in the integration of adult new born neurons [79]. There is evidence that exercise significantly increases the number of astrocytes in hippocampus and other regions of the brain [80,81], and lengthens the processes of astrocytes in hippocampus [81]. In addition, exercise can also induce transporters plastic changes in astrocytes such as improving the expression of glucose transporter1 (GLUT1) to support the increasing demand of glucose as neural activity enhancement [82]. Collectively, the effects of exercise on astrocyes may be partly responsible for the underling mechanism of exercise-induced hippocampal neurogenesis.

The vasculatures of the neurogenic niche regulate neural stem cell behavior by providing circulating and secreted factors. Various forms of cerebrovascular insufficiency such as reduced blood supply or disrupted microvascular integrity in cortical regions may occupy an initiating or intermediate position in the cognitive decline [83]. In addition, proliferating cells and putative neural progenitors in SGZ are closely associated with the vasculature, indicating that blood-derived factors may have a direct impact on adult

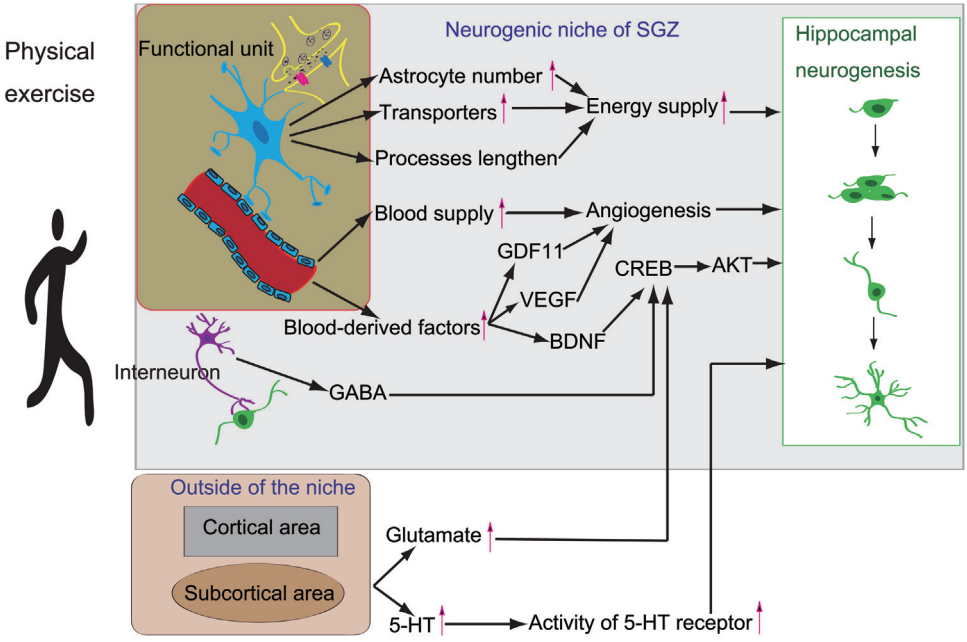

Fig. 2. Mechanisms of physical exercise induced hippocampal neurogenesis. In the neurogenic niche of the SGZ, physical exercise can regulate functions of both functional unit and local interneurons, which up-regulate the energy supply and the release of some regulation factors to improve the hippocampal neurogenesis. Physical exercise can also increase the release of neurotransmitters such as glutamate and 5-HT from cortical area or subcortical area (outside of the niche) to promote hippocampal neurogenesis. SGZ, subgranular zone; GDF11, growth differentiation factor 11; CREB, cAMP-response element binding protein; VEGF, vascular endothelial growth factor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; 5-HT, serotonin.

neural progenitors [84]. Indeed, factors such as growth differentiation factor 11 (GDF11) found in young blood induce vascular remodeling and increase neurogenesis in aging mice [85]. Moreover, vascular endothelial growth factor (VEGF) a common factor regulating angiogenesis secreted by endothelial cells, is implicated in improving neurogenesis in the SGZ [86] and exercise-induced neurogenesis in the hippocampus with improvement cognition acts in part through VEGFR2/Flk-1 signaling [87]. Conversely, blockade of VEGF abolishes exercise-induced neurogenesis [88].

