Review

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The Effects of Vitamin D_3 on Brain Development and Autism

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ABSTRACT:

The effects of vitamin D_3 on brain development and autism

Vitamin D_3 has long been known to affect the skeletal system and mineral metabolism. In recent years, there has been an increasing interest in the effects of vitamin D_3 on different systems. The relation of vitamin D_3 with brain development and autism is an intensely researched area in this context. The aim of this paper is to review the current evidence on the effects of vitamin D_3 on brain development and autism and to provide insights for future scientific studies.

Vitamin D_3 has been shown to have direct effects on neural development, neural cell proliferation and apoptosis. Moreover, this vitamin also has effects on the immune system, inflammation processes, and antioxidation, which in turn are known to have effects on brain development. Current evidence suggests that vitamin D_3 has a critical effect on brain development and that vitamin D_3 deficiency might have detrimental effects on mental development.

Similarly, vitamin D_3 deficiency and autism show many similarities in their etiopathogenesis. However, clinical studies showing the link between vitamin D_3, brain development and autism are limited. The data obtained in this area are based on animal studies, and current data do not seem to be sufficient to allow for direct conclusions.

Keywords: vitamin D_3, autism, brain development

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INTRODUCTION

Vitamin D_3 has long been known to have effects on bone and mineral metabolism, and in the Eastern cities of Turkey, vitamin D_3 deficiency due to the long winter season has commonly been observed to lead to health problems[1]. Recently, vitamin D_3 has also been demonstrated to have pro-differential, anti-proliferative, pro-apoptotic and anti-inflammatory effects, besides affecting the skeletal system. The number of studies on the effects of vitamin D_3 on different systems has increased dramatically[1]. Brain development and psychiatric disorders are among the most commonly researched areas with respect to the effects of vitamin D_3[1-6].

The purpose of this review is to examine the effects of vitamin D_3 on brain development and autism, and to provide insights for future scientific studies looking into neurobiological hypotheses that can explain this relationship.

Vitamin D_3 and the Brain

Effects of vitamin D_3 on the brain have been gaining importance in recent years. In earlier studies, it was revealed that vitamin D_3 metabolites can pass the blood–brain barrier, and

the presence of vitamin D_3 was identified in human cerebrospinal fluid[7,8]. Subsequent studies have been conducted to determine whether vitamin D_3 synthesis and metabolism occur in the brain. In related studies, it has been determined that, besides the 25-hydroxyvitamin D_3-1 alpha hydroxylase enzyme playing a role in vitamin synthesis, cytochrome P450 enzymes such as CYP24A1 (24-alpha hydroxylase), which take part in vitamin D_3 inactivation, are also present in brain cells[9,10].

Another area of research on vitamin D_3 and the brain is the work carried out on VDRs (vitamin D_3 receptors). Johnson and his team revealed the presence of VDRs in rat fetus brain dorsal stem ganglion cells[11], and in subsequent studies, it was proven that VDRs are present in both the neuronal and glial cells of human and rodent brains[10]. While these data do not provide proof of a causal relationship, they suggest that vitamin D_3 might have an effect on cell apoptosis and the cell cycle in the brain.

The mechanisms of actions of vitamin D_3 on the brain and its development is another research topic. Studies conducted in this area have focused on many different mechanisms, which will be explained in the subsequent section.

1. Direct Effects of Vitamin D_3 on Neural Development

Numerous studies demonstrate that vitamin D_3 also plays a role in cellular differentiation. In a study that examined the effects of vitamin D_3 on mitosis and axon development and used nerve growth factor (NGF) production as an alternative mediator, Brown et al. confirmed that vitamin D_3 added to their hippocampal cell culture caused a decrease in the number of the proliferative cells and led to an increase in the development of neurites[6]. In a study on the effects of maternal vitamin D_3 deficiency on cell reproduction and apoptosis in the rat embryo cortex at different developmental stages, it was revealed that vitamin D_3 has a regulatory role at both cellular and molecular levels. After comparison with the control group, it was confirmed that apoptosis decreases more significantly at birth and, irrespective of developmental stage, mitosis increases in newborns and embryos born to mothers with vitamin D_3 deficiency[3]. In rats born to mothers with vitamin D_3 deficiency, it has been found that the brain cortex is longer, the lateral ventricles are widened, and there is more cell reproduction in the brain tissue where the cortex is thinner[10,12]. Furthermore, a decrease in the NGF, glial cell line-derived neurotrophic factor (GNDF) levels and expression of neurotrophin receptor p75NTR is also reported in vitamin D_3-deficient rats[12]. In support of these results, Cui et al. found that vitamin D_3 regulates cellular proliferation in the developing brain[13]. All of this research suggests that vitamin D_3 may have a direct effect on neural expansion, differentiation, and cell death in the human brain.

