Clareus Scientific Medical Sciences
Volume 1 Issue 1 June 2024

Vitamin D Status and Brain Development

Citation: Damilola Mildred Ajayi. "Vitamin D Status and Brain Development". Clareus Scientific Medical Sciences 1.1 (2024): 03-08.

Article Type: Review Article

Received: June 06, 2024

Published: June 17, 2024

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Abstract

This seminar paper aims to explore the intricate relationship between vitamin D status and brain development, shedding light on the molecular and biological role of this crucial nutrient. Vitamin D plays a pivotal role in a wide range of physiological processes, including brain development, making it a vital component for optimal neural functioning. To provide a comprehensive understanding, the paper begins by presenting an overview of vitamin D, including its sources. It then delves into the absorption, metabolism, and functions of vitamin D within the body.

Moving forward, the paper focuses on the impact of vitamin D on brain development during both prenatal and postnatal stages. During prenatal development, vitamin D influences critical processes such as neuronal proliferation, differentiation, and maturation. The paper elucidates the intricate relationship between maternal vitamin D levels and fetal brain development, highlighting the importance of adequate prenatal vitamin D exposure.

To provide insights into the underlying mechanisms, the paper investigates potential pathways through which vitamin D exerts its influence on brain development. These include gene regulation, the modulation of neurotrophic factors, and the synthesis of neurotransmitters, all of which play crucial roles in shaping neural circuits and supporting cognitive functions.

In conclusion, this seminar paper highlights the profound impact of vitamin D on brain development, emphasizing its role during both prenatal and postnatal stages. It underscores the need for further research in this field to enhance our understanding of the molecular mechanisms and the potential therapeutic applications of vitamin D in promoting optimal brain development and preventing neurodevelopmental disorders.

Keywords: Vitamin D' Pregnancy; Brain; Neural defect

List of Abbreviations

25(OH)D - 25-hydroxyvitamin D.
VDR - Vitamin D Receptor.
PTH - Parathyroid Hormone.
ADHD - Autism Spectrum Disorders.
BDNF - derived neurotrophic factor.
GABA - gamma-aminobutyric acid.

Introduction

Background and Significance

Vitamin D, a steroid hormone and fat-soluble hormone, has diverse impacts on the regulation of calcium and phosphorus levels as well as the immune system and bone health of individuals. In children, a severe lack of vitamin D can lead to rickets, while in adults, it can cause osteomalacia. Yet, even mild deficiencies in vitamin D have recently been linked to the development of diabetes mellitus and other persistent diseases characterized by low-grade chronic inflammation.

Furthermore, emerging research has highlighted its importance beyond these functions, particularly in brain development. The brain is a complex organ that undergoes rapid growth and development during prenatal and postnatal stages, and emerging evidence suggests that vitamin D status may significantly influence these processes. Understanding the relationship between vitamin D and brain development is essential for promoting optimal cognitive, emotional, and behavioral outcomes. The primary objective of this seminar paper is to comprehensively analyze the relationship between vitamin D status and brain development.

Specifically, the paper aims to explore the impact of vitamin D on brain development during prenatal and postnatal stages. Additionally, it will investigate the association between vitamin D deficiency and the risk of neurodevelopmental disorders and will delve into the potential mechanisms underlying the influence of vitamin D on brain development, such as gene regulation, neurotrophic factors, and neurotransmitter synthesis (Zittermann A. 2003)., (Garland CF, et al. 2006).

Vitamin D

Vitamin D can be obtained from two main sources: sunlight and dietary intake. Sunlight exposure triggers the synthesis of vitamin D in the skin, primarily through the conversion of 7-dehydrocholesterol to previtamin D3, which is then converted to active vitamin D (calcitriol) in the liver and kidneys. Dietary sources of vitamin D include fatty fish, fortified dairy products, and dietary supplements. Vitamin D absorption primarily occurs in the small intestine, where it is incorporated into chylomicrons and transported to the liver.

In the liver, vitamin D undergoes hydroxylation, forming 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D. Because the parent compound vitamin D or cholecalciferol has a brief half-life of 12-24 h, it is its metabolite 25-hydroxy-vitamin D or 25(OH)D with its 2-3 weeks-half-life that is used as the indicator of vitamin D status (Wagner C.L et al, 2018).