Neurogenic niche are richly innervated by axonal inputs from local interneurons and distant cortical or subcortical regions [56]. Release of neurotransmitters and other factors by afferent inputs may regulate precursors at different stages of the stem cell lineage [76]. A number of different neurotransmitters such as serotonin (5-HT), GABA and glutamate play a role in the exercise-induced hippocampus neurogenesis. In the adult SGZ, GABA presumably from local interneurons has a depolarization effect on the maturing granule neurons during the initial period of hippocmpal neurogenesis [4]. The GABA-mediated activity seems to be important for the survival and maturation of adult born DGCs via cyclic AMP response element-binding protein (CREB) [89]. It is suggested that transcription factor CREB is activated by exercise-induced brain-derived neurotrophic factor (BDNF) expression and activation of cellular survival AKT signaling [90]. 5-HT also has an important role in the exercise-induced neurogenesis because stimulation of the 5-HT3 receptor promoted neurogenesis and 5-HT3 receptor subunit deficiency results in loss of exercise-induced hippocampal neurogenesis and antidepressant effects [91]. One type of the glutamate receptors, N-methyl-D-aspartate (NMDA) receptor, is involved in the increase of exercise-induced long-term potentiation (LTP) [92]. LTP induction dependents upon the activation of NMDA receptors, the competitive antagonist could block the effect [92,93]. In addition, exercise up-regulates the mRNA levels of NR2b, a subtype of NMDA receptor, and enhances BDNF expression in the dentate gyrus as well [92], indicating that enhanced secretion of glutamate and BDNF by local neurons or neurons outside of the neurogenic niche may contribute to the regulation of exercise-induced hippocapal neurogenesis.

Moreover, Bergami et al. recently highlighted that there is a critical time window during the new DGCs maturation in rodents [56]. In this time period, the new neurons are most sensitive to the stimuli such as enriched environment and physical exercise and exhibit stronger synaptic plasticity than mature DGCs, as indicated by the lower threshold for the induction of LTP and higher LTP amplitude [2,54,94]. This transient enhancement in plasticity may provide a fundamental rationale for the timing of exercise intervention implement which would produce optimal therapeutic effects. Literatures available revealed that the time window was 2–6 weeks and 4–6 weeks birth age of neurons in mice and in rats respectively [2,54,56]. Notably, if the hypothesis above proved to be correct, the critical time window may be coming later and time period may be longer in humans than in rodents because of the slower mitotic division rate and longer maturation time period in humans. Hence, understanding the details of the critical time window in humans seems important in exercise intervention to delay or halt brain aging and to get best therapeutic efficacy, as well as to develop adjunctive therapeutic strategies for neurodegenerative diseases or mental disorders.

6. Potential therapeutic and preventive implications of physical exercise in cognitive decline of aging-related neurodegenerative diseases

Aging, depression, AD and PD are characteristic of cognitive decline which is one of the major health challenges faced by modern society. Hippocampal neurogenesis decreases along with age, which may underlie cognitive impairments associated with aging-related neurodegenerative diseases such as AD and PD [95]. In addition, hippocampal neurogenesis reduction is a prominent feature in rodent models of stress and depression [9]. Intriguingly, some anti-depressant treatments result in enhancement of hippocampal neurogenesis as well as induction of LTP [34,96].

A growing body of evidence suggests that promotion of adult hippocampal neurogenesis improves cognition such as pattern separation and spatial memory [97]. Thus, improvement of hippocampal neurogenesis has the hope to delay or halt cognitive decline in these diseases.

Over the last decade, the use of NSCs transplantation to treat cognitive impairment has received growing attention, NSCs transplanted into the hippocampus give rise to neurons, astrocytes and oligodendrocytes [98] and reverse progressive cognitive decline associated with aging [99]. Furthermore, human NSCs injected into the lateral ventricle or transplanted into the hippocampus of aged rats incorporate into the host brain and improve cognition function as assessed by the Morris water maze [100,101]. However, this novel approach faces several issues such as reliable characterization, experimental reproducibility as well as mitotic capacity [22]. In addition, NSCs transplantation has a quite low rate of efficiency in the aged brain compared to the young [85]. Collectively, it seems a long way to go before NSCs transplantation can be used to cure cognition decline in humans.

Since the goal of stem cell transplantation is to introduce new neurons that could contribute to functional enhancement or reconstruction of impaired neuronal circuitry [10], physical exercise could be an alternative to achieve the goal. As discussed above, age related decline of neurogenesis and cognitive function is associated with reduced blood flow and decreased numbers of NSCs. Interestingly, physical exercise can rejuvenize the neurogenic niche with increased blood flow into brain and enhanced hippocampal neurogenesis and neuronal plasticity, thereby, should counteract the negative effects of aging. Recent meta-analysis reports unraveled that regular physical activity performed by elderly people plays a certain protective role against AD by improving cognition [102], and suggested that drug therapy for AD and mild cognitive impairment should be combined with exercise intervention [103]. In the Tg4-42 mouse model of AD, physical activity delays hippocampal neurodegeneration and rescues spatial memory deficits [104]. Altogether, physical exercise has emerged as an effective, low-cost, and low-tech way for prevention or slowdown of cognitive decline in aging and aging associated neurodegenerative diseases.

