FOCUS: NEUROSCIENCE

Environmental Enrichment: Aging and Memory

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A decline in learning and memory is a feature of the normal aging process and associated with neurodegenerative diseases such as dementia and Alzheimer's disease. Moreover, certain forms of dementia and memory loss are inevitable due to the normal aging process. The unavoidable effect of age on memory is an ongoing study, as the findings assist in identifying cortical functions of the brain. Histone acetylation is a mechanism in synaptic plasticity and a key function in learning and memory because changes within the process alter gene transcription and the quantity of synthesized proteins. Similar to histone acetylation, environmental enrichment has also been found to improve memory formation by stimulating synaptic plasticity. Through understanding the mechanisms by which environmental enrichment and histone acetylation interact in the brain and affect learning and memory, novel applications can be developed for therapeutic interventions to neurodegenerative diseases and aging.

INTRODUCTION

Have you ever wondered why crossword puzzles, exercising, and recreational activities are highly recommended by doctors as you get older? Or how these activities are supposed to increase your memory? Odds are that most of us would like to know. Many studies have focused on the effect of aging on the brain, particularly concerning memory. Results have identified critical questions to address our understanding of age-related memory decline. But what exactly is age-related memory decline? Who does it affect? And how can enrichment restore lost memories?

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†Abbreviations: AAMI, age-associated memory impairment; EE, environmental enrichment; HA, histone acetylation; LTP, long-term potentiation; HAT, histone acetyltransferase; HDAC, histone deacetylase; BDNF, brain-derived nerve growth factor; NGF, anti-nerve growth factor; AD, Alzheimer's disease; Aβ, beta-amyloid; HD, Huntington's disease; PD, Parkinson's disease.

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In early development, the brain is characterized by an increasing amount of connections that lead to the storage of memories. However, as aging occurs and the mean life expectancy extends, a concern for the quality of life in relation to mental health arises. This concern goes beyond diseases associated with aging, such as dementia and Alzheimer’s disease (AD†). The “normal” aging process is often associated with specific impairments in both learning and memory. The mild memory deficits commonly experienced during age-related memory decline are called age-associated memory impairment (AAMI) [1]. Even though the various cognitive deficits included in AAMI are often subtle, they are disturbing to those affected by it. Deficits range from difficulty to learn new information to the inability to recognize family members or remember past memories and stored information. Neurodegenerative disorders affect much of the population, but normal aging is inevitable. A 1998 study suggests that subject memory in AAMI subjects is not impaired pathologically, like it is in neurodegenerative diseases, and that initial intellectual level more significantly influences a patient being diagnosed with AAMI [2]. The aim of recent studies has been to identify the mechanisms of neurodegeneration and memory decline in aging and neurodegenerative diseases.

WHAT IS ENVIRONMENTAL ENRICHMENT?

Environmental enrichment (EE) is a noninvasive strategy that has been seen to improve learning and memory performance. While EE has no true definition, it usually consists of the addition or implementation of sensory, cognitive, and motor stimuli in a subject’s environment. It is assumed that increased levels of complexity and novelty will lead to increased levels of stimulation that would affect the process of learning and memory. Many findings have supported the beneficial effects of EE and its increase of behavioral performance and synaptic plasticity, specifically in the hippocampus [3,4,5,6]. However, the molecular mechanism of EE in relation to enhancement of learning and memory processes is still unknown.

Environmental enrichment is achieved in the laboratory by housing animal models, such as rodents, in large cages, providing more area for exploration [5,7,8,9]. The environmentally enriched conditions also include the presence of complex objects that vary in shapes, sizes, colors, and textures. This paradigm includes running wheels, plastic tunnels and balls, stairs, and shelters (Figure 1) [7,10]. Compared to standard housing conditions, the conditions provide increased exposure to social interaction, exploratory behavior, and physical activity.

Figure 1. Environmental enrichment through increased social interaction, physical activity, and exploratory behavior can promote neuronal activation and synaptic plasticity.
However, it is important to determine the variables in utilizing EE, such as age at which animals are first exposed to EE, duration of EE exposure, enrichment paradigm setup, and gender of subjects, which could also contribute to the effects seen. In current studies, new techniques and strategies are constantly being explored to re-establish memory formation and learning abilities in cases where these abilities have been compromised. The use of EE as a therapeutic treatment for aging and neurodegenerative diseases is an important deviation from the standard methods of treatment.

**Environmental Enrichment at a Molecular Level**

Environmental enrichment increases learning and memory formation through various stimuli that are mostly directed at the hippocampus [11,12]. Furthermore, learning and memory processes take place with an increase in necessary gene transcription and protein synthesis [13]. Consequently, histone acetylation (HA) is a proposed molecular mechanism for learning and memory because it facilitates gene transcription and protein synthesis leading to learning and memory formation [9]. Therefore, the assumption can be made that there must be a decrease in the functionality of the mechanism — in this case, HA.

