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Adult Hippocampal Neurogenesis and Depression: The Role of Neuronal Autophagy and BDNF in Pathological Mechanisms

Wenjing Ma

College of Veterinary Medicine, China Agricultural University, Beijing, 100193, China

zoe192469@gmail.com

Abstract. Adult hippocampal neurogenesis (AHN) means that new neurons emerge among adult brains, which is strongly associated with emotional regulation and cognitive functions. Some studies have revealed that the changes in AHN can be a key player in the appearance of behaviors similar to depression. This review examines the correlation between AHN and antidepressant activities, with special neuronal autophagy and brain-derived neurotrophic factor (BDNF). Moreover, this review put forward an overview of evidence illustrating that corticosterone (CORT)-induced neuronal autophagy outcomes of a decrease in BDNF levels, which consequently inhibits the AHN while inducing depressive-like behaviors. Finally, this research explores influence of the factors, like pressure and exercise, on AHN and their possible clinical practices.

Keywords: Adult Hippocampal Neurogenesis, Depression, Neuronal Autophagy, BDNF.

1. Introduction

1.1. Background and Importance of Adult Hippocampal Neurogenesis (AHN)

Adult hippocampal neurogenesis (AHN) refers to a central procedure in brain recovery and self-renewal, which exerts far-reaching effects on emotional control and cognitive functions[1]. Depression is a common psychological disorder with an intricate and multifactorial pathogeny. The evidence obtained illustrates that impaired AHN may stand for a central pathological mechanism inducing depression.

Adult hippocampal neurogenesis implies that new neurons in adult brains largely develop in the hippocampus which is an indispensable part of normal brain functions, like memory, study, and emotional regulation. It is proven that AHN has an important part in creating fresh memories and sustaining cognitive abilities[2-4]. Moreover, it is a pivotal player in mood control. Alternations in the AHN are connected to numerous neuropsychiatric diseases, such as Alzheimer's disease (AD) and depression, which denotes an underlying connection between these conditions[5].

1.2. Epidemiologic Characteristics and Impact of Depression

Depression becomes a common prevalent psychological disease reflecting lessened interest, low mood, sleep disorders, shifts, etc. These factors have been proven to trigger serious psychological and

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physiological harm to persons while imposing vast economic and public health burdens on society. The universality of depression is intensive and is affected by inheritance and environment[6].

1.3. Historical Context of AHN and Depression Research

The research on AHN began in the 1960s and preliminarily observed neuron emergence among adult animal models[7]. Next, it was manifested that AHN persisted in adult human brains and tightly correlated with numerous neuropsychiatric disorders[8, 9]. Patients with depression usually show a reduction in AHN, which may lead to impaired emotional control and cognitive decline[5]. Recently, there has been a remarkably increased interest in the pertinence between AHN and depression. Hence, AHN might contribute to the progress and therapy of depression through potential mechanisms.

2. The Role of AHN in Depression

Much evidence illustrates a significantly decreased AHN in depression patients. This is closely linked to emotional dysregulation and cognitive impairments. Substantial evidence from many studies highlights the AHN function in the depression pathophysiology. A meta-analysis of brain imaging research has revealed that individuals diagnosed with depression suffer from a reduced size of their hippocampus[10, 11]. The intensity and duration of depressive episodes directly relate to the size of the hippocampus. To give an example, research illuminates that longer periods of uncured depression are connected to more decreases in hippocampal size[12]. These changes in the hippocampal structure are significantly linked with the occurrence of depressive symptoms, like cognitive impairments and low mood. The hippocampus function of cognitive functions and mood modulations is deeply supported by proof of its associations with other brain areas, like the prefrontal cortex, amygdala, and nucleus accumbens. They all get involved in emotional regulation[13-17].

Animal model studies have proven causality between decreased depressive-like behaviors and AHN[18]. As an illustration, studies in rodent models have unveiled that long-ranging pressure is associated with a reduction in the adult hippocampus's ability to generate new neurons. This is often followed by actions similar to those of depressive individuals. Accordingly, it is demonstrated that lessened neurogenesis in the hippocampus might be helpful for the emergence and progression of depressive symptoms. In addition, animal studies have manifested that ongoing modest pressure significantly affects cell growth in the ventral hippocampus, rather than in the dorsal hippocampus[19]. Such discrepant results highlight the special function of the ventral hippocampus in modulating and coping with pressure.

