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Exploring Potential Mechanisms by which Early Life Stress Impairs Adult Hippocampal Neurogenesis

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ABSTRACT

Prolonged stressful experiences prior to adolescence have been linked to an increased risk of a multitude of neurological disorders, from depression and anxiety to schizophrenia and bipolar disorder. In particular, early life stress (ELS) has been shown to significantly impair adult hippocampal neurogenesis (AHN). While the long term effects of early life stress are well studied, the underlying mechanisms through which ELS impairs AHN are still largely unknown. This paper reviews the current literature surrounding early life stress and AHN and discusses potential mediators that impact AHN during ELS including changes in telomere length, alterations in telomerase activity, and dysregulation of DNA methylation.

Introduction

Adverse experiences in pre-pubescent years have been strongly associated with an increased risk of a range of neurological disorders [1-4]. Specifically, numerous studies have linked stressful early life experiences—such as abuse and neglect—to conditions like ADHD, anxiety, depression, and schizophrenia [1-4]. The hippocampus, in particular, plays a significant role in the stress response as it contains the largest concentration of receptor sites for the glucocorticoid hormone [5]. It is also involved in controlling the circadian glucocorticoid rhythm as well as the HPA axis—both of which play significant roles in the stress response [5-6]. The hippocampus is also one of the only regions in the brain in which new neurons are formed, through a process known as adult hippocampal neurogenesis (AHN). Specifically, AHN takes place in the dentate gyrus of the hippocampus [7]. Since mediating the stress response involves the hippocampus and there is continual maturation of this region during adolescence, the hippocampus becomes especially vulnerable to the effects of early life stress, and subsequently, adult hippocampal neurogenesis may be altered [8-9].

Adult hippocampal neurogenesis is a type of cell replication; notably, one that focuses on generating integrated and functional neurons. AHN also includes the differentiation and maturation of the new neurons [10, 19]. The cell replication process has many moving parts, but throughout the process two components are crucial: telomeres and telomerase. Telomeres are the regions at the end of the chromosomes that consist of repeating nucleotides, and they serve to prevent the end-to-end fusion of chromosomes. They also behave as “caps” to repress the chromosome double strand break and prevent the ends of chromosomes from fraying or “sticking together”, ultimately preventing the cell from losing genetic information while replicating [11-12]. Telomeres shorten normally with each cell division, until eventually reaching the Hayflick limit—a point in which telomeres become critically short and are unable to recruit enough telomere-binding proteins, thereby failing to protect the DNA from sticking together and fraying. As a result, critically short telomeres are considered a sign of biological aging, as cells can no longer replicate [11-13]. Telomerase is an enzyme found in certain cells—including neurons and progenitor cells—that maintains the length of telomeres by allowing the addition of repeated sequences of nucleotides for each cell replication cycle [15]. Figure 1 shows how

telomerase adds additional nucleotide sequences to the telomere overhang; ultimately increasing telomere length. Because telomere length is directly related to cellular aging, telomerase allows the cell to replicate for a longer period of time and consequently, increases cellular lifespan [11, 13, 14].