7. Conclusions and future directions

Neurogenesis in the hippocampus represents a form of morphological and functional plasticity in the mammalian adult brain. Activity-dependent regulation of neurogenesis and experience-dependent participation of adult born DGCs in information processing imply the contribution of adult born DGCs in hippocampus-dependent functions. Neurogenesis ablation and IEG labeling methods consistently suggest the involvement of adult born DGCs in learning and memory. Reduction of hippocampal neurogenesis is always accompanied with cognitive decline in diseases such as depression, AD and PD. Improvement of hippocampal neurogenesis induced by exercise benefits some but not all hippocampus-dependent functions. The precise mechanisms of exercise-induced neurogenesis are largely unclear. However, physical exercise may regulate the overall dynamic balance in the neurogenic niche through increasing proliferation of astrocytes and enhancing the secretion of some transmitters, growth factors or neurotrophic factors. The non-invasive imaging techniques have been developed for monitoring hippocampal neurogenesis in humans [24,25], despite their validity and precision await further testing. These techniques pave the ways for us to investigate the functions of hippocampal neurogenesis in living persons under various physiological or pathological conditions, which will hopefully lead to novel diagnoses and therapies for neurological disorders.

The potential that adult hippocampal neurogenesis can be manipulated has inspired hope for treatments to slow or even repair brain damage from diseases or injuries. Exogenous introduction of new neurons by transplantation of human NSCs [98–100,105] or perfusion of young blood into the aging brain to rejuvenate the neurogenic niche seems to be promising techniques in inducing brain plasticity for some diseases associated with cognitive decline. From this perspective, physical exercise known as a non-drug, non-invasive, low-cost and low-tech method to induce up-regulation of endogenous neurogenesis in the hippocampus and appears to be an available alternative therapeutic method. Bare in mind that hippocampal neurogenesis deviates between species and little information available to know how far the situation in animal models would reflect the conditions in the adult human brain. However, we speculate that neurogenesis generates more adult born DGCs, has slower mitotic division rate, owns higher granule neurons turnover rate and longer maturation time period in humans than in rodents based on the literatures available. Thus, more precise non-invasive techniques are warranted to further investigate hippocampal neurogenesis on physiological and pathological conditions in humans.

Moreover, understanding the time window of hippocampal neurogenesis in humans could be important for exercise intervention to delay or halt brain aging, as well as to develop adjunctive therapeutic strategies for neurodegenerative diseases or mental disorders.

Acknowledgements

This work was supported by the Science and Technology Department of Hubei Province [grant number, 2015CFA084]; and the Hubei Provincial Department of Education [grant numbers, D20144101, T201523]. The authors apologize to all whose original work could not be cited due to the limitation of the space.

References

[1] C. Pierret, J.A. Morrison, P. Rath, R.E. Zigler, L.A. Engel, C.L. Fairchild, et al., Developmental cues and persistent neurogenic potential within an in vitro neural niche, BMC Dev. Biol. 10 (2010) 5 (PubMed: 20074373).
[2] W. Deng, J.B. Aimone, F.H. Gage, New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat. Rev. Neurosci. 11 (2010) 339–350 (PubMed: 20354534).
[3] H. van Praag, A.F. Schinder, B.R. Christie, N. Toni, T.D. Palmer, Gage FH: Functional neurogenesis in the adult hippocampus, Nature 415 (2002) 1030–1034 (PubMed: 11875571).
[4] S. Ge, E.L. Goh, K.A. Sailor, Y. Kitabatake, G.L. Ming, H. Song, GABA regulates synaptic integration of newly generated neurons in the adult brain, Nature 439 (2006) 589–593 (PubMed: 16341203).
[5] N. Kee, C.M. Teixeira, A.H. Wang, P.W. Frankland, Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus, Nat. Neurosci. 10 (2007) 355–362 (PubMed: 17277773).
[6] S. Jessberger, R.E. Clark, N.J. Broadbent, G.D. Clemenson Jr., A. Consiglio, D.C. Lie, et al., Dentate gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in adult rats, Learn. Mem. 16 (2009) 147–154 (PubMed: 19181621).
[7] A. Sahay, K.N. Scobie, A.S. Hill, C.M. O'Carroll, M.A. Kheirbek, N.S. Burghardt, et al., Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation, Nature 472 (2011) 466–470 (PubMed: 21460835).
[8] A. Sahay, D.A. Wilson, R. Hen, Pattern separation: a common function for new neurons in hippocampus and olfactory bulb, Neuron 70 (2011) 582–588 (PubMed: 21609817).
[9] A. Sahay, R. Hen, Adult hippocampal neurogenesis in depression, Nat. Neurosci. 10 (2007) 1110–1115 (PubMed: 17726477).
[10] O. Lazarov, M.P. Mattson, D.A. Peterson, S.W. Pimplikar, H. van Praag, When neurogenesis encounters aging and disease, Trends Neurosci. 33 (2010) 569–579 (PubMed: 20961627).
[11] Y. Brehmer, G. Kalpouzos, E. Wenger, M. Lovden, Plasticity of brain and cognition in older adults, Psychol. Res. 78 (2014) 790–802 (PubMed: 25261907).
[12] G.L. Ming, H. Song, Adult neurogenesis in the mammalian brain: significant answers and significant questions, Neuron 70 (2011) 687–702 (PubMed: 21609825).