The efficiency of antidepressant medications tightly relates to neurogenesis. Vast quantities of antidepressant medications, like tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), have been shown to improve the generation of new neurons in the adult hippocampus[20]. To give an example, studies have uncovered that neurogenesis is important to the behavioral influences of antidepressants, including fluoxetine and imipramine in mouse models. The medications seem to play important parts by facilitating the survival and combination of newly-shaped neurons in the hippocampus, which might underlie their capability of enhancing cognitive function and mood. However, the AHN contribution to the comprehensive treatment effect of antidepressants becomes a variable and might rely on factors, like the individual genetic structure and the specific antidepressant attributes.

3. The Role of Neuronal Autophagy and BDNF in Ahn

Neuronal autophagy stands for an essential process for sustaining cellular homeostasis, especially when dealing with pressure and nutrient achievement. Such a process encompasses autophagosome formation, maturation, and decomposition. All those are crucial in clearing injured cellular components and recycling the crucial essential molecules. The autophagy effect in neurons is intricate and context-dependent. Hence, autophagy also has detrimental effects[21].

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3.1. Mechanisms of Neuronal Autophagy

In fact, neuronal autophagy is a cell decomposition process that is important to sustain intracellular homeostasis. In terms of depression, abnormal activation of neuronal autophagy has been recognized as a crucial mechanism beneficial for injured adult hippocampal neurogenesis (AHN). As explored by Zhang et al., superfluous neuronal autophagy triggered by CORT remarkably decreases the level of the BDNF. As a result, the progression and specialization of neural stem cells (NSCs) are suppressed and finally, depressive-like behaviors emerge[22].

The phagophore has a precursor membrane construction and forms at the beginning of the autophagic procedure. Next, such construction enlarges and sequesters cytoplasmic components, therefore formulating the autophagosome with a dual-membrane vesicle. The involvement of crucial proteins, like Atg5 and LC3, is crucial to the optimum function of this procedure[23]. Atg5 is a key player in elongating autophagosome membranes. Besides, its expression can be intensified to deal with a spectrum of incentives, encompassing glucocorticoids like corticosterone (CORT). In recent years, it has been proved that CORT is capable of triggering hyperactive autophagy among dentate gyrus (DG) neurons of the hippocampus, which leads to a prominent improvement of autophagic flux. Such a process is differentiated by an increase in the number of autolysosomes and autophagosomes, with increased numbers of autophagy-associated proteins, like LC3-II and Atg5[22].

It is worth noting that hyperactive autophagy can exert side effects, especially in neurodegenerative conditions. Actually, hyperactive autophagy can give rise to the decomposition of key cell components, such as the Golgi apparatus and the endoplasmic reticulum (ER), which are important to protein synthesis and treatment. Under the action of neuronal autophagy, this process has been confirmed to be involved in the regulation of synaptic plasticity and the decomposition of synaptic proteins. More specifically, autophagy has been validated to decompose crucial synaptic proteins, like SHANK3, PSD-95, and PICK1, which are imperative for synaptic construction and functionality[23].

3.2. Role of BDNF in Neurogenesis and Synaptic Plasticity

Brain-derived neurotrophic factor (BDNF) is an important mediator of synaptic plasticity and neurogenesis[24]. It is a pivotal player in neuron survival, decomposition, and maturation. Under physiological conditions, the BDNF signaling induces downstream cascades, like the PI3K/Akt pathway through the receptor TrkB, which is capable of suppressing autophagy [23]. Such suppression is important to preserve synaptic plasticity and form memories, especially under the influence of nutritional pressure.

Under pressure conditions, like those triggered by CORT, there exist prominently decreased BDNF levels in the hippocampus. This decrease is connected to increased autophagic activities. This issues in the decomposition of mRNA and the BDNF protein. The hyperactive autophagy consumes BDNF, and even affects the wider neural stem cells (NSCs)[25, 26]. Some studies have revealed that corticosterone-induced autophagy inhibits the viability and progression of neural stem cells (NSCs), neuroblasts, and neural progenitor cells (NPCs), which destroys the AHN[22]. This inhibition of neurogenesis is linked to the occurrence of cognitive impairments and depressive-like behaviors.