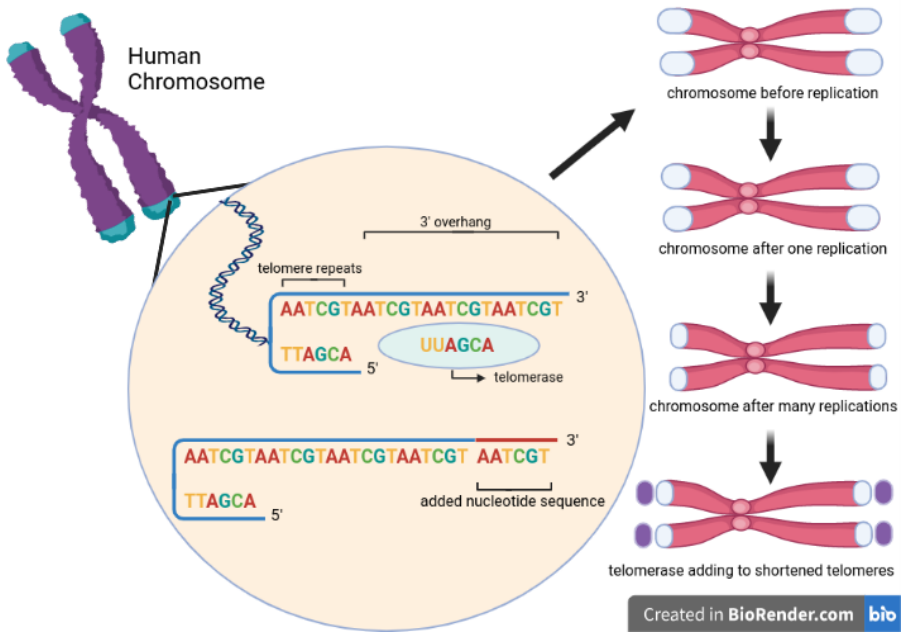

Figure 1. The role of telomeres and telomerase in cell replication
Created with BioRender. Adapted from Telomere Length as a Marker of Biological Age (2021) and Lumen Learning: DNA Structure and Replication (2021). Retrieved from https://www.frontiersin.org/articles/10.3389/fgene.2020.630186/ful and https://courses.lumenlearning.com/wm-biology1/chapter/reading-telomeres/

In addition to the potential role of telomerase and telomeres in AHN, DNA methylation may also play an important role in regulating the DNA and genetic information associated with neural progenitor cells. DNA methylation is an important epigenetic mechanism that incorporates direct chemical modifications to DNA [16]. The process regulates gene expression in two ways: by inhibiting the binding of transcription factors to DNA through the addition of methyl groups to cytosine—a process called DNA methylation—or by removing the added methyl group on the cytosine to allow gene transcription—a process called DNA demethylation [16]. Specifically, the process occurs through regulation of CpG islands, which are large stretches of DNA about 1,000 base pairs in length that contain higher CpG densities [17]. DNA methylation of CpG islands regulates gene expression during the differentiation and development of progenitor cells [17-18]. Many studies suggest that DNA methylation is a critical factor in adult hippocampal neurogenesis by modulating progenitor cell maintenance and proliferation, neuronal differentiation, and synaptogenesis [19]. In fact, DNA methylation is predominantly prevalent in the brain, as the brain contains the highest levels of DNA methylation found in the body [16].

Since studies concerning the effects of early-life stress on adult hippocampal neurogenesis are both fairly recent and limited, further investigation on the exact mechanisms by which ELS modulates AHN is necessary. This paper aims to explore possible mechanisms through which ELS stress may impair AHN.

Review of Literature

Over 60 pieces of scientific literature were read and analyzed for this narrative review, including mostly original lab research as well as some review papers and clinical/university literature. The information provided from these sources focused on three mechanisms of the body that have been known to play a large role in adult hippocampal neurogenesis: telomeres, telomerase, and DNA methylation factors. In addition, the literature analyzed the effects of early life stress on each mechanism to elucidate potential mediators of AHN. All literature included in this review paper have provided distinct and thorough insight into the mechanisms crucial to adult hippocampal neurogenesis and have helped shed light on the specific mechanisms by which ELS impairs AHN.

Telomeres and Telomerase

Telomeres and telomerase play pronounced roles in the cell replication process; however, both are largely susceptible to the effects of early life stress.

Telomeres

Countless studies have shown a connection between excessive activation of the stress response over a prolonged time period (chronic stress) and shortened telomere length [20]. In recent years, studies have assessed the impact of ELS on telomere length.