[13] C. Zhao, E.M. Teng, R.G. Summers Jr., G.L. Ming, F.H. Gage, Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus, J. Neurosci. 26 (2006) 3–11 (PubMed: 16399667).
[14] S.Y. Yau, J. Gil-Mohapel, B.R. Christie, K.F. So, Physical exercise-induced adult neurogenesis: a good strategy to prevent cognitive decline in neurodegenerative diseases? BioMed. Res. Int. 2014 (2014) 403120 (PubMed: 24818140).
[15] K. Inoue, M. Okamoto, J. Shibato, M.C. Lee, T. Matsui, R. Rakwal, et al., Long-term mild, rather than intense, exercise enhances adult hippocampal neurogenesis and greatly changes the transcriptomic profile of the hippocampus, PLoS One 10 (2015) e0128720 (PubMed: 26061528).
[16] M.C. Lee, K. Inoue, M. Okamoto, Y.F. Liu, T. Matsui, J.S. Yook, et al., Voluntary resistance running induces increased hippocampal neurogenesis in rats comparable to load-free running, Neurosci. Lett. 537 (2013) 6–10 (PubMed: 23352660).
[17] Y.H. Sung, Effects of treadmill exercise on hippocampal neurogenesis in an MPTP/probenecid-induced Parkinson's disease mouse model, J. Phys. Sci. 27 (2015) 3203–3206 (PubMed: 26644675).
[18] C. Vivar, B.D. Peterson, H. van Praag, Running rewires the neuronal network of adult-born dentate granule cells, Neuroimage 131 (2016) 29–41 (PubMed: 26589333).
[19] P.S. Eriksson, E. Perfilieva, T. Bjork-Eriksson, A.M. Alborn, C. Nordborg, D.A. Peterson, et al., Neurogenesis in the adult human hippocampus, Nat. Med. 4 (1998) 1313–1317 (PubMed: 9809557).
[20] R. Knoth, I. Singec, M. Ditter, G. Pantazis, P. Capetian, R.P. Meyer, et al., Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years, PLoS One 5 (2010) e8809 (PubMed: 20126454).
[21] N.S. Roy, S. Wang, L. Jiang, J. Kang, A. Benraiss, C. Harrison-Restelli, et al., In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus, Nat. Med. 6 (2000) 271–277 (PubMed: 10700228).
[22] T.I. Park, H. Monzo, E.W. Mee, P.S. Bergin, H.H. Teoh, J.M. Montgomery, et al., Adult human brain neural progenitor cells (NPCs) and fibroblast-like cells have similar properties in vitro but only NPCs differentiate into neurons, PLoS One 7 (2012) e37742 (PubMed: 22675489).
[23] K.L. Spalding, O. Bergmann, K. Alkass, S. Bernard, M. Salehpour, H.B. Huttner, et al., Dynamics of hippocampal neurogenesis in adult humans, Cell 153 (2013) 1219–1227 (PubMed: 23746839).
[24] L.N. Manganas, X. Zhang, Y. Li, R.D. Hazel, S.D. Smith, M.E. Wagshul, et al., Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain, Science 318 (2007) 980–985 (PubMed: 17991865).
[25] A.C. Pereira, D.E. Huddleston, A.M. Brickman, A.A. Sosunov, R. Hen, G.M. McKhann, et al., An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 5638–5643 (PubMed: 17374720).
[26] J.S. Snyder, H.A. Cameron, Could adult hippocampal neurogenesis be relevant for human behavior? Behav. Brain Res. 227 (2012) 384–390 (PubMed: 21736900).
[27] H.G. Kuhn, H. Dickinson-Anson, F.H. Gage, Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation, J. Neurosci. 16 (1996) 2027–2033 (PubMed: 8604047).
[28] B. Leuner, Y. Kozorovitskiy, C.G. Gross, E. Gould, Diminished adult neurogenesis in the marmoset brain precedes old age, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 17169–17173 (PubMed: 17940008).
[29] I. Imayoshi, M. Sakamoto, T. Ohtsuka, K. Takao, T. Miyakawa, M. Yamaguchi, et al., Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain, Nat. Neurosci. 11 (2008) 1153–1161 (PubMed: 18758458).