**Epigenetics in Learning and Memory**

Gene transcription and expression is essential for learning and memory processes. It is generally supported that new protein synthesis is required for long-term potentiation (LTP), or memory formation, to occur. LTP is a form of synaptic plasticity, activity-dependent changes in synaptic strength. Modifications to DNA and nuclear proteins produce lasting changes in chromatin structure and therefore produce lasting alterations in gene expression and patterns of protein synthesis. One well-established method of such modification is histone acetylation. HA is the addition of an acetyl group directly to the histone proteins, more specifically, histone 3 (H3) and histone 4 (H4). Histone acetyltransferases (HATs) are enzymes that assist in the addition of acetyl groups that decrease the affinity of the DNA molecules to histone proteins, allowing easier access to the genes for gene transcription and expression (Figure 2). HA is reversible through enzymes, known as histone deacetylases (HDACs), which catalyze the removal of the acetyl group and inhibit the process of gene transcription. Therefore, it has been postulated that HA is the mechanism in which new memories are formed.

Inhibitors of HDACs have advantageous effects on HA. Since altered transcription is known to be essential for the formation of long-term memories, HDAC inhibitors have the potential to enhance memory formation. This has been demonstrated with the use of sodium butyrate, which was seen to increase HA leading to new protein synthesis and memory formation [9,14]. Research has shown that HDAC inhibitors and EE are capable of restoring
the capacity for spatial memory. Environmental enrichment rescued the p25 transgenic mice’s ability to form new memories (spatial and fear conditioning) and allowed the mice to re-establish access to memories lost after neurodegeneration [5]. This was not only determined by the behavioral tests, but also the increase in synaptic-related proteins with the presence of new dendritic spine branching and synaptogenesis, which is correlated to learning. Fischer et al. indicate that the role of increased neurogenesis in their model remains to be addressed.

Environmental enrichment has also been found to play a role in age-dependent memory impairment. Some groups have extended these findings through accelerated aging mouse models with both learning and memory impairments, while others have explored the effect of EE on normal aging mouse models [3,5,12,15]. Altered HA was also noted in such aged mouse models [3,12]. This research is novel because it focused on the normal aging model rather than accelerated or genetically manipulated aging.

Figure 3. Possible mechanisms of EE and HDAC inhibitors on an aged or neurodegenerative model.
What about recovering memories that have been lost instead of preventing memories from being lost?

Fischer et al. allowed the memories for the fear conditioning test to decay over time through neurodegeneration and then administered an HDAC inhibitor (sodium butyrate or trichostatin A), which restored the ability of the animals to recall that memory that had been lost. The experiment demonstrated that HDAC inhibitors restore spatial memory by increasing the levels of HA in the hippocampus. The importance of this study was that the results exhibited that promoting HA, via HDAC inhibitor or EE, restored learning and access to lost memories after significant brain atrophy, synaptic loss, and neuronal loss occurred (Figure 3) [5,16]. This study suggested that ‘‘memory loss’’ was a reflection of inaccessible memories.” Additionally, Fischer and colleagues indicate that any behavioral effects of HDAC inhibitors could be due to alterations in the acetylation of non-histone proteins, meaning that it is essential for future studies to determine the consequences of the off-target effects of the drugs on non-histone proteins. Future studies also need to determine the specific HDACs that regulate distinct forms of synaptic plasticity, learning, and memory in the hippocampus [17].

The hippocampus is essential for long-term memory formation, but remembering memories involves neocortical networks [18]. EE has also been shown to enhance visual cortical plasticity and memory consolidation through increased expression of growth factors, such as the brain-derived nerve growth factor (BDNF) and enhancing HA as well as protecting against loss of neurogenesis in the dentate gyrus [15,19,20,21,22]. This means that the effects of environmental enrichment are widespread within the brain and that the associations of the many factors, as well as the locations in the brain, need to be addressed. Additionally, localizations and associations of HA in the brain need to be addressed because studies focusing on the use of HDAC inhibitors have seen an effect when injected systematically that is similar to the effect seen through direct infusion within the amygdala [20,23].

As aforementioned, during the process of HA, other proteins such as transcription factors, cytoskeletal proteins, metabolic enzymes, microtubulins, and actin are affected [24]. While many studies focus on the histones specifically affected by HA, the experimental effect on other proteins in the vicinity of chromatin may interfere or be involved in the results produced. In other words, the acetylation being invoked may be increasing the production of other proteins. Therefore, it is important to look at the protein expression of other proteins and changes in genetic expression in those proteins.

Tests to Determine Learning and Memory

Cognitive performance is often assessed by three tests: novel object recognition, fear conditioning, and the Morris water maze. A common experiment to test for learning and memory is the novel object recognition test. This test is a learning model that is dependent on the hippocampus and involves the learned association of a novel context and a familial context [6]. Novel object recognition affects the hippocampus specifically, with the effects primarily seen in the CA1 region. However, the effects of learning paradigm have not been sufficiently explored, so it may affect more than one region of hippocampus, such as CA3 region or the dentate gyrus. Contextual fear conditioning, a learning model that is dependent on the hippocampus, involves the learned association of a novel context and an adverse stimulus [25]. Acetylation of histone H3 is significantly increased after an animal has learned through this model [9,14]. The Morris water maze test focuses on spatial memory formation in the CA1 region of the hippocampus. In this test, mice are trained to locate a hidden platform in a circular tank. Mice with significant neurodegeneration and aging displayed a substantial impairment in escape latency, the time it takes to find the platform [12]. Other tests that have recently been used to demonstrate enhanced HA within the hippocampus and rhinal cortices, such as eyeblink classical condition-
ing, should also be studied to demonstrate learning and memory consolidation through EE and HDAC inhibitors [15]. Overall, these tests indicate that epigenetic changes, more specifically HA, occurs during consolidation of long-term memories within the brain.