In one particular study, two groups of adults were examined: the first group with reports of childhood maltreatment—such as physical and emotional abuse and neglect—and the second group with no such reports [20]. The researchers ultimately discovered that the group of participants with reports of physical and emotional neglect had significantly shorter telomere lengths than participants in the control group [20]. Another study conducted on rhesus monkeys resulted in similar findings. Two groups of monkeys were studied: the first group was reared by their mothers and the second group was reared individually [21]. The study revealed that telomere lengths were significantly shorter in the individually-reared group than in the group that had been reared maternally [21]. When taken together, these studies demonstrate that chronic stressors such as early life stress are associated with shortened telomere lengths post-puberty, potentially suggesting a role in which ELS affects the cell cycle. These findings implicate telomere length as a possible mediator of AHN during ELS because cellular replication, like that occurring during AHN, relies on sufficient telomere lengths to produce new cells. When telomere lengths are insufficient, cellular replication does not occur [14]; therefore, AHN may not produce new progenitor cells.

Telomerase

Telomerase, another crucial component of the cell cycle, is also affected by early life stress [27-28]. When the body detects an acute stressor, the hypothalamus activates the HPA axis, which elevates levels of the stress hormone cortisol followed by physiological changes like higher blood pressure, an increased heart rate, and sharpening of the senses [22]. This part of the stress response is well studied; however, recent research has also started to look at telomerase activity during stress.

Telomerase Activity Levels

Numerous studies have found that during acute stress, telomerase activity increases, potentially as a regulatory mechanism in response to high cortisol levels present during stress [23-25]. Nevertheless, chronic stress appears to have the opposite effect on telomerase [26-28].

Multiple studies have found that telomerase activity decreases rather than increases with a continual presence of high cortisol levels associated with chronic stress [26-27]. This suggests the presence of a complex stress-complex interaction: acute stressors and excessive telomerase loss may cause large drops in telomerase activity; adversely, prolonged exposure to stress can cause large drops in telomerase activity [28]. One study, which tested healthy participants, found that the group with chronically high stress levels had significantly lower telomerase activity (decrease of 48%) than the group with low stress levels [27]. These studies highlight the detrimental effects of stress on telomerase and allude to the importance of telomerase in neuron generation, differentiation, and maturation as studies have found very high levels of telomerase in neural progenitor cells [29-30] before and after neural differentiation begins [31-32]. A decrease in telomerase activity would likely cause impairment of the cell cycle because telomerase maintains telomere length to permit mitosis [15]. A lack of telomerase combined with critically short telomeres would impair cell replication, thus telomerase may be another potential mediator of AHN during ELS.

Telomerase BDNF Regulation

Telomerase also plays a crucial role in AHN through brain derived neurotrophic factor (BDNF) [31,35]. BDNF is a protein that promotes the survival of embryonic and postmitotic neurons, making it necessary for neurogenesis as the protein is required for terminal differentiation of new neurons in the hippocampus [33-34]. Many studies have indicated that telomerase activity decreases with the presence of a chronic stressor such as early life stress [26-28]. Additionally, multiple mouse studies have found that a lack of telomerase downregulates the BDNF protein [31,35], thus affecting postmitotic neuron survival. Indeed, one study found that the telomerase-deficient mice showed 2.2-fold lower hippocampal BDNF expression levels when compared to the control group [35]. Downregulation of BDNF would likely cause significant impairment to AHN as the protein is needed to complete terminal differentiation of new neurons [34]. BDNF is also crucial in protecting embryonic neurons from excitotoxic stressors [37]. Excitotoxicity occurs when certain neurotransmitter levels—such as glutamate or N-methyl-D-aspartic-acid (NMDA)—reach dangerously high levels, causing excessive stimulation of the neurotransmitter receptor sites [36], ultimately causing neural cell damage and death. This is particularly severe in embryonic neurons as their immature state makes them more susceptible to excitotoxicity [37]. When BDNF is downregulated, it cannot effectively protect embryonic neurons against excitotoxic stressors, thus the protein likely plays an important role in neurogenesis by protecting embryonic neurons from excitotoxic stress. When taken together, this highlights downregulation of BDNF as another mechanism by which telomerase mediates AHN during ELS.

