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Chronic Stress and Adult Hippocampal Neurogenesis: Unraveling the Complex Interplay

Xiaoyue Wang

Department of Biological Science, Huazhong Agricultural University, Wuhan, 430070, China

2681812091@qq.com

Abstract. The hippocampus in mammalian brain is one of the first regions experimentally demonstrated for adult neurogenesis, which is the evidence overturned Cajal's hypothesis. Adult hippocampal neurogenesis (AHN) involves the incorporation of newly generated neurons into the innermost granule cell layer (GCL) of the dentate gyrus, and the integration of new neurons into the existing hippocampal circuitry is associated with increased resilience to stress. However, chronic stress, as an upstream factor that can be controlled by neurogenesis, also have counterproductive effects on adult hippocampal neurogenesis. Considering the current trend of increasing social chronic stressors and soaring incidence of major depressive disorder (MDD), analyzing the complex interactions between chronic stress and AHN is particularly important.

Keywords: adult hippocampal neurogenesis, hippocampus, chronic stress.

1. Introduction

The neuroscientist Cajal has made numerous hypotheses about the nervous system [1]. Despite they were mostly correct, one prediction that newborn neurons could not form in adulthood, which later became a dogma in the field of neuroscience all over a century, has been disproved. Since Joseph Altman's report was "rediscovered", the phenomenon of adult neurogenesis has become an accepted occurrence in mammals, for the experimental evidence identified in increasingly multiple brain regions.

Two discrete places were firstly identified for housing adult neurogenesis stem cells [2], namely the subgranular zone of hippocampus and the wall of lateral ventricles. Recently, adultborn neurons have also been found in other brain regions of the mammalian brain, including the amygdala, striatum, cortex, substantia nigra, and hypothalamus [3]. These adult neural stem cells retain self-renewal capacity, and could differentiate into neurons as well as glia [4]. Among them, the subgranular region of the hippocampus produces adultborn neurons for the dentate gyrus. Due to the continuous integration of granulosa cells, the dentate gyrus shows neuroplasticity, which is termed adult hippocampal neurogenesis (AHN). As the ability of neural networks to alter through rearrangement and development [5], neuroplasticity is proved to be linked to the stress response [6].

Although AHN is relevant for the resilience to stressful situations [7-9], the occurrence of these adultborn neurons could be inhibited by various intrinsic and extrinsic cues [10]. For example, organisms can be effected by numerous uncontrollable or unpredictable stressors repetitively during lifetime, which is the phenomenon called "chronic stress". This factor is further subdivided into a variety of subclasses and can be triggered by reasons like loneliness, depression, adversity, anxiety and

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social isolation [8]. The activation of prefrontal cortex caused by chronic stress may indirectly affect the differentiation and migration of neurons in the hippocampal neurogenic microenvironment through the interconnectivity between the two brain regions [11], leading to individual behavioral changes. Therefore, this review will focus on both the effects of chronic stress on AHN in the brain, and also on the resilience mechanisms of adult neurogenesis to stressors and relevant disorders.

2. The Cellular Mechanisms of AHN: a Brief Description

In hippocampus, the granule cell layer (GCL) of the dentate gyrus (DG) houses neurons produced from embryo stage to adult life, and consistently-generated adultborn neurons are developed and integrates into the existing circuitry during adulthood. This morphogenic phenomenon forms a stratified GCL, with adult-born cells in the innermost layers [12].

Adultborn neurons are generated from quiescent neural progenitors (QNPs), differentiate to become mature granule cells (GCs) by various steps, and integrated into the preexisting circuitry in the end [9]. The majority of newborn granule neurons are added to the GCL throughout lifetime, extending the layer of granule cells [13].

3. AHN and Stress Resilience

The hippocampus has long been regarded as the major region for stress regulation [14]. Adultborn neurons in the hippocampus buffers responses to stress, for their birth and maturation regulates antidepressant treatment efficacy [15]. Such processes may be related to the outcome of stress resilience, and the failure of stress regulation could cause mental dysfunctions. Ablation or reduction of adult neurogenesis results in a lack of memory, as well as depression-like behaviors [16,17]. On the contrary, increasing neurogenesis could reduce such behaviors [18]. For example, antidepressant restores hippocampal neurogenesis to normal levels, suggesting that AHN is a kind of stress resilience mechanisms [19-21].

4. Counteraction of Chronic Stress on AHN

AHN can be regulated by both intrinsic and environmental stimuli [14], including enriched environment (EE), exercise and physical signals from specific hormones or metabolites. The generation and survival rate of adultborn neurons could be either accelerated or hindered under these effects [15].