[30] S.J. Kohler, N.I. Williams, G.B. Stanton, J.L. Cameron, W.T. Greenough, Maturation time of new granule cells in the dentate gyrus of adult macaque monkeys exceeds six months, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 10326–10331 (PubMed: 21646517).
[31] L.R. Squire, L. Genzel, J.T. Wixted, R.G. Morris, Memory consolidation, Cold Spring Harb Perspect. Biol. 7 (2015) a021766 (PubMed: 26238360).
[32] S. Kim, A.J. Dede, R.O. Hopkins, L.R. Squire, Memory, scene construction, and the human hippocampus, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 4767–4772 (PubMed: 25825712).
[33] A.J. Dede, J.T. Wixted, R.O. Hopkins, L.R. Squire, Hippocampal damage impairs recognition memory broadly, affecting both parameters in two prominent models of memory, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 6577–6582 (PubMed: 23576763).
[34] A. Sahay, R. Hen, Hippocampal neurogenesis and depression, Novartis Found. Symp. 289 (2008) 152–160 (discussion 60-4, 93-5. [PubMed: 18497101]).
[35] R.A. Countryman, N.L. Kaban, P.J. Colombo, Hippocampal c-fos is necessary for long-term memory of a socially transmitted food preference, Neurobiol. Learn Mem. 84 (2005) 175–183 (PubMed: 16122949).
[36] C.A. Smith, R.A. Countryman, L.L. Sahuque, P.J. Colombo, Time-courses of Fos expression in rat hippocampus and neocortex following acquisition and recall of a socially transmitted food preference, Neurobiol. Learn Mem. 88 (2007) 65–74 (PubMed: 17448703).
[37] A. Tashiro, H. Makino, F.H. Gage, Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage, J. Neurosci. 27 (2007) 3252–3259 (PubMed: 16906136).
[38] V. Ramirez-Amaya, A. Angulo-Perkins, M.K. Chawla, C.A. Barnes, S. Rosi, Sustained transcription of the immediate early gene Arc in the dentate gyrus after spatial exploration, J. Neurosci. 33 (2013) 1631–1639 (PubMed: 23345235).
[39] J.S. Snyder, N.S. Hong, R.J. McDonald, J.M. Wojtowicz, A role for adult neurogenesis in spatial long-term memory, Neurosci 130 (2005) 843–852 (PubMed: 15652983).
[40] M.D. Saxe, F. Battaglia, J.W. Wang, G. Malleret, D.J. David, J.E. Monckton, et al., Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 17501–17506 (PubMed: 17088541).
[41] A.S. Hill, A. Sahay, R. Hen, Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors, Neuropsychopharmacology 40 (2015) 2368–2378 (PubMed: 25833129).
[42] Y. Mu, F.H. Gage, Adult hippocampal neurogenesis and its role in Alzheimer's disease, Mol. Neurodegener. 6 (2011) 85 (PubMed: 22192775).
[43] D.J. Jhaveri, C.J. Taylor, P.F. Bartlett, Activation of different neural precursor populations in the adult hippocampus: does this lead to new neurons with discrete functions? Dev. Neurobiol. 72 (2012) 1044–1058 (PubMed: 22505142).
[44] Y.C. Hsu, D.C. Lee, I.M. Chiu, Neural stem cells, neural progenitors, and neurotrophic factors, Cell Transplant. 16 (2007) 133–150 (PubMed: 17474295).
[45] C. Zhao, W. Deng, F.H. Gage, Mechanisms and functional implications of adult neurogenesis, Cell 132 (2008) 645–660 (PubMed: 18295581).
[46] J. Song, C. Zhong, M.A. Bonaguidi, G.J. Sun, D. Hsu, Y. Gu, et al., Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision, Nature 489 (2012) 150–154 (PubMed: 22842902).
[47] N. Toni, D.A. Laplagne, C. Zhao, G. Lombardi, C.E. Ribak, F.H. Gage, et al., Neurons born in the adult dentate gyrus form functional synapses with target cells, Nat. Neurosci. 11 (2008) 901–907 (PubMed: 18622400).
