Role of Antioxidant Vitamins in Neurogenesis

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ABSTRACT

Neurogenesis is vital in the preservation of cognition. Previous studies have reported antioxidant vitamins as a key regulatory factor in neurogenesis. However, current research investigating their role is inconclusive due to the limited number of studies that have been conducted and conflicting results. This review evaluates the scientific evidence behind the potential roles of antioxidant vitamins in neurogenesis. Observations concerned with the mechanistic and functional aspects of how antioxidant vitamins modulate neurogenesis are both assessed. Vitamin A is evidently involved in cell cycle regulation and cell proliferation; vitamin C reportedly promotes neural differentiation and maturation while inhibiting neurite outgrowth; vitamin E is identified to inhibit cell proliferation while improving cell viability. Varying antioxidant vitamin concentrations have been implicated in facilitating cognition in terms of attention, memory, language, and executive function. Moreover, this review suggests a threshold antioxidant vitamin concentration that should be maintained to promote optimal levels of adult neurogenesis.

Keywords: Neurogenesis, Antioxidants, Vitamin A, Vitamin C, Vitamin E

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INTRODUCTION

Given the increase in life expectancy across the globe, it is important to understand the various factors implicated in preserving the quality of human life. Epidemiological studies have highlighted neurodegenerative diseases as a factor that contributes to a deteriorating quality of life, with approximately 50 million Americans affected each year¹. Neurodegenerative diseases are a clinically heterogeneous group of illnesses that are progressive and lead to death either by primary dysfunction of the central nervous system (CNS) or as a consequence of related medical complications². These diseases are characterized by the accumulation of protein aggregates, or by the loss of existing neurons and alterations in neuronal replacement via neurogenesis²⁻³. Alzheimer's disease (AD) and Parkinson's disease are both neurodegenerative diseases that are affecting increasing populations every year⁴⁻⁵.

Throughout the years, research has associated cognitive decline with many neurodegenerative diseases. For instance, Cloutier et al. identified memory loss as a common indicator for dementia and AD⁶. Patients with Parkinson's disease, a disease primarily characterized by motor function loss, have shown nonmotor symptoms related to cognition including dysexecutive syndrome and visuospatial disturbances⁷. Although the pathology behind many neurodegenerative diseases is still under investigation, impaired adult neurogenesis has been recognized in patients with neurological diseases including AD, Huntington's disease, and Parkinson's disease⁸. Interestingly, decreased levels of neurogenesis have been linked to age-related decline in cognition⁹.

Neurogenesis is the process through which neural progenitor cells generate new neurons¹⁰. The adult brain preserves the ability to undergo neurogenesis in three regions of the brain: the subgranular zone in the dentate gyrus of the hippocampus, the subventricular zone of the lateral ventricles, and the third ventricles of the hypothalamus¹¹. Neural stem cells within the hippocampal subgranular zone develop into intermediate progenitors, which further develop into immature neurons or neuroblasts. Immature neurons move into the inner granule cell layer and differentiate into new granule neurons of the hippocampus¹¹. The hippocampus plays a critical role in learning and memory¹². Current evidence has proposed a significant role for adult-born neurons in pattern separation, learning new conflicting information, and also in memory clearance¹³. Therefore, the preservation of neurogenesis in the adult hippocampus may prove vital in maintaining optimal levels of cognition¹³. Neurogenesis is recognized to be an extremely sensitive process, especially to oxidative stress¹⁴.

Oxidative stress is caused by increased levels of reactive oxygen species and has been implicated in the decline of neurogenesis and cognition¹⁵. Superoxide Dismutase (SD) is a primary defense mechanism against superoxide radicals. In SD deficient mouse models, there was a reduction in hippocampal neuron generation after cranial radiation; a form of brain tumor treatment that leads to increased oxidative stress¹⁶⁻¹⁷. A study done by Ale et al. suggested that oxidative stress promotes accelerated age-dependent decline in adult neurogenesis¹⁸. Through conditional deletion of the clock gene *Bmal1* (*Bmal1*^{-/-}) in mice, they observed neurodegeneration, accelerate aging, and cognitive deficits through oxidative damage.