In addition, the suppression of hyperactive autophagy is regarded as an underlying therapeutic tactic. Studies have elucidated that side effects of CORT are capable of being alleviated by knocking Atg5 down among DG neurons, recovering the BDNF levels while normalizing AHN[22]. Such intervention is efficient in enhancing cognitive function and reversing depressive-like behaviors, as well as carrying on the complicated pertinence between autophagy and neurotrophic support among brains.

To sum up, neuronal autophagy is a double player in brain functionality and features as an important sustenance mechanism and an underlying contributor to etiology in terms of dysregulation. Under the action of pressure and neurogenesis, the interaction between BDNF and autophagy is excessively noteworthy. A comprehension of the pathways provides pivotal knowledge about potential therapy approaches for neurodegenerative illness and mood disorders and focuses on the importance of sustaining a meticulous balance between neurotrophic support and autophagic activity.

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4. The Modulation of AHN by External Factors

Adult hippocampal neurogenesis (AHN) is affected by armies of exterior factors influence, such as pressure, dietary options, and physical exercise. An integrated comprehension of the manner in which factors mediate AHN is crucial in the progress of efficacious treatment tactics for a series of psychiatric and neurological disorders, such as depression.

4.1. Stress

It is widely known that pressure is a dominant factor in the progression of depression. It chiefly activates the hypothalamic-pituitary-adrenal (HPA) axis, thereby significantly affecting AHN[27]. HPA axis stands for a primary pressure response system and even releases glucocorticoids, such as corticosterone (CORT) among rodents as well as cortisol among humans[28]. It has been confirmed that high levels of such hormones have an adverse effect on AHN[26, 29]. Studies have elucidated that long-ranging pressure blocks the progression and specialization of NSCs. As a consequence, neurogenesis declines, which is fulfilled via some mechanisms, encompassing inducing inflammatory responses and decreasing BDNF. What`s more, research has expounded that pressure hormones, like corticosterone (CORT), suppress AHN by activating neuronal autophagy pathways[25]. AHN impairment from chronic pressure is linked to behavioral results, such as cognitive impairment and depressive-like behaviors[30].

4.2. Physical Exercise

Numerous studies have demonstrated participating in physical activities is an exceedingly valid method of enhancing adult hippocampal neurogenesis (AHN); besides, such participation is associated with extensive helpful influences on brain health[31]. Including resistance training and aerobic activities, disparate forms and intensities of exercises affect the levels of BDNF levels as well as subsequent neurogenesis. Especially, aerobic exercises as the subject of wide research raise the expression of BDNF and improve synaptic plasticity as well as cognitive function. Research has substantiated that periodical physical activity works as a valid non-pharmacological intervention for depressive patients, and enhances their moods and cognitive functions. At least to some degree, these benefits are capable of being ascribed to the increase in BDNF and the production of a neurogenic circumstance in the hippocampus. Additionally, it has been substantiated that extra exterior factors, like exercise, raise BDNF levels, thus improving AHN and having antidepressant effects[32].

4.3. Diet and Nutrition

Nutritional variables are highly important in mediating adult hippocampus neurogenesis. Some studies have manifested that nutrients, such as omega-3 fatty acids and antioxidants, exert a helpful impact on neurogenesis[33-35]. Omega-3 fatty acids are contained in fish oil, and they are key constituents of cell membranes with anti-inflammatory attributes. These acids improve BDNF signaling pathways, so they have the capability of regulating neurogenesis and synaptic plasticity. Antioxidants are discovered in vegetables and fruits; besides they help to alleviate the oxidative pressure and back up the new neuron survivals. As an adjunctive therapy for depression, the potential of dietary interventions draws increasing attention since they provide an accessible and natural approach to improving brain health.

In the end, Regulating adult hippocampal neurogenesis is a many-sided process that is affected by diverse exterior factors, such as pressure, food, drink, and physical activities. It has been revealed that chronic pressure exerts a side effect on neurogenesis. This might in turn facilitate the occurrence of depressive-like behaviors. Reversely, proofs illuminate that special dietary components and physical exercise boost neurogenesis while improving comprehensive brain function. Thoroughly understanding these associations is essential to formulating efficacious therapy approaches for neurological and psychological disorders, which underscores the significance of lifestyle improvement in psychological healthcare.