Telomeres and telomerase; however, aren't the only mechanisms by which AHN is impaired by ELS.

DNA Methylation

Since adult hippocampal neurogenesis is a cell replication process, epigenetics have significant influence in the AHN mechanism because of their ability to silence and activate genes involved in AHN [51].

DNA Methyltransferases

DNA methylation is an epigenetic modification; specifically, one that regulates transcription of genes through addition or removal of a methyl group [16]. DNMT3a, a type of DNA methyltransferase, is found to have an important role in hippocampal neurogenesis [38-41]. The enzyme is part of the DNA methyltransferase (DNMT) family, which includes enzymes with many roles such as maintenance of DNA methylation patterns, transcriptional activation or silencing, and post-transcriptional regulation [38]. DNMTs also have influence on AHN through stem cell proliferation and neural differentiation [57] and are predominantly expressed in embryonic neural precursor cells and post-mitotic neurons [39]. One study compared wild type mice to transgenic mice with downregulated DNMT3a and found that the

transgenic mice had increased p53 signaling—a cell-cycle-arrest-protein that is associated with apoptosis [40,61]. Increased p53 signaling in neural progenitor populations results in a decrease in progenitor cell proliferation [40]; these results suggest that DNMT3a plays a significant role in hippocampal neurogenesis, potentially through p53 pathways that modulate progenitor cell differentiation and proliferation. Another mouse study demonstrated similar results: the DNMT family is crucial in regulating proper DNA methylation patterns in post-mitotic CNS neurons [41]. Modifications in DNMT regulation would cause changes in DNA methylation patterns in progenitor cell populations, ultimately resulting in decreases in the proliferation of NPCs and post mitotic neurons [40], thus impairing AHN through the resulting reduced cell populations.

Recent studies have found that early life stress caused changes in DNA methyltransferase of both infant and adult rats [42-43]. Both studies used maternal separation to induce ELS in rats and found that stress significantly upregulated DNMT expression and induced DNA hypomethylation [42-43]. DNA hypomethylation causes a decrease in the amount of post-mitotic cells that are viable into adulthood, thus impairing the efficacy of AHN [56]. Despite these findings, it remains unclear the mechanisms by which early life stress impacts DNMT expression; thereby suggesting additional research must be conducted to highlight DNMTs as mediators of AHN during ELS through DNA methylation patterns.

Ten Eleven Translocation

Another epigenetic gene family associated with AHN is the ten-eleven translocation (TET) family that activates DNA demethylation in mammals and is involved in determining stemness of cells [44]. TET loss of function has been associated with DNA hypomethylation, which causes a decrease in the amount of viable post-mitotic neurons [45, 56]. A recent mouse study revealed that mice lacking Tet1 exhibited impaired AHN [46] because the neural progenitor pool was diminished as methylation of genes associated with neurogenesis was altered in Tet1 deficient mice [47]. Another study demonstrated the prominence of Tet1 in the embryonic stem cells of mice and revealed that Tet1 promoted the transcriptionally active state of embryonic stem cell genes by maintaining a hypomethylated promoter state of the genes [48]. A hypomethylated promoter state allows for proper transcription of genes associated with AHN, thus promoting the process by regulating AHN gene expression [48]. When taken together, these studies demonstrate the importance of TET in AHN since it regulates DNA methylation—and subsequently expression—of genes critical to the process [48].

Similar to DNMTs; however, there is limited research on the ways in which early life stressors modify TET regulation. A recent study found that ELS alters TET regulation in embryonic chicks [49]. The study simulated environmental stress with heat during the embryonic stage and showed increased TET activity in the midbrain of the embryonic chicks [49]. Other studies have found that ELS changes TET regulation in other regions of the brain such as the prefrontal cortex and midbrain; therefore, ELS may have a similar effect on TET expression in the hippocampus [49-50]. Because TET regulates DNA methylation, particularly in neural progenitor cells [47], any change in regulation of TET would have a substantial impact on the progenitor cell population and subsequently, AHN. Conducting more research on the ways in which ELS modifies TET regulation can highlight TET as a mediator of AHN during ELS through DNA methylation patterns.