Recent literature has described the consumption of antioxidants as a potential method to attenuate cognitive decline caused by deficiencies in adult neurogenesis. Multiple studies have reported the consumption of antioxidants preventing the decline of adult neurogenesis and preserving cognition¹⁹⁻²⁰. Vitamins A, C, and E are essential vitamins necessary for biological functioning. These three vitamins are further recognized for their antioxidant properties²¹. Given their therapeutic ability to override free radicals, this review aims to evaluate their significance in preserving adult neurogenesis against oxidative stress.

This review critically analyzes the results of 23 studies to develop a holistic understanding of how antioxidant vitamin intake is implicated in neurogenesis. Previous literature assessing both the mechanistic and functional role of antioxidant vitamins will be analyzed to account for any significant correlations. In the context of this study, the term "mechanistic" refers to the specific biochemical process through which antioxidant vitamins regulate adult neurogenesis. The term "functional" refers to explaining antioxidation in neurogenesis through its functional purpose, which will be operationalized by assessing cognitive function in humans as neurogenesis is a proven contributor to cognition⁷⁻⁸.

ANALYSIS OF ANTIOXIDANT VITAMIN ROLE IN NEUROGENESIS

Vitamin A

Retinoic acid (RA), a morphogen derived from vitamin A, is involved in cell growth and differentiation²². A study by Mishra et al. suggests that RA plays an indirect role in mediating neural stem and precursor cell proliferation in the adult hippocampus²³. By disrupting the synthesis of RA in their mouse model, they identified RA as a hypoxia-independent regulator of hypoxia-inducible factor-1 α . The deficiency of RA synthesis extended the length of the cell cycle, decreased S-phase entry, and increased cell-cycle exit, which was synchronous with alterations in cell-cycle regulators that would prevent G1-S-phase

transition²³. Similarly, Haushalter et al. showcased a decrease in proliferation of radial glial progenitors along with premature neuron production in a developing cerebral cortex of an RA-deficient mouse model²⁴. They observed a diminished population of radial glial progenitors in the RA-deficient mouse model, which led to a smaller telencephalic vesicle. The supportive role of RA is seen in two other studies using a rat and chick model²⁵⁻²⁶. It is important to note that these studies used models where RA-deficiency was induced. Altogether, these studies using RA-deficient models indicate that RA is necessary for maintaining the development of neurons. Interestingly, Hu et al. observed suppression of cell proliferation, neurogenesis, and newborn cell survival in the adult hippocampus of rats with chronic RA treatment²⁷. Since both the RA deficient models and the RA abundant model displayed decreased neurogenesis, there appears to be a threshold level of RA that effectively supports neurogenesis. Future studies should evaluate the role of RA in neurogenesis by comparing varying RA dosages to a control group. By having multiple experimental groups of varying RA dosages, researchers may be able to determine an optimal amount of RA required for healthy levels of neurogenesis.

Vitamin A has been showcased as a crucial component of nutrition, particularly in maintaining optimal levels of cognition. Shahrar et al. identified vitamin A deficiency as a predictor of mild cognitive impairment in humans²⁸. They evaluated neurocognitive performance using comprehensive tests and classified subjects with mild cognitive impairment according to criteria from the Mayo Clinic Definitions. These tests included the Rey Auditory Verbal Learning Test, Wechsler Memory Scale, and the Clock Drawing Test. Binary logistic regression analysis identified vitamin A deficiency as a predictor of mild cognitive impairment in terms of impaired executive function and memory. Similarly, Zeng et al. observed significant cognitive improvements with vitamin A supplementation in mice with Alzheimer's disease (AD)²⁹. Using the Morris Water Maze Test, they reported approximately 75% of mice with vitamin A insufficiency as cognitively impaired.

