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Mini review article

WHAT DO WE KNOW ABOUT ADULT MAMMALIAN HIPPOCAMPAL NEUROGENESIS SO FAR?

ŠTA ZNAMO O ADULTNOJ NEUROGENEZI U HIPOKAMPUSU?

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Abstract

It is known that the adult mammalian brain can add new neurons throughout the whole lifespan. Neural stem cells reside in the subgranular zone of the dentate gyrus of the hippocampus and the subventricular zone of the rostral lateral ventricle. Neural stem cells in the subgranular zone give the excitatory granular cells of the dentate gyrus, and in the subventricular zone give new interneurons that migrate to the olfactory bulb.

The following review will focus on characteristics of adult mammalian neurogenesis in the hippocampus. Furthermore, it will emphasize what happens to adult neurogenesis in Alzheimer's disease and depression. Also, it will discuss the still open question of the existence of adult neurogenesis in humans.

Even though adult neurogenesis has been demonstrated in several species, we still do not know what the exact differences are between species and why some animals, like cetaceans, do not have the ability to generate new neurons in the hippocampus. Future studies must focus on the exact conditions and factors required for the proper development of adult neurogenesis, as it is conserved in different species. Also, interdisciplinary studies are required to explore the function of neurogenesis in the context of species adaptation to the environment as an evolutionary mechanism. More importantly, adult neurogenesis in humans remains an open question.

Keywords:
adult neurogenesis,
hippocampus,
dentate gyrus,
subgranular zone

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Sažetak

Poznato je da mozak odraslih sisara može da stvara nove neurone tokom celog života. Neuralne stem ćelije se nalaze u subgranularnoj zoni dentatnog girusa hipokampusa i u subventrikularnoj zoni lateralnih komora mozga. Neuralne stem ćelije u subgranularnoj zoni stvaraju ekscitatorne granularne neurone dentatnog girusa, a u subventrikularnoj zoni nove interneurone koji migriraju u olfaktorni bulbus.

Ovaj revijski rad će se fokusirati na karakteristike neurogeneze u hipokampusu kod odraslih sisara. Pokušaćemo i da razmotrimo trenutno poznate činjenice o još uvek aktivnom pitanju o postojanju neurogeneze kod odraslih ljudi. Između ostalog, dotaći ćemo se pitanja šta se dešava sa procesom adultne neurogeneze kod osoba obolelih od Alchajmerove bolesti i depresije.

Iako je postojanje adultne neurogeneze pokazano u različitim vrstama, još uvek ne znamo koje su tačne razlike između vrsta i zašto neke životinje ne mogu da stvaraju nove neurone u hipokampusu. Veoma je važno da se nove studije fokusiraju na uslove i faktore koji su neophodni za pravilno odvijanje adultne neurogeneze. Takođe su neophodne interdisciplinarne studije koje će pokazati koja je funkcija adultne neurogeneze u evolutivnom procesu. Adultna neurogeneza kod ljudi i dalje ostaje otvoreno pitanje.

Ključne reči:
adultna neurogeneza,
hipokampus,
dentatni girus,
subgranularna zona

Introduction

For a long time, scientists followed Santiago Ramon y Cajal's statement, which stated that new mature neurons in the adult brain could not be generated (1). It was believed that only during prenatal and early postnatal development neural stem cells (NSCs) could proliferate and generate mature neurons, which can integrate into the neuronal circuits (2). Altman, Bayer, Kaplan, Nottebohm, and others dismissed this thesis as they showed that new neurons do generate in the adult brain (3). Although adult mammalian neurogenesis has been discussed for more than 40 years, the term itself has only recently been accepted (4). Tremendous effort has been put forth for the scientific community to approve that the adult mammalian brain can add new neurons through adulthood (3). Based on a growing body of evidence, it is now known that a lot of mammalian species can produce new neurons (5).

Some parts of the adult brain can provide the essential environment, such as specific characteristics of the extracellular matrix (6), necessary for the existence, proliferation, and differentiation of NSCs (7). Having that in mind, in a healthy brain NSCs are placed in the privileged parts of the brain, so-called neurogenic regions: the subgranular zone (SGZ) of the dentate gyrus of the hippocampus and subventricular zone (SVZ) of the rostral lateral ventricle (8). In brief, NSCs in the SGZ give the excitatory granular cells (GCs) of the dentate gyrus (7), while NSCs in the SVZ give new interneurons that migrate to the olfactory bulb (9). In addition to the SGZ and SVZ, adult neurogenesis has been reported in other parts of the brain, like the amygdala, neocortex, and striatum (10).