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5. Future Directions and Clinical Applications

5.1. Neuronal Autophagy and Depression Treatment

Through the activators or suppressors, antophagy regulation has the potential to recover normal neuron function and mitigate depressive behaviors. Preliminary clinical trials manifest that autophagy might be a feasible target for impacting pressure-related neurotransmitters and hormones and thus provide novel pathways for treatment intervention in depression. Nevertheless, an in-depth explanation is indispensable for special molecular mechanisms and pathways in these processes. Incorporating these discoveries into clinical practice is a key domain for subsequent studies.

5.2. Genes and Molecular Biomarkers

Recognizing specific molecular biomarkers and genes is capable of boosting a more delicate comprehension of individual reactions to antidepressants. Genetic and molecular profiling is widely applied, through which personalized healthcare develops and related therapies are customized in light of a person's distinctive genetic structure. This approach has the potential to improve therapeutic effects and lessen the trial-and-error process of recognizing efficient antidepressants. As a result, a more accurate approach is provided to treat depression.

5.3. Multidisciplinary Research Collaboration

In view of the intricate correlation between depression and AHN, a comprehensive approach is indispensable, which should integrate neuroscience, psychiatry, and other related research domains. In order to address wide problems, researchers should come from disparate disciplines and cooperate in comprehensively comprehending depression as well as optimizing therapies and treatments. In view of psychological, biological, and environmental elements, the cooperative efforts will promote the progress of more cohesive and efficient treatment approaches.

6. Conclusion

To sum up, subsequent studies on AHN and depression reveal vast numbers of potentials and provide ways of remarkable development in treatment interventions and interdisciplinary cooperation. These efforts will improve understanding while enhancing therapeutic effects for depressive patients.

References

[1] H.A. Cameron, L.R. Glover, Adult neurogenesis: beyond learning and memory, Annu Rev Psychol 66 (2015) 53-81.

[2] M.J. Alam, T. Kitamura, Y. Saitoh, N. Ohkawa, T. Kondo, K. Inokuchi, Adult Neurogenesis Conserves Hippocampal Memory Capacity, J Neurosci 38(31) (2018) 6854-6863.

[3] C. Anacker, R. Hen, Adult hippocampal neurogenesis and cognitive flexibility - linking memory and mood, Nat Rev Neurosci 18(6) (2017) 335-346.

[4] G. Kempermann, H. Song, F.H. Gage, Neurogenesis in the Adult Hippocampus, Cold Spring Harb Perspect Biol 7(9) (2015) a018812.

[5] T. Berger, H. Lee, A.H. Young, D. Aarsland, S. Thuret, Adult Hippocampal Neurogenesis in Major Depressive Disorder and Alzheimer's Disease, Trends Mol Med 26(9) (2020) 803-818.

[6] P.F. Sullivan, M.C. Neale, K.S. Kendler, Genetic epidemiology of major depression: review and meta-analysis, Am J Psychiatry 157(10) (2000) 1552-62.

[7] J. Altman, G.D. Das, Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats, J Comp Neurol 124(3) (1965) 319-35.

[8] G.L. Ming, H. Song, Adult neurogenesis in the mammalian brain: significant answers and significant questions, Neuron 70(4) (2011) 687-702.

[9] 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(4) (2007) 559-66.