[48] J. Song, J. Sun, J. Moss, Z. Wen, G.J. Sun, D. Hsu, et al., Parvalbumin interneurons mediate neuronal circuitry-neurogenesis coupling in the adult hippocampus, Nat. Neurosci. 16 (2013) 1728–1730 (PubMed: 24212671).
[49] N. Toni, E.M. Teng, E.A. Bushong, J.B. Aimone, C. Zhao, A. Consiglio, et al., Synapse formation on neurons born in the adult hippocampus, Nat. Neurosci. 10 (2007) 727–734 (PubMed: 17486101).
[50] R.L. Faulkner, M.H. Jang, X.B. Liu, X. Duan, K.A. Sailor, J.Y. Kim, et al., Development of hippocampal mossy fiber synaptic outputs by new neurons in the adult brain, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14157–14162 (PubMed: 18780780).
[51] A.G. Dayer, A.A. Ford, K.M. Cleaver, M. Yassaee, H.A. Cameron, Short-term and long-term survival of new neurons in the rat dentate gyrus, J. Comp. Neurol. 460 (2003) 563–572 (PubMed: 12717714).
[52] H.Y. McDonald, J.M. Wojtowicz, Dynamics of neurogenesis in the dentate gyrus of adult rats, Neurosci. Lett. 385 (2005) 70–75 (PubMed: 15967575).
[53] C. Schmidt-Hieber, P. Jonas, J. Bischofberger, Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus, Nature 429 (2004) 184–187 (PubMed: 15107864).
[54] S. Ge, C.H. Yang, K.S. Hsu, G.L. Ming, H. Song, A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain, Neuron 54 (2007) 559–566 (PubMed: 17521569).
[55] A. Tashiro, V.M. Sandler, N. Toni, C. Zhao, F.H. Gage, NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus, Nature 442 (2006) 929–933 (PubMed: 16906136).
[56] M. Bergami, G. Masserdotti, S.G. Temprana, E. Motori, T.M. Eriksson, J. Gobel, et al., A critical period for experience-dependent remodeling of adult-born neuron connectivity, Neuron 85 (2015) 710–717 (PubMed: 25661179).
[57] I. Niederer, S. Kriemler, J. Gut, T. Hartmann, C. Schindler, J. Barral, et al., Relationship of aerobic fitness and motor skills with memory and attention in preschoolers (Ballabeina): a cross-sectional and longitudinal study, BMC Pediatr. 11 (2011) 34 (PubMed: 21569343).
[58] C.H. Hillman, S.M. Buck, J.R. Themanson, M.B. Pontifex, D.M. Castelli, Aerobic fitness and cognitive development: event-related brain potential and task performance indices of executive control in preadolescent children, Dev. Psychol. 45 (2009) 114–129 (PubMed: 19209995).
[59] A.L. Fedewa, S. Ahn, The effects of physical activity and physical fitness on children's achievement and cognitive outcomes: a meta-analysis, Res Q Exer Sport. 82 (2011) 521–535 (PubMed: 21957711).
[60] M.A. Aberg, N.L. Pedersen, K. Toren, M. Svartengren, B. Backstrand, T. Johnsson, et al., Cardiovascular fitness is associated with cognition in young adulthood, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 20906–20911 (PubMed: 19948959).
[61] P.J. Smith, J.A. Blumenthal, B.M. Hoffman, H. Cooper, T.A. Strauman, K. Welsh-Bohmer, et al., Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials, Psychosom. Med. 72 (2010) 239–252 (PubMed: 20223924).
[62] C.H. Chu, A.G. Chen, T.M. Hung, C.C. Wang, Y.K. Chang, Exercise and fitness modulate cognitive function in older adults, Psychol. Aging 30 (2015) 842–848 (PubMed: 26652724).
[63] F. Li, P. Harmer, Y. Liu, L.S. Chou, Tai Ji Quan and global cognitive function in older adults with cognitive impairment: a pilot study, Arch. Gerontol. Geriatr. 58 (2014) 434–439 (PubMed: 24398166).
[64] H. van Praag, B.R. Christie, T.J. Sejnowski, F.H. Gage, Running enhances neurogenesis, learning, and long-term potentiation in mice, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 13427–13431 (PubMed: 10557337).