Further hydroxylation takes place in the kidneys, leading to the formation of the biologically active form of vitamin D, known as 1,25-dihydroxyvitamin D [1,25(OH)2D]. Vitamin D exerts its functions through binding to the vitamin D receptor (VDR) present in various tissues, including the brain. The VDR regulates the expression of genes involved in calcium homeostasis, cellular proliferation, differentiation, and immune response.

In the brain, vitamin D plays a crucial role in neurodevelopment, neuroplasticity, and cognitive function. This step is under tight feedback control that is dependent on the body's calcium requirements. It is now clear that a wide range of tissues possess the 1-hydroxylase enzyme, so that local conversion of 25(OH)D to the active 1,25(OH)2D may occur. (Bikle, D. 2009) The active hormone is best known for its role in maintaining serum calcium levels in conjunction with parathyroid hormone (PTH). 1,25(OH)2D increases intestinal calcium absorption, (Holick, M.F., 1994) thereby suppressing PTH secretion (Bikle, D., 2009), and promoting mineralization

(and decreasing de-mineralization) of the skeleton. (DeLuca, H.F et al., 1998).

The brain is one of the earliest fetal organs to develop, and some evidence suggests that vitamin D, owing to its biological role in the genesis of fetal brain development, can affect fetal brain functions and influence neurodevelopment later in life. Vitamin D acts to control levels of neurotransmitters and plays a role in enhancing the sensitivity of neurotransmitter receptors and in activating signal transduction pathways (Bailey L. 2015), (Patrick R.P et al, 2014), (Murthi P, 2017).

Although vitamin D is undoubtedly important for fetal development and for bone development in childhood, we are beginning to learn that it plays a much wider role in health and disease prevention. It is important to understand that vitamin D is not really a vitamin; vitamin D3 is a preprohormone made in the skin in response to ultraviolet- B light exposure.

It also serves as a transcriptional regulator by expressing several genes vital to brain (Murthi P., 2017) and seems to have a role in brain protection by regulating several neurotrophic factors protecting during inflammation and blocking toxic effects on the brain through production of calcium-binding proteins and blockage of calcium influx. Finally, vitamin D also plays a role similar to that of neurosteroids, which control neuronal excitability and circuitry. This "fine-tuning" of the neuronal circuitry is thought to be important in relation to memory, cognition, and behavior. (Janbek et al., 2019).

Active form of vitamin D can be produced by the brain and vitamin D receptors are widely distributed across distinct brain systems (e.g., the prefrontal cortex and limbic system) (Smith E., et colleagues, 2005), providing a mechanistic account for the role of vitamin D in emotion, cognition, and neuropsychiatric diseases (Di Somma et al., 2017; Eyles et al., 2013; Schlogl & Holick, 2014).

Vitamin D and Brain Development

Placental Transfer of Vitamin D

Vitamin D can traverse the placenta, delivering a direct supply to the developing fetus. Some earlier investigations demonstrated that rats with vitamin D deficiency experienced diminished fertility and litter size, accompanied by impaired ovarian function and spermatogenesis. The latter process seemed to be influenced by calcium levels and could be reversed through calcium administration. Another animal model, VDR null mutant mice, exhibited reduced sperm count and motility, along with histological abnormalities in the testes.

In traditional vitamin D endocrinology, the conversion of the precursor hormone 25(OH)D3 into its active form, 1,25(OH)2D3, primarily takes place in the kidneys. The enzyme responsible for this conversion, CYP27B1, is expressed mainly in the proximal tubule cells. However, it is now evident that CYP27B1 is present in many other tissues beyond the kidneys. Of particular importance is the placenta, which was identified more than three decades ago as a significant site, apart from the kidneys, for the conversion of 25OHD3 to 1,25(OH)2D3.

Vitamin D plays a vital role in regulating neurogenesis and neural migration, critical processes during fetal brain development. Experimental studies have demonstrated that vitamin D deficiency during prenatal stages can disrupt these processes, leading to altered brain structure and function.

Myelination, the process of forming a protective sheath around nerve fibers, and synaptogenesis, the formation of synapses between neurons, are essential for proper brain functioning. Vitamin D has been implicated in these processes, with deficiency potentially impairing myelination and synaptic connectivity.

Influence on Neuroplasticity and Cognitive Function

Postnatally, vitamin D continues to impact brain development, particularly neuroplasticity and cognitive function. Adequate vitamin D levels have been associated with improved memory, attention, and learning abilities. In contrast, insufficient vitamin D during early childhood may increase the risk of cognitive impairments.