[10] P. Videbech, B. Ravnkilde, Hippocampal volume and depression: a meta-analysis of MRI studies, Am J Psychiatry 161(11) (2004) 1957-66.
[11] S. Campbell, M. Marriott, C. Nahmias, G.M. MacQueen, Lower hippocampal volume in patients suffering from depression: a meta-analysis, Am J Psychiatry 161(4) (2004) 598-607.
[12] G.M. MacQueen, S. Campbell, B.S. McEwen, K. Macdonald, S. Amano, R.T. Joffe, C. Nahmias, L.T. Young, Course of illness, hippocampal function, and hippocampal volume in major depression, Proc Natl Acad Sci U S A 100(3) (2003) 1387-92.
[13] S. Maren, J.A. Hobin, Hippocampal regulation of context-dependent neuronal activity in the lateral amygdala, Learn Mem 14(4) (2007) 318-24.
[14] J.E. Lisman, A.A. Grace, The hippocampal-VTA loop: controlling the entry of information into long-term memory, Neuron 46(5) (2005) 703-13.
[15] T. Seidenbecher, T.R. Laxmi, O. Stork, H.C. Pape, Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval, Science 301(5634) (2003) 846-50.
[16] M.B. Moser, E.I. Moser, Functional differentiation in the hippocampus, Hippocampus 8(6) (1998) 608-19.
[17] P. O'Donnell, A.A. Grace, Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input, J Neurosci 15(5 Pt 1) (1995) 3622-39.
[18] M. Alonso, A.C. Petit, P.M. Lledo, The impact of adult neurogenesis on affective functions: of mice and men, Mol Psychiatry (2024).
[19] M.N. Jayatissa, C. Bisgaard, A. Tingström, M. Papp, O. Wiborg, Hippocampal cytogenesis correlates to escitalopram-mediated recovery in a chronic mild stress rat model of depression, Neuropsychopharmacology 31(11) (2006) 2395-404.
[20] L. Santarelli, M. Saxe, C. Gross, A. Surget, F. Battaglia, S. Dulawa, N. Weisstaub, J. Lee, R. Duman, O. Arancio, C. Belzung, R. Hen, Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants, Science 301(5634) (2003) 805-9.
[21] R.A. Nixon, The role of autophagy in neurodegenerative disease, Nat Med 19(8) (2013) 983-97.
[22] K. Zhang, F. Wang, M. Zhai, M. He, Y. Hu, L. Feng, Y. Li, J. Yang, C. Wu, Hyperactive neuronal autophagy depletes BDNF and impairs adult hippocampal neurogenesis in a corticosterone-induced mouse model of depression, Theranostics 13(3) (2023) 1059-1075.
[23] V. Nikoletopoulou, K. Sidiropoulou, E. Kallergi, Y. Dalezios, N. Tavernarakis, Modulation of Autophagy by BDNF Underlies Synaptic Plasticity, Cell Metab 26(1) (2017) 230-242 e5.
[24] H. Park, M.M. Poo, Neurotrophin regulation of neural circuit development and function, Nat Rev Neurosci 14(1) (2013) 7-23.
[25] S. Jung, S. Choe, H. Woo, H. Jeong, H.K. An, H. Moon, H.Y. Ryu, B.K. Yeo, Y.W. Lee, H. Choi, J.Y. Mun, W. Sun, H.K. Choe, E.K. Kim, S.W. Yu, Autophagic death of neural stem cells mediates chronic stress-induced decline of adult hippocampal neurogenesis and cognitive deficits, Autophagy 16(3) (2020) 512-530.
[26] S. Hitoshi, N. Maruta, M. Higashi, A. Kumar, N. Kato, K. Ikenaka, Antidepressant drugs reverse the loss of adult neural stem cells following chronic stress, J Neurosci Res 85(16) (2007) 3574-85.
[27] E.L. Belleau, M.T. Treadway, D.A. Pizzagalli, The Impact of Stress and Major Depressive Disorder on Hippocampal and Medial Prefrontal Cortex Morphology, Biol Psychiatry 85(6) (2019) 443-453.
[28] E.R. de Kloet, M. Joëls, F. Holsboer, Stress and the brain: from adaptation to disease, Nat Rev Neurosci 6(6) (2005) 463-75.
[29] B.S. McEwen, Physiology and neurobiology of stress and adaptation: central role of the brain, Physiol Rev 87(3) (2007) 873-904.
[30] R.M. Sapolsky, Stress and the brain: individual variability and the inverted-U, Nat Neurosci 18(10) (2015) 1344-6.

DOI: 10.54254/2753-8818/73/2024.19375

[31] M.S. Nokia, S. Lensu, J.P. Ahtiainen, P.P. Johansson, L.G. Koch, S.L. Britton, H. Kainulainen, Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained, J Physiol 594(7) (2016) 1855-73.

[32] C.W. Cotman, N.C. Berchtold, Exercise: a behavioral intervention to enhance brain health and plasticity, Trends Neurosci 25(6) (2002) 295-301.

[33] C. Lassale, G.D. Batty, A. Baghdadli, F. Jacka, A. Sánchez-Villegas, M. Kivimäki, T. Akbaraly, Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies, Mol Psychiatry 24(7) (2019) 965-986.

[34] J. Firth, W. Marx, S. Dash, R. Carney, S.B. Teasdale, M. Solmi, B. Stubbs, F.B. Schuch, A.F. Carvalho, F. Jacka, J. Sarris, The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials, Psychosom Med 81(3) (2019) 265-280.

[35] C. Féart, C. Samieri, P. Barberger-Gateau, Mediterranean diet and cognitive function in older adults, Curr Opin Clin Nutr Metab Care 13(1) (2010) 14-8.