[65] E. L, J.M. Burns, R.H. Swerdlow, Effect of high-intensity exercise on aged mouse brain mitochondria, neurogenesis, and inflammation, Neurobiol. Aging 35 (2014) 2574–2583 (PubMed: 25002036).
[66] H. van Praag, T. Shubert, C. Zhao, F.H. Gage, Exercise enhances learning and hippocampal neurogenesis in aged mice, J. Neurosci. 25 (2005) 8680–8685 (PubMed: 16177036).
[67] J.F. Ji, S.J. Ji, R. Sun, K. Li, Y. Zhang, L.Y. Zhang, et al., Forced running exercise attenuates hippocampal neurogenesis impairment and the neurocognitive deficits induced by whole-brain irradiation via the BDNF-mediated pathway, Biochem. Biophys. Res. Commun. 443 (2014) 646–651 (PubMed: 24333433).
[68] J.S. Snyder, R. Radik, J.M. Wojtowicz, H.A. Cameron, Anatomical gradients of adult neurogenesis and activity: young neurons in the ventral dentate gyrus are activated by water maze training, Hippocampus 19 (2009) 360–370 (PubMed: 19004012).
[69] D. Dupret, J.M. Revest, M. Koehl, F. Ichas, F. De Giorgi, P. Costet, et al., Spatial relational memory requires hippocampal adult neurogenesis, PLoS One 3 (2008) e1959 (PubMed: 18509506).
[70] T.J. Shors, G. Miesegaes, A. Beylin, M. Zhao, T. Rydel, E. Gould, Neurogenesis in the adult is involved in the formation of trace memories, Nature 410 (2001) 372–376 (PubMed: 11268214).
[71] S. [71].Trouche, B. Bontempi, P. Roullet, C. Rampon, Recruitment of adult-generated neurons into functional hippocampal networks contributes to updating and strengthening of spatial memory, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 5919–5924 (PubMed: 19321751).
[72] Vivar C, B.D. Peterson, H. van Praag, Running rewires the neuronal network of adult-born dentate granule cells, Neuroimage (2015) (PubMed: 26589333]).
[73] T.J. Shors, D.A. Townsend, M. Zhao, Y. Kozorovitskiy, E. Gould, Neurogenesis may relate to some but not all types of hippocampal-dependent learning, Hippocampus 12 (2002) 578–584 (PubMed: 12440573).
[74] E.H. Park, N.S. Burghardt, D. Dvorak, R. Hen, A.A. Fenton, Experience-dependent regulation of dentate gyrus excitability by adult-born granule cells, J. Neurosci. 35 (2015) 11656–11666 (PubMed: 26290242).
[75] L.S. Shihabuddin, P.J. Horner, J. Ray, F.H. Gage, Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus, J. Neurosci. 20 (2000) 8727–8735 (PubMed: 11102479).
[76] P.A. Riquelme, E. Drapeau, F. Doetsch, Brain micro-ecologies: neural stem cell niches in the adult mammalian brain, Philos. Trans. R. Soc. Lond. B. Bio. Sci. 363 (2008) 123–137 (PubMed: 17322003).
[77] A. Panatier, M. Arizono, U.V. Nagerl, Dissecting tripartite synapses with STED microscopy, Philos. Trans. R. Soc. Lond. B. Bio. Sci. 369 (2014) 20130597 (PubMed: 25225091).
[78] M.R. Freeman, Specification and morphogenesis of astrocytes, Science 330 (2010) 774–778 (PubMed: 21051628).
[79] H.J. Song, C.F. Stevens, F.H. Gage, Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons, Nat Nurosci. 5 (2002) 438–445 (PubMed: 11953752).
[80] J. Li, Y.H. Ding, J.A. Rafols, Q. Lai, J.P. McAllister, Y. 2nd Ding, Increased astrocyte proliferation in rats after running exercise, Neurosci. Lett. 386 (2005) 160–164 (PubMed: 16024173).
[81] L. Saur, P.P. Baptista, P.N. de Senna, M.F. Paim, P. do Nascimento, J. Ilha, et al., Physical exercise increases GFAP expression and induces morphological changes in hippocampal astrocytes, Brain Struct. Funct. 219 (2014) 293–302 (PubMed: 23288255).
[82] A. Allen, C. Messier, Plastic changes in the astrocyte GLUT1 glucose transporter and beta-tubulin microtubule protein following voluntary exercise in mice, Behav. Brain Res. 240 (2013) 95–102 (PubMed: 23201358).
[83] E. Farkas, P.G. Luiten, Cerebral microvascular pathology in aging and Alzheimer's disease, Prog. Neurobiol. 64 (2001) 575–611 (PubMed: 11311463).
[84] T.D. Palmer, A.R. Willhoite, F.H. Gage, Vascular niche for adult hippocampal neurogenesis, J. Comp. Neurol. 425 (2000) 479–494 (PubMed: 10975875).
[85] L. Katsimpardi, N.K. Litterman, P.A. Schein, C.M. Miller, F.S. Loffredo, G.R. Wojtkiewicz, et al., Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors, Science 344 (2014) 630–634 (PubMed: 24797482).
[86] K. Jin, Y. Zhu, Y. Sun, X.O. Mao, L. Xie, D.A. Greenberg, Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 11946–11950 (PubMed: 12181492).