To our knowledge, NSCs can be in an active or quiescence state (11). When cells are in the quiescence state, they are in the G0 or G2 phase of the cell cycle so that they can reenter the cell cycle (12). Depending on the surrounding conditions, these cells can choose whether they would be active or quiescence (11). According to this, many physiological or pathological factors (**figure 1**) can either enhance or inhibit adult neurogenesis (13).

The following review will focus on characteristics of adult mammalian neurogenesis in the hippocampus. Also, it will discuss the active question about the existence of adult neurogenesis in humans.

Adult mammalian neurogenesis in the dentate gyrus

The hippocampus is a part of the limbic system, placed in the temporal lobe (13). It is known that the dorsal hippocampus regulates cognitive functions compared to the ventral hippocampus, which regulates emotional functions, like mood, anxiety, and stress- and fear-based behavior (14). In addition, the hippocampus plays an essential role in the first steps of processing information and learning and forming episodic and spatial memory (5).

Hippocampus consists of the dentate gyrus (DG) and hippocampus proper (CA1, CA2, and CA3 region) (15). Dentate gyrus has a laminar stratification and contains the molecular layer, granular cell layer (GCL), and hilus. The GCL of the DG is further divided into the outer, middle, and inner third of granular neurons and the subgranular zone (SGZ), where the NSCs are located (16). The GCs are densely packed neurons placed in the granular layer, and they play the most significant roles in the physiological functions attributed to the hippocampus (17). However, the GCL is not the only place where the GCs can be located, and according to their different position, they can be named semilunar or ectopic. Semilunar GCs rise in the inner molecular layer, while ectopic GCs exist in the hilus (18). The newly generated GCs first make synapses with GABAergic inhibitory interneurons, then with the glutaminergic hilar mossy cells and the neurons in the entorhinal cortex (7). Finally, they project axons as mossy fibers through the hilus to the CA3 region, making glutaminergic synapses with pyramidal cells. The CA3 pyramidal cells make synapses with the CA1