Vitamin D is a potent inducer of nerve growth factor synthesis (Wion, D et al., 1991). Genes of the vitamin D pathway (25 hydroxylase, 1 hydroxylase and 24 hydroxylase) and VDR are expressed in rat brain cells (Almeras L et al., 2007) and the distribution of VDR and 1-hydroxylase is thought to be similar in rat and human brains (Eyles, D.W et colleagues., 2005). In experimental studies, rats deprived of vitamin D prenatally had enlarged lateral ventricles, decreased cortical thickness and heavier and longer brains, and altered patterns of apoptosis (Ko P, et other., 2004, Eyles D., et al, 2003).

Seasonal and population level patterns of schizophrenia incidence indicate the possible role of low intrauterine vitamin D in increasing later schizophrenia risk. This is a difficult but important area to research (McGrath et al., 1999, Torrey et al., 1997), with animal work indicting transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats (Becker, A et al., 2005). In a Finnish birth cohort study, regular vitamin D supplementation (maternal self-report) during the first year of offspring life was associated with a reduced risk of schizophrenia in males (but not females) (McGrath, J et al., 2004).

Observational studies provide indirect evidence that low vitamin D status during early life may increase the risk of multiple sclerosis (van der Mei, I.A., 2003). These findings include a striking season-of-birth pattern in a large cohort of Northern Hemisphere MS cases (Willer, C.J., 2005), and a congruent pattern in the Southern hemisphere (Staples, J., 2010).

Several studies have investigated the relationship between vitamin D status and behavioral and emotional development. Vitamin D deficiency has been associated with an increased risk of autism spectrum disorders, ADHD, and emotional disturbances. Emerging evidence suggests that vitamin D plays a crucial role in motor development and coordination. Insufficient vitamin D levels have been linked to delayed motor milestones and increased risk of neuromuscular disorders.

Vitamin D Deficiency and Neurodevelopmental Disorders

Several epidemiological studies have reported an association between maternal vitamin D deficiency during pregnancy and an increased risk of autism spectrum disorders in offspring. However, further research is required to establish a causal relationship.

Limited evidence suggests a potential link between vitamin D deficiency and ADHD. Although the exact mechanisms remain unclear, vitamin D may modulate dopamine pathways, which are involved in ADHD pathology.

Studies have found an association between low vitamin D levels during prenatal and early postnatal periods and an increased risk of developing schizophrenia later in life. Vitamin D may influence neurodevelopmental processes implicated in schizophrenia pathogenesis.

While the evidence is limited, some studies have suggested an association between vitamin D deficiency and an increased risk of depression and anxiety disorders. Vitamin D may affect serotonin synthesis and neuroinflammatory pathways involved in mood regulation.

Vitamin D regulates the expression of numerous genes involved in brain development, including those related to neuronal differentiation, synaptic plasticity, and neurotrophin production. Epigenetic modifications, such as DNA methylation and histone acetylation, may mediate the long-lasting effects of vitamin D on gene expression.

Vitamin D can modulate the production and release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which promote neuronal survival, growth, and differentiation. Dysregulation of these neurotrophic factors may contribute to neurodevelopmental abnormalities.

Vitamin D influences the synthesis and regulation of neurotransmitters, including dopamine, serotonin, and gamma-aminobutyric acid (GABA), which are crucial for proper brain functioning. Altered neurotransmitter levels may underlie the association between vitamin D deficiency and neurodevelopmental disorders.

Conclusion

This seminar paper has provided a comprehensive analysis of the relationship between vitamin D status and brain development. The evidence suggests that vitamin D plays a vital role in various aspects of brain development, including neurogenesis, neural migration, myelination, synaptogenesis, neuroplasticity, and cognitive function. Vitamin D deficiency during prenatal and postnatal stages has been associated with an increased risk of neurodevelopmental disorders, including autism spectrum disorders, ADHD, schizophrenia, and mood disorders.

Understanding the influence of vitamin D on brain development has important implications for public health and clinical practice. Strategies to optimize vitamin D status during pregnancy and early childhood may have long-term benefits for neurodevelopmental outcomes. Further research is needed to elucidate the precise mechanisms underlying the effects of vitamin D on brain development and to explore potential interventions targeting this pathway. Additionally, large-scale prospective studies and randomized controlled trials are necessary to establish causal relationships and inform evidence-based recommendations regarding vitamin D supplementation for brain development.

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