[87] L. Cao, X. Jiao, D.S. Zuzga, Y. Liu, D.M. Fong, D. Young, et al., VEGF links hippocampal activity with neurogenesis, learning and memory, Nat. Genet. 36 (2004) 827–835 (PubMed: 15258583).
[88] K. Fabel, K. Fabel, B. Tam, D. Kaufer, A. Baiker, N. Simmons, et al., VEGF is necessary for exercise-induced adult hippocampal neurogenesis, Eur. J. Neurosci. 18 (2003) 2803–2812 (PubMed: 14656329).
[89] R. Jagasia, K. Steib, E. Englberger, S. Herold, T. Faus-Kessler, M. Saxe, et al., GABA-cAMP response element-binding protein signaling regulates maturation and survival of newly generated neurons in the adult hippocampus, J. Neurosci. 29 (2009) 7966–7977 (PubMed: 19553437).
[90] M.J. Chen, A.A. Russo-Neustadt, Running exercise-induced up-regulation of hippocampal brain-derived neurotrophic factor is CREB-dependent, Hippocampus 19 (2009) 962–972 (PubMed: 19294650).
[91] M. Kondo, Y. Nakamura, Y. Ishida, S. Shimada, The 5-HT3 receptor is essential for exercise-induced hippocampal neurogenesis and antidepressant effects, Mol. Psychiatry 20 (2015) 1428–1437 (PubMed: 25403840).
[92] J. Farmer, X. Zhao, H. van Praag, K. Wodtke, F.H. Gage, B.R. Christie, Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo, Neurosci 124 (2004) 71–79 (PubMed: 14960340).
[93] L. Muller, T. Tokay, K. Porath, R. Kohling, T. Kirschstein, Enhanced NMDA receptor-dependent LTP in the epileptic CA1 area via upregulation of NR2B, Neurobiol. Dis. 54 (2013) 183–193 (PubMed: 23313317).
[94] M.S. Esposito, V.C. Piatti, D.A. Laplagne, N.A. Morgenstern, C.C. Ferrari, F.J. Pitossi, et al., Neuronal differentiation in the adult hippocampus recapitulates embryonic development, J. Neurosci. 25 (2005) 10074–10086 (PubMed: 16267214).
[95] S. Couillard-Despres, B. Iglseder, L. Aigner, Neurogenesis, cellular plasticity and cognition: the impact of stem cells in the adult and aging brain–a mini-review, Gerontology 57 (2011) 559–564 (PubMed: 21311170).
[96] D.J. David, B.A. Samuels, Q. Rainer, J.W. Wang, D. Marsteller, I. Mendez, et al., Neurogenesis-dependent and −independent effects of fluoxetine in an animal model of anxiety/depression, Neuron 62 (2009) 479–493 (PubMed: 19477151).
[97] C.D. Clelland, M. Choi, C. Romberg, G.D. Clemenson Jr., A. Fragniere, P. Tyers, et al., A functional role for adult hippocampal neurogenesis in spatial pattern separation, Science 325 (2009) 210–213 (PubMed: 19590004).
[98] H. Hodges, T. Veizovic, N. Bray, S.J. French, T.P. Rashid, A. Chadwick, et al., Conditionally immortal neuroepithelial stem cell grafts reverse age-associated memory impairments in rats, Neurosci 101 (2000) 945–955 (PubMed: 11113344).
[99] A.K. Shetty, M.S. Rao, B. Hattiangady, Behavior of hippocampal stem/progenitor cells following grafting into the injured aged hippocampus, J. Neurosci. Res. 86 (2008) 3062–3074 (PubMed: 18618674).
[100] T. Qu, C.L. Brannen, H.M. Kim, K. Sugaya, Human neural stem cells improve cognitive function of aged brain, Neuroreport 12 (2001) 1127–1132 (PubMed: 11338178).
[101] R.R. Ager, J.L. Davis, A. Agazaryan, F. Benavente, W.W. Poon, F.M. LaFerla, et al., Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss, Hippocampus 25 (2015) 813–826 (PubMed: 25530343).
[102] A. Santos-Lozano, H. Pareja-Galeano, F. Sanchis-Gomar, M. Quindos-Rubial, C. Fiuza-Luces, C. Cristi-Montero, et al., Physical activity and Alzheimer disease: a protective association, Mayo Clin. Proc. 91 (2016) 999–1020 (PubMed: 27492909).
[103] A. Strohle, D.K. Schmidt, F. Schultz, N. Fricke, T. Staden, R. Hellweg, Drug and exercise treatment of Alzheimer disease and mild cognitive impairment: a systematic review and meta-analysis of effects on cognition in randomized controlled trials, Am. J. Geriatr. Psychiatry 23 (2015) 1234–1249 (PubMed: 27492909).
[104] M. Huttenrauch, A. Brauss, A. Kurdakova, H. Borgers, F. Klinker, D. Liebetanz, et al., Physical activity delays hippocampal neurodegeneration and rescues memory deficits in an Alzheimer disease mouse model, Transl Psychiatry. 6 (2016) e800 (PubMed: 27138799).
[105] H.C. Dunn, R.R. Ager, D. Baglietto-Vargas, D. Cheng, M. Kitazawa, D.H. Cribbs, et al., Restoration of lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse model, J. Alzheimers Dis. 43 (2015) 893–903 (PubMed: 25125468).