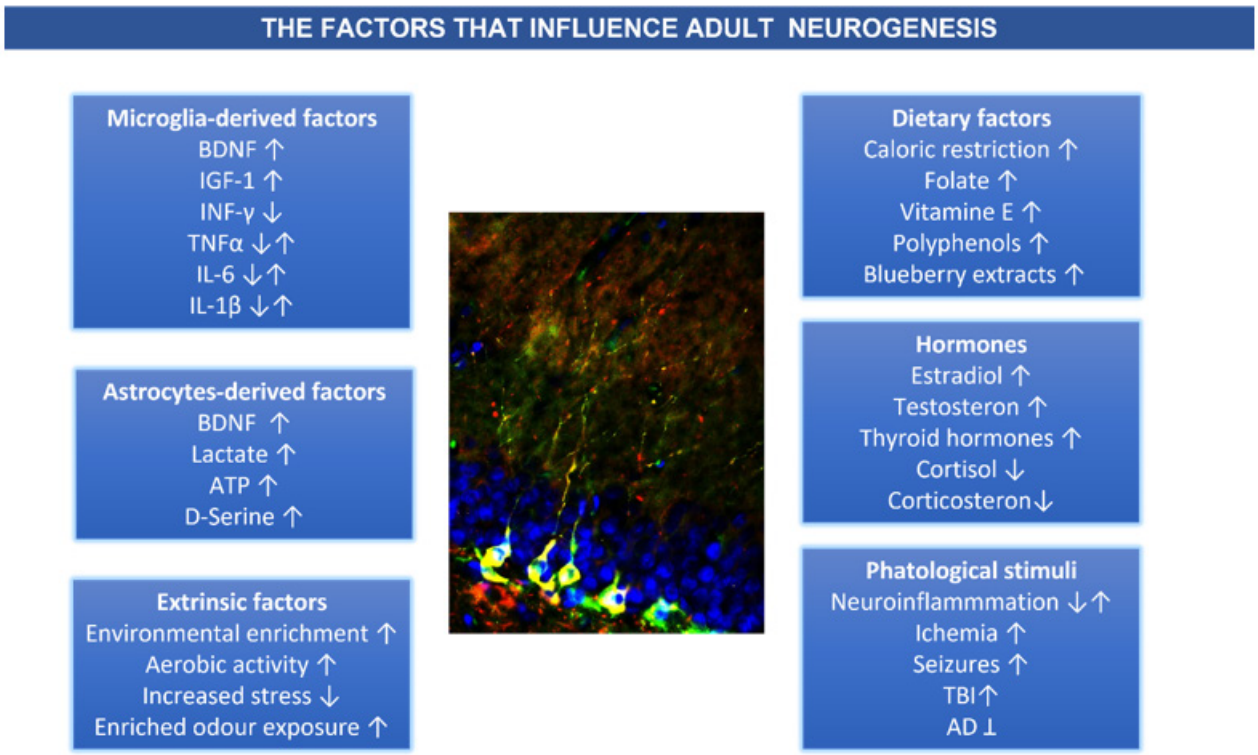

Figure 1. Factors that influence adult neurogenesis in the dentate gyrus of the hippocampus.

Proliferating neurons are labeled with doublecortin (DCX, marker of immature neurons) and DAPI. ↑ - enhance adult neurogenesis, ↓ - inhibits adult neurogenesis, ↑↓ - effect on neurogenesis depends on dose, ⊥ - conflicting results. Abbreviations: BDNF - brain-derived neurotrophic factor; IGF-1 - insulin-like growth factor-1; IFN-γ - interferon-γ; TNF-α - tumor necrosis factor alfa; IL-6 - interleukin 6; IL-1β - interleukin 1β; ATP - adenosine triphosphate; TBI - traumatic brain injury; AD - Alzheimer disease.

pyramidal cells, sending axons out of the hippocampus (19). Furthermore, they also send signals to mossy cells (excitatory hilar neurons), to the pyramidal cells in the CA2 region, to inhibitory interneurons in the CA3 region, and to the whole DG (7).

A prominent feature of the DG is that neurons are added throughout the lifespan in this brain region. According to the different studies, it is assumed that adult neurogenesis in the DG enhances neuronal plasticity, increasing the hippocampus's function (4, 20). As stated, in the adult hippocampus, neural stem cells reside in the SGZ of the DG, which is placed between the GCL and the hilus (20). Upon activation, NSCs develop into neural progenitors that migrate radially to the GCL of the DG and integrate after differentiation into the existing neural network (21).

To date, scientists know that the NSCs can self-renewal (7), and they exhibit multipotency (4). However, the NSCs must go through distinct stages during adult neurogenesis. This process, from the NSCs to fully integrated granular cells, may last for months (21). Throughout this period, cells can proliferate, differentiate, maturate, migrate, integrate into neuronal circuits, or die via apoptosis (15). In case of neuronal death, microglia will phagocytize them (7).

Type 1 cells in the DG, so-called radial glial-like cells, undergo rapid division and, in that manner, produce intermediate progenitor cells (type 2a and type 2b), which can proliferate and differentiate. Furthermore, type 2b become neuroblasts (type 3 cells), which migrate, differentiate, and maturate into the GCs (4, 7).

During the aforementioned processes, these cells change their shape, physiology, and markers that they express on the surface of the cell membrane. The NSCs in the DG at the end can generate either granular neurons of the DG or astrocytes (4). In addition, these cells may be identified by location, morphology, and expression of different markers on their surface (22).

Type 1 cells have specific morphology. They have a triangular body and an apical process. This process goes through the granular layer to the inner molecular layer, where it makes a lot of branches (15). These cells express the glial fibrillary acidic protein (GFAP), nestin, and sex-determining region Y-box 2 (SOX2) (23). Additionally, they express bone morphogenic proteins, which are essential for regulating the maturation rate (24).

As emphasized, there are two subtypes of type 2 cells. Type 2a cells represent the heterogeneous population of cells with the characteristics of glial cells. Morphologically they have short, thick processes that have the same orientation as the SGZ (25). Even though type 2b cells have a similar shape to type 2a, they have the neuronal phenotype and cannot proliferate (15). Typically, type 2 cells can be identified by expressing $GABA_A$ receptors (26). These receptors are essential because GABAergic input is believed to be necessary for differentiation into the neurons (27). Type 2a cells express the same glial markers as type 1 cells, except that they may or may not express GFAP (23). Type

2b cells express doublecortin (DCX), which is crucial for the differentiation and migration of neurons (28), Prox1, and NeuroD1, which are important for the specific development of granular cells (23).

