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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.

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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).

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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