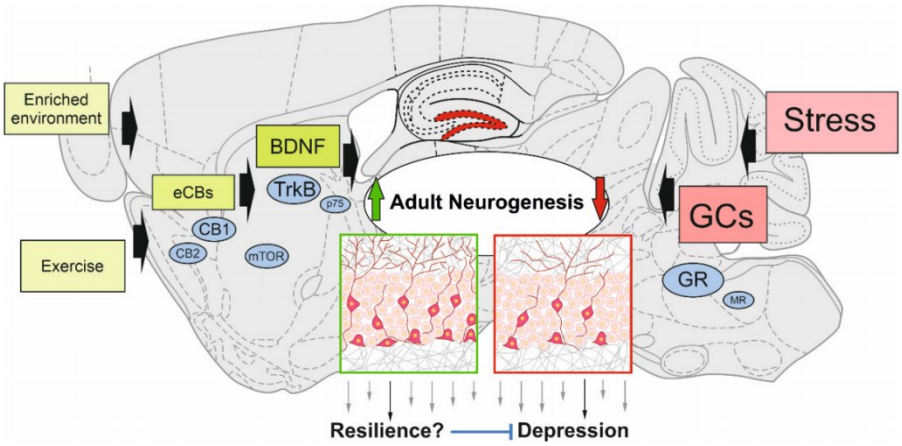

Figure 1. Several modulating factors of AHN

In the 1990s, Gould revealed that in the adult hippocampus, cell proliferation decreases during the exposure to stressors [22,23]. Since then, other studies have reported the decline of AHN during the exposure to various stressors in adulthood. Reduced hippocampal neurogenesis has been commonly

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observed in multiple stress paradigms, including chronic mild unpredictable stress [24,25], social defeat stress [26] and chronic corticosteroid treatment [27-29]. Studies have shown that chronic stress affects cell proliferation, disrupts cell differentiation, and reduces the survival of adult neurons [26]. This imbalance of neuronal circuitry decreases cognition, mood and decision making ability, and in turn affects neurogenesis and behavior via neuroendocrine, autonomic, immune and metabolic mediators [30].

5. Adult Neurogenesis under Chronic Stress is Relevant to Disorders like Major Depressive Disorder (MDD)

Major depressive disorder (MDD) can severely affect mood and physical functions such as appetite and sleep, and even leads to suicidal behaviour [31]. Prolonged exposure to a combination of psychological, physical, and environmental stressors is recognized as a contributing factor to Major Depressive Disorder (MDD), also known as stress-induced disorders [32].

Individual susceptibility to stress hinges on several internal and external factors, such as gene, lifestyle and surrounding environment [33]. Resilience and coping behaviors to stress imply cognitive and emotional processing of experience, which coincides with functions of AHN such as behavioral flexibility and pattern separation [34].

Intense and persistent stressors, including repetitive work disputes, bereavement, diagnosis of disability illness and abuse, can precipitate the onset of depressive symptoms. However, the precise mechanisms underlying the development of MDD are not yet fully elucidated at the levels of neurophysiology and molecular biology. Research indicates that the process of AHN plays a crucial role in modulating stress responses [35, 36]. Rodents with depressive-like behavior or depressed human individuals have thinner granule cell layer, and agnetic resonance imaging (MRI) has found that depressed patients have reduced hippocampal volume [37,38].

Additionally, cortisol in humans and corticosterone in rodents are key stress hormones that exhibit significant increases during periods of chronic stress [35]. Patients with exogenous glucocorticoids or hypercortiolemia treatment are more susceptible to MDD [38], thus Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation may be another significant cause of mental disorders.

6. Conclusion

At present, with the acceleration of the pace of social life, chronic stress has become increasingly common in the population. Due to the significance of relevant investigations, the intricate relationship between AHN and chronic stress has been extensively studied, revealing a complex interplay of stressors that influence cognitive and behavioral responses.

AHN, a process once thought impossible, is now recognized as a critical component of the brain's adaptability. Although the hippocampus's ability to generate new neurons offers a resilience mechanism against the detrimental effects of stress, this capacity is delicately balanced and can be easily disrupted by prolonged exposure to adverse conditions, collectively known as chronic stress, impeding neurogenesis and potentially contributing to stress-related disorders. Understanding the cellular mechanisms and the influence of chronic stress on AHN is crucial for developing therapeutic strategies to promote mental health and resilience. As research continues to unravel the nuances of this process, the potential for targeted interventions to enhance cognitive and emotional well-being becomes increasingly tangible.

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