Type 3 cells have vertical positions, dendrites that go to the molecular layer, and axons that go first to the hilus. These cells express the same markers as type 2b cells. Newly expressed genes in this cell line are Reelin, cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF). With maturation, immature GCs acquire complex dendrite branching and extension of the axonal length (15). In this maturation phase, neurons start expressing NeuN as a mature neuronal marker (23).

Adult neurogenesis and Alzheimer's disease

The most common cause of neurodegenerative dementia in the elderly is Alzheimer's disease (AD) (29). It is characterized by the formation of β-amyloid plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein (P-tau) (30). It can be sporadic or familial (31). Mutations of genes encoding presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) are present in known AD (32). Because memory loss is an important symptom of AD, scientists are very interested in the hippocampus.

Notably, different AD models show that adult neurogenesis is altered in the SGZ of DG (33). However, the exact relationship between AD and adult neurogenesis is still unknown. The evidence for the trend of changes in adult neurogenesis in AD is conflicting. Conclusions range from suppression to enhancement of adult neurogenesis. Two different transgenic mouse models are used to study adult neurogenesis in rodents: APP overexpressing and APP knock-in mouse models (33). Transgenic single mutation of PSEN1 and APP has been shown to suppress adult neurogenesis. On the other hand, the combination of APP mutations increases the proliferation of NSCs (34). Furthermore, neurogenesis was shown to be enhanced in the experimental model of intracerebroventricular injection of streptozotocin, consistent with sporadic AD in humans (35).

Similar results have been observed in humans. First, it is shown that neurogenesis in the hippocampus decreases with age in adults. As expected, this decline is particularly pronounced in patients with AD, begins early in life, and has a more detrimental effect (33). In contrast, Jin and Ziabreva suggested an increase in adult neurogenesis in patients with AD to compensate for the loss of neurons (36, 37). Although these results shook the scientific community, they should be taken with caution since the samples were taken from postmortem human brains without knowing the complete medical history of these patients.

Adult neurogenesis and depression

Depression is an enormous burden on the healthcare system since it is one of the most common psychiatric disorders (38). Even though AD and depression are intertwined, their exact relationship is still unknown. Yet, it is certain that AD increases the probability of developing depression and vice versa (39). Since the hippocampus is involved in regulating mood and learning and is affected by these diseases, the primary link between AD and depression may be the hippocampus (40). It is known that adult neurogenesis decreases in depressive patients (41). Postmortem analysis of the hippocampus of depressive patients reveals a reduction in NeuN+ granular neurons and nestin+ cells, as well as a decrease in hippocampal volume (39). Additionally, treatment with antidepressants such as selective serotonin reuptake inhibitors or monoaminergic antidepressants increases adult neurogenesis (39, 40). This suggests that the promotion of adult neurogenesis might be a potential therapeutic mechanism for depression.

Adult mammalian neurogenesis in humans

With the development of adult neurogenesis as a field of research, scientists are asking the question: Does adult neurogenesis exist in humans? After years of research, results have shown that NSCs in humans generate new neurons only in the hippocampus (23). Despite previous evidence for the existence of adult neurogenesis in humans, recent studies on this topic showed conflicting results, some in favor and some against. Sorrelis et al. (42) showed that neurogenesis decreases in adulthood. They showed that the production of new neurons already decreases in children and that neurogenesis is no longer detectable in adults. In contrast, Boldrini et al. (43) showed that the number of NSCs decreases, but these cells continue to produce new neurons in the hippocampus, even in the elderly. As noted by Gandhi et al. (44), these opposite results may be the consequence of different approaches and methods.

Conclusion

This review is devoted to adult neurogenesis, particularly adult neurogenesis in the hippocampus. Although adult neurogenesis has been demonstrated in several animal species, we still do not know what the exact differences are between species and why some animals, such as cetaceans, are unable to generate new neurons in the hippocampus. Future studies must focus on the exact conditions and factors required for the proper development of adult neurogenesis, as this is the case in different species. In addition, interdisciplinary studies are needed to examine the function of neurogenesis in the context of species adaptation to the environment as an evolutionary mechanism. More importantly, adult neurogenesis in humans remains an open question. Future work will attempt to solve this puzzle.