Discussion

This review attempts to provide possible mechanisms by which ELS can modulate AHN. An important consideration; however, is the vast range of meanings “early life stress” can have. Being a psychological phenomenon, ELS encompasses a wide range of stressors as well as intensities [52]. For instance, ELS encompasses emotional, physical, and environmental stressors, and there are nuances in the severity of impact from these stressors across individuals [53]. These impacts vary from person to person [53], making it difficult to assess the true impact of ELS on the HPA-axis

for each individual and the exact manner of neurogenesis impairment. It is quite possible that neurogenesis impairment is dose-dependent on the intensity and duration of the stressor.

Animal Models

Though numerous studies included in this review involved animals and not human participants, animals serve as robust models that can be manipulated to recapitulate genetic pathways and determine the underpinnings of human disease, development, and experience. For instance, maternal separation was used as a stressor for the studies conducted on monkeys, a stressor that has been validated and can elicit similar long term effects observed in humans [54]. Similarly, thermal stressors in chicks elicit reactions similar to ones faced by humans undergoing physical or emotional ELS [49].

Physiological and Environmental Variation

The studies included in this review also did not assess biological sex differences in response to ELS, thus future research studies should consider the role that biological sex plays in the relationship between ELS and AHN. Estrogen, a female hormone involved in sexual and reproductive development of the female body [55], has been previously linked to reducing oxidative stress, suggesting that sex differences may play a role in how ELS alters AHN since sex differences may alter the impact of ELS as they do with other types of stress [57]. The ultimate goal of future studies such as the one proposed is to better understand the molecular underpinnings by which ELS impairs AHN. In addition, better understanding the mechanisms by which ELS modulates AHN can allow for more efficient treatments to be created to combat the long-term impacts caused by ELS.

Similar to biological sex, other physiological differences can create nuances in the effects of ELS. An individual's race often causes differences in childhood experiences [58-59]. Institutionalized racism; for example, causes certain racial groups to face more obstacles, discrimination, and opression in society than others [58]. These factors create additional unique stressors for particular groups of people and can thus cause variations in the exact impacts of ELS [59]. Future research should consider the effect of race on the specifics of how ELS affects individuals in order to better understand the underlying mechanisms by which ELS modulates AHN. Geographical location can also have a large impact on ELS [60]. A majority of studies used in this paper were conducted in developed countries such as the United States and European countries. For children living in countries ravaged by poverty, civil war, and other threatening conditions; however, childhood stressors are different and have distinctly different effects [60]. Studies have found that children in developing countries often have impaired psychological development due to factors like malnutrition and poverty that are prevalent in these places [60]. Therefore, both the severity and impact of ELS on children living in these countries will be inconsistent with the impact of ELS on children living in developed countries, potentially creating additional variations in the way ELS modulates AHN. By taking these factors into consideration and continuing research, potential treatments for the long term impacts of early life stress can be more effectively applied to a larger and more diverse population.

Conclusion and Implications

Early life stress increases the risk of contracting many illnesses after adolescence [1-4]. It has also been connected to altering adult hippocampal neurogenesis, a process that generates new and integrated neurons and one that is critical for proper nervous system function. Despite this, the mechanisms by which ELS impairs AHN are largely unknown and inadequately studied. Because of the way ELS impacts telomeres, telomerase, and DNA methylation; each of

these are likely possible mechanisms by which ELS mediates AHN. Conducting more research on each of these can highlight the mechanisms through which ELS mediates AHN, establishing a path to create treatments that can combat the long-term effects of ELS on individuals and even potentially revealing a way to prevent these negative effects altogether. Conducting nuanced research; furthermore, can allow for potential treatments to be more effective for a global diverse population.

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