Vitamin C

Vitamin C, commonly referred to as Ascorbic Acid (AA), is involved in many biosynthetic pathways and functions as an antioxidant³⁰. According to Scheffler et al., AA interferes with viability and neurite outgrowth³⁰. Their study involved PC12 cells as the model for neural plasticity, where neurite outgrowth is dependent on ERK1/2 phosphorylation via the Nerve Growth Factor receptor. The-AA induced PC12 model showed increased levels of phosphorylation of ERK1/2; however, it remains unclear whether AA-induced formation of advanced glycation end products is responsible for the inhibition of neurite outgrowth³¹. Furthermore,

PC12 cells have been widely used as a neuron cell model. These cells have served as strong models to assess neurite outgrowth, but they do have their limitations such as their tumor origin, non-development of synaptic endings even after 14-day differentiation, and high morphological variability³²⁻³³. Future studies should test the validity of these results by using primary neuronal cell cultures and in vivo models. The negative effect of AA on neurite outgrowth is contrasted by the observations of Nam et al., where AA is reported to improve neuronal differentiation and maturation³⁴. This study used mice that were co-treated with D-galactose (D-gal) (a long-term treatment known to induce oxidative stress and reduce hippocampal neurogenesis) and AA. In comparison to the control mice, the D-gal-induced hippocampus experienced a weight reduction, whereas the D-gal-AA-induced hippocampus weight remained stable. Nam et al. described this observation by stating that the AA co-treatment with D-gal reduced the D-gal induced reduction of Ki67-immunoreactive proliferating cells, DCX-immunoreactive neuroblasts and immature neurons, and BrdU-incorporated NeuN-immunoreactive mature neurons³⁴. Overall, these results from these studies investigating the role of vitamin C in adult neurogenesis indicate that vitamin C has a multifaceted role in terms of cell growth. When neurons begin to differentiate and mature, vitamin C supports their growth by maintaining oxidative stress³⁴. However, vitamin C may become an inhibitory factor for neurite outgrowth as indicated by Scheffler et al.³². Like vitamin A, these findings suggest there may be a certain threshold concentration of vitamin C that must be maintained to balance the multiple effects it can have on adult neurogenesis.

To further understand the role of vitamin C in adult neurogenesis, it is important to note the functional aspect of AA in the human brain. Across two cross-sectional studies from 2016 to 2019, human participants who were supplemented with vitamin C exhibited higher cognitive abilities³⁵⁻³⁶. Their results demonstrated a positive association between vitamin C supplementation and immediate memory, delayed recall, visuospatial skills, language, attention, and working memory. Pearson et al. found similar results when evaluating plasma vitamin C concentrations³⁷. They observed lower levels of mild cognitive impairment in individuals with higher plasma vitamin C concentrations; a 1 $\mu\text{mol/L}$ increase in plasma vitamin C was associated with 3% reduced odds of mild cognitive impairment.

Vitamin E

Vitamin E, or α -Tocopherol, is a fat-soluble nutrient recognized for its antioxidant properties, yet many studies have correlated this nutrient with a decline in neurogenesis. Using 5-Bromo-2'-deoxyuridine-labeled cells as a quantitative study for neurogenesis, Ciaroni et al. demonstrated enhanced layers of neurogenesis

Figure 1 Summary of the roles of each antioxidant vitamin in neurogenesis and their observed outcomes in maintaining cognition.

within the adult dentate gyrus of the vitamin E deficient rat model³⁸. Furthermore, in a separate study, Ciaroni et al. observed elevated levels of cell proliferation during adult neurogenesis in vitamin E deficient rat models compared to their age-matched controls³⁹. Cecchini et al. noted an increase in the number of sciatic neurons in vitamin E deficient rats compared to normal rats⁴⁰. Specifically, they noted an increase of about 30%. This observation is further supported by a study done by Cecchini et al. where cell proliferation was inhibited in α -Tocopherol supplemented rats⁴¹. Cuppini et al. also observed a decrease in the number of newborn cells after α -Tocopherol supplementation in the dentate gyrus of adult rats⁴². Vitamin E deficiency has been linked to cell death during adult rat neurogenesis³⁹. However, a study by Ferri et al. later displayed that cell death by vitamin E deficiency is not related to neurogenesis, particularly in the dentate gyrus of rats where neurogenesis occurs⁴³. Cecchini et al. observed lower levels of dying cells in adult hippocampal neurogenesis of α -Tocopherol supplemented rats⁴¹. This observation is further supported by Cuppini et al., where more newborn cells survive in α -Tocopherol treated rats⁴².