**ENVIRONMENTAL ENRICHMENT — POTENTIAL TREATMENT IN NEURODEGENERATIVE DISORDERS**

EE has been indicated as beneficial in reducing cognitive deficits in several models of human neurodegeneration. Many of the factors regulated by EE have been shown to be neuroprotective, promote plasticity, and ameliorate behavioral deficits. The results implicate HDAC inhibitors as potential treatments for disorders such as Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, and other human cognitive disorders that arise from neurodegeneration (Table 1). It is important to note that normal aged animal models are essential to study because limited studies depict the effects of EE and HA in normal aging; this should be considered for future studies. Furthermore, it has been crucial to investigate the therapeutic potential of environmental enrichment on HA and subsequently learning and memory.

**Alzheimer’s Disease**

Recently, environmental enrichment has been used as a potential strategy to influence the progression of human neurodegenerative diseases that are characterized by memory loss and cognitive decline. One such devastating disorder is Alzheimer’s disease. Hallmarks of AD include a decrease in the size and weight of the hippocampus and cortex and the loss of functioning neurons and synapses. Environmental enrichment tested on AD11 mouse model, which expresses anti-nerve growth factor (NGF) to induce neurodegeneration in the hippocampus, showed a reduction in AD-like neurodegenerative characteristics [7]. Another
animal model mimicking AD through beta-amyloid (Aβ) peptides (APP and PS1 variants) showed a pronounced reduction in amyloid deposits after the application of an enriched environment [8,26]. But other studies demonstrated an increased level of Aβ [27] or a stable level of Aβ [28]. Like EE, sodium butyrate was also found to improve memory function in an AD model [29,30]. It was also observed that the AD mouse models showed impaired HA upon exposure to a learning stimulus [31,32].

**Huntington’s Disease**

Huntington’s disease (HD) is characterized by degeneration of the cerebral cortex, producing a movement disorder and dementia. Mouse models such as R61/HD develop adult-onset motor and cognitive deficits that have been delayed by EE [33,34]. Subsequent studies with two other HD transgenic mice models confirmed the beneficial effects of EE [35,36]. EE was also shown to ameliorate reduced adult neurogenesis in the dentate gyrus and hippocampus in R61/HD mice [37]. HD mouse models showed decreased HA and treatment with HDAC inhibitors was shown to attenuate neuronal loss, increase motor function, and extend survival [38,39,40].

**Parkinson’s Disease**

Parkinson’s disease (PD) is clinically identified by motor symptoms, but cognitive impairments with dementia accompany PD in the late stages. Toxin-induced lesions are used to mimic PD-like symptoms in animal models. Such animal models exposed to EE exhibited resistance to the toxins’ insult and showed improvement in motor function [4,41,42]. HDAC inhibitors have been shown to rescue the toxin toxicity and reverse the decreased histone acetylation seen in PD animal models [43].

**EPIGENETICS IN HUMAN COGNITION**

There is a considerable body of evidence from aged and neurodegenerative mouse models implicating the disruption of histone acetylation as the causal basis of cognitive dysfunction. Also, there are numerous studies demonstrating the beneficial effects of environmental enrichment and HDAC inhibitors on aged and neurodegenerative animal models. However, the question arises of how these studies translate to humans. Clinical trials and human studies in psychology have begun to develop the importance of EE integration into the daily lives of the elderly and neurodegenerative patients; unfortunately, much of the EE work done in humans is through psychiatry and does not use the same criteria as used in animal models, making the two types of studies difficult to compare. These differences in variables between animal models and clinical trials are also comparable to the use of HDACs in learning and memory in humans, making it difficult to completely translate the research into humans [44-52]. Data from the previous studies on humans have confirmed the beneficial use of EE in the aging and neurodegenerative disorders, as well as the potential therapeutic use of HDAC inhibitors in neurodegenerative disorders.

**CONCLUSIONS AND OUTLOOK**

Recent findings implicate that the regulation of chromatin in LTP and brain plasticity involves molecular and cellular mechanisms that have yet to be fully identified. These findings indicate that the functional disruption of HA can impair long-term memory formation and restoration; however, these studies do not directly address whether promoting HA via HDAC inhibitors or EE or both is beneficial in human neurodegenerative pathologies and aging. The focus for future research should be to provide insight into a candidate mechanism in which EE functions to improve learning, memory, and the regulation of HA in an aging brain. EE simultaneously used with HDAC inhibitors could be a promising therapeutic intervention in aging and neurodegenerative related disorders, but in the meantime, the use of environmental enrichment as a treatment for age-associated memory impairments could be the answer to the questions always on our mind.
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