Literature

1. Gross CG. Neurogenesis in the adult brain: death of a dogma. Nat Rev Neurosci. 2000; 1(1):67-73.
2. Balu DT, Lucki I. Adult hippocampal neurogenesis: regulation, functional implications, and contribution to disease pathology. Neurosci Biobehav Rev. 2009; 33(3):232-52.
3. Owji S, Shoja MM. The History of Discovery of Adult Neurogenesis. Clin Anat. 2020; 33(1):41-55.
4. Toda T, Gage FH. Review: adult neurogenesis contributes to hippocampal plasticity. Cell Tissue Res. 2018; 373(3):693-709.
5. Terranova JI, Ogawa SK, Kitamura T. Adult hippocampal neurogenesis for systems consolidation of memory. Behav Brain Res. 2019; 372:112035.
6. Tavazoie M, Van der Veken L, Silva-Vargas V, Louissaint M, Colonna L, Zaidi B, et al. A specialized vascular niche for adult neural stem cells. Cell Stem Cell. 2008; 3(3):279-88.
7. Cope EC, Gould E. Adult Neurogenesis, Glia, and the Extracellular Matrix. Cell Stem Cell. 2019; 24(5):690-705.
8. Horgusluoglu E, Nudelman K, Nho K, Saykin AJ. Adult neurogenesis and neurodegenerative diseases: A systems biology perspective. Am J Med Genet B Neuropsychiatr Genet. 2017; 174(1):93-112.
9. Cebrian-Silla A, Nascimento MA, Redmond SA, Mansky B, Wu D, Obernier K, et al. Single-cell analysis of the ventricular-subventricular zone reveals signatures of dorsal and ventral adult neurogenesis. Elife. 2021; 10:e67436.
10. Jorgensen C. Adult mammalian neurogenesis and motivated behaviors. Integr Zool. 2018; 13(6):655-72.
11. Urbán N, Blomfield IM, Guillemot F. Quiescence of Adult Mammalian Neural Stem Cells: A Highly Regulated Rest. Neuron. 2019; 104(5):834-48.
12. Otsuki L, Brand AH. Cell cycle heterogeneity directs the timing of neural stem cell activation from quiescence. Science. 2018; 360(6384):99-102.
13. Fares J, Bou Diab Z, Nabha S, Fares Y. Neurogenesis in the adult hippocampus: history, regulation, and prospective roles. Int J Neurosci. 2019; 129(6):598-611.
14. Loxton D, Canales JJ. Long-term cognitive, emotional, and neurogenic alterations induced by alcohol and methamphetamine exposure in adolescent rats. Prog Neuropsychopharmacol Biol Psychiatry. 2017; 74:1-8.
15. Abbott LC, Nigussie F. Adult neurogenesis in the mammalian dentate gyrus. Anat Histol Embryol. 2020; 49(1):3-16.
16. Kempermann G, Gast D, Kronenberg G, Yamaguchi M, Gage FH. Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. Development. 2003; 130(2):391-9.
17. Yu DX, Marchetto MC, Gage FH. How to make a hippocampal dentate gyrus granule neuron. Development. 2014; 141(12):2366–75.
18. Scharfman HE. The enigmatic mossy cell of the dentate gyrus. Nat Rev Neurosci. 2016; 17(9):562-75.
19. Kempermann G. What Is Adult Hippocampal Neurogenesis Good for? Front Neurosci. 2022; 16:852680.
20. Yu TS, Washington PM, Kernie SG. Injury-Induced Neurogenesis: Mechanisms and Relevance. Neuroscientist. 2016; 22(1):61-71.
21. Niklison-Chirou MV, Agostini M, Amelio I, Melino G. Regulation of Adult Neurogenesis in Mammalian Brain. Int J Mol Sci. 2020; 21(14):4869.
22. Zhao X, van Praag H. Steps towards standardized quantification of adult neurogenesis. Nat Commun. 2020; 11(1):4275.
23. Kempermann G, Song H, Gage FH. Neurogenesis in the Adult Hippocampus. Cold Spring Harb Perspect Biol. 2015; 7(9):a018812.
24. Gonçalves JT, Bloyd CW, Shtrahman M, Johnston ST, Schafer ST, Parylak SL, et al. In vivo imaging of dendritic pruning in dentate granule cells. Nat Neurosci. 2016; 19(6):788-91.