The functional component to assessing the role of vitamin E remains unsettled. Morris et al. observed lower levels of cognitive decline in terms of attention,

perceptual/motor speed, memory, and language in humans with vitamin E intake⁴⁴. They used the East Boston Memory Test, the Mini-Mental State Examination, and the Symbol Digit Modalities Test in their longitudinal population-based study. Their results indicated a 36% reduction in the rate of cognitive decline among those in the highest quintile of total vitamin E intake. Farina et al. searched databases and grey literature⁴⁵. Their search identified one study with a moderate quality of evidence supporting the role of vitamin E in preserving cognition. Sano et al. conducted a randomized, double-blind controlled clinical trial to evaluate whether vitamin E would slow the progression of cognitive deterioration and dementia in aging individuals with Down syndrome⁴⁶. Through the Brief Praxis Test and measures of clinical global change, cognition, function, and behavior, they concluded that vitamin E does not slow the progression of cognitive deterioration in older individuals with Down syndrome.

LIMITATIONS

This review is limited by many of the studies using mice as model organisms for adult neurogenesis. Although mice serve as effective model organisms, they are not a direct representation of humans and oftentimes elicit very different responses to experimental interventions. Secondly, it is important to recognize that a disruption

in neurogenesis due to varied vitamin levels may not be the only reason for changes in cognition. The brain is an intricate organ in terms of how various processes are related. A decline in cognition in vitamin-deficient patients may not directly be due to the vitamin deficiency or excess affecting neurogenesis. Studies evaluating patient cognition were incorporated into this review to develop a possible relationship between varied vitamin levels and cognition. Given neurogenesis is involved with various aspects of cognition, the relationship between vitamin levels and cognition is used to provide some direction that addresses the contrast in mechanistic studies of antioxidant roles in neurogenesis.

Vitamins A, C, and E exhibited multifaceted roles in regulating various aspects of adult neurogenesis. Due to their multiple roles and functions in adult neurogenesis, there appears to be a certain threshold level at which these vitamins need to be maintained. An excess or deficiency in either of these vitamins can lead to complications in neurogenesis. However, it is inconclusive whether antioxidant vitamin levels need to be maintained at consistent, adequate amounts for optimal neurogenesis, or if these vitamin levels can fluctuate around a threshold.

CONCLUSION

In this review, various studies implicating the involvement of antioxidant vitamins in neurogenesis were evaluated. Vitamin A reportedly facilitates cell cycle regulation and cell proliferation. Moreover, vitamin A deficiencies have been associated with cognitive decline, particularly in executive function and memory. Vitamin C evidently promotes neural differentiation and maturation while inhibiting neurite outgrowth. Supplementation of vitamin C is correlated with improved immediate memory, delayed recall, visuospatial skills, language, attention, and working memory. Vitamin E is noted to inhibit cell proliferation while maintaining cell viability. However, studies have identified that vitamin E supplementation reduces the rate of cognitive decline in terms of attention, perceptual/motor speed, memory, and language in humans. Furthermore, this review suggests that there is a threshold level for antioxidant vitamin concentration. Deficiencies or excess in antioxidant vitamin levels can carry negative consequences that will lead to cognitive impairments. Many current studies have evaluated the effect of these vitamins on neurogenesis by measuring the weight of cells produced or using markers to evaluate cell quantity. Future studies should focus on identifying the direct biochemical mechanism by which these vitamins regulate neurogenesis. Moreover, further studies need to assess how different levels of each vitamin affect neurogenesis through their respective mechanism. When evaluating the results of

different vitamin levels, it is important to note whether a consistent moderate amount of vitamin concentration is needed to promote optimal neurogenesis, or if a fluctuation in vitamin concentration within a specific threshold is tolerable. Overall, antioxidant vitamins are important regulators in adult neurogenesis and have the potential to be therapeutically managed to preserve the cognitive decline experienced by the aging human brain.

COMPETING INTERESTS

No competing interests declared.

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