25. Llorens-Martín M, Jurado-Arjona J, Bolós M, Pallas-Bazarra N, Ávila J. Forced swimming sabotages the morphological and synaptic maturation of newborn granule neurons and triggers a unique pro-inflammatory milieu in the hippocampus. Brain Behav Immun. 2016; 53:242-54.
26. Jin J, Kim SN, Liu X, Zhang H, Zhang C, Seo JS, et al. miR-17-92 Cluster Regulates Adult Hippocampal Neurogenesis, Anxiety, and Depression. Cell Rep. 2016; 16(6):1653-63.
27. Dieni CV, Nietz AK, Panichi R, Wadiche JI, Overstreet-Wadiche L. Distinct determinants of sparse activation during granule cell maturation. J Neurosci. 2013; 33(49):19131-42.
28. Sánchez-Huerta K, García-Martínez Y, Vergara P, Segovia J, Pacheco-Rosado J. Thyroid hormones are essential to preserve non-proliferative cells of adult neurogenesis of the dentate gyrus. Mol Cell Neurosci. 2016; 76:1-10.
29. Lincoln P, Fenton K, Alessi C, Prince M, Brayne C, Wortmann M, et al. The Blackfriars Consensus on brain health and dementia. The Lancet. 2014; 383(9931):1805–6.
30. Babcock KR, Page JS, Fallon JR, Webb AE. Adult Hippocampal Neurogenesis in Aging and Alzheimer's Disease. Stem Cell Reports. 2021; 16(4):681-93
31. Mantzavinos V, Alexiou A. Biomarkers for Alzheimer's Disease Diagnosis. Curr Alzheimer Res. 2017; 14(11):1149-54.
32. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2018; 25(1):59-70.
33. Kim TA, Syty MD, Wu K, Ge S. Adult hippocampal neurogenesis and its impairment in Alzheimer's disease. Zool Res. 2022; 43(3):481-96.
34. Sung PS, Lin PY, Liu CH, Su HC, Tsai KJ. Neuroinflammation and Neurogenesis in Alzheimer's Disease and Potential Therapeutic Approaches. Int J Mol Sci. 2020; 21(3):701.
35. Sun P, Knezovic A, Parlak M, Cuber J, Karabeg MM, Deckert J, et al. Long-Term Effects of Intracerebroventricular Streptozotocin Treatment on Adult Neurogenesis in the Rat Hippocampus. Curr. Alzheimer Res. 2015; 12(8):772–84.
36. Jin KL, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, et al. Increased hippocampal neurogenesis in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(1):343–7.
37. Ziabreva I, Perry E, Perry R, Minger SL, Ekonomou A, Przyborski S, et al. Altered neurogenesis in Alzheimer's disease. Journal of Psychosomatic Research. 2006; 61(3):311–6.
38. Monroe SM, Harkness KL. Major Depression and Its Recurrences: Life Course Matters. Annu Rev Clin Psychol. 2022; 18:329-57.
39. Berger T, Lee H, Young AH, Aarsland D, Thuret S. Adult Hippocampal Neurogenesis in Major Depressive Disorder and Alzheimer's Disease. Trends Mol Med. 2020; 26(9):803-18.
40. Micheli L, Ceccarelli M, D'Andrea G, Tirone F. Depression and adult neurogenesis: Positive effects of the antidepressant fluoxetine and of physical exercise. Brain Res Bull. 2018; 143:181-93.
41. Fang J, Demic S, Cheng S. The reduction of adult neurogenesis in depression impairs the retrieval of new as well as remote episodic memory. PLoS One. 2018; 13(6):e0198406.
42. Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature. 2018; 555(7696):377-81.
43. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, et al. Human Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell. 2018; 22(4):589-99.e5.
44. Gandhi S, Gupta J, Tripathi PP. The Curious Case of Human Hippocampal Neurogenesis. ACS Chem Neurosci. 2019; 10(3):1131-2.