Neurotrophins are also thought to be related to vitamin D_3 and neuronal development. It has been determined that vitamin D_3 has an indirect effect on neuronal development through a change in neurotrophic factor production in glial cells[14]. In a study by Neveu et al., it was demonstrated that supplementing primary cultures of astrocytes with vitamin D_3 decreases the synthesis of neurotrophin-4 (NT-4) mRNA and increases NGF and neurotrophin-3 (NT-3) mRNA levels[15]. Brown et al. found that there is an increase in neurite outgrowth following vitamin D_3 supplementation to rat hippocampal cell culture and an increase in the NGF levels in proportion to the decrease in mitotic division rates[6]. Saporito et al. also determined that NGF expression increases in the hippocampus of adult rats after the application of vitamin D_3[16]. Nerve growth factor has been found to have an effect on the growth and survival of many neurons in the brain, including cholinergic neurons of the basal forebrain[17], besides having a role in neuronal plasticity, neuronal membrane excitability, and the development and regulation of immune cells[18]. Reduced serum NGF levels have been observed in psychiatric disorders such as schizophrenia[18]. From the background of these studies, vitamin D_3 can be thought to regulate the life cycle of neurons.

Glial cell-derived neurotrophic factor, also known as GDNF is also a crucial component in the development of dopaminergic and noradrenergic systems[19,20]. It has been thought that GDNF plays a role in heroin dependence[21]. Naveilhan et al. have shown that supplementing C6 glioma cells with 1,25(OH)2D increases the synthesis of GDNF mRNA[22]. There are cases indicating that GDNF might play a role in various behavioral mechanism models that include sensorimotor behaviors and schizophrenia[23,24].

Moreover, in animal research, developmental vitamin D_3 deficiency has been found to have an effect on long-term memory and learning disorders[25]. Results of another study with rats born to mothers with a temporary vitamin D_3 deficiency compared to a control group indicated that there were structural changes in the brain, including a decrease in NGF levels and gene expression of some factors that affect the neuronal structure of the brain. These results demonstrate that temporary vitamin D_3 deficiency in early developmental stages causes permanent changes in the adult brain. These findings are important for community health, in particular with regard to D_3 hypovitaminosis in women of fertility age[4]. In a study carried out in Turkey, no significant differences in NGF levels was found in control groups compared to subjects with low vitamin D_3 levels. However, a significant negative correlation was found between vitamin D_3 and NGF levels[26].

2. The Role of Vitamin D_3 in Neuroprotection

In the cell, there is a balance between the reactive oxygen types produced during aerobic metabolism and the anti-oxidant protective mechanisms that play a role in free radical inactivation. There are two protective mechanisms—enzymatic and non-enzymatic. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and ceruloplasmin are enzymatic protective mechanisms. Glutathione and its precursors—folate, vitamin B_6 and vitamins A, C and E—are non-enzymatic protectors[27]. It has been found that vitamin D_3 increases glutathione levels, raising the level and activity of the gamma-glutamyl enzyme responsible for glutathione production in physiologic concentrations[28]. In a study by Wang et al., vitamin D_3 was shown to decrease ischemia-based brain damage in the adult rat cortex[29]. Further, vitamin D_3 has been found to protect the brain against the cytotoxicity induced by the excitatory neurotransmitter glutamate and dopaminergic toxins[30,31].

Intracellular free calcium imbalance is neurotoxic in both embryonic and adult brain tissue[9]. Vitamin D_3 is considered to increase the expression of proteins that connect intracellular calcium, thus protecting neurons from calcium-mediated toxicity[9,32]. Brewer et al. found that the active form of vitamin D_3 regulates L-type voltage-sensitive calcium channels in embryonic cortical neurons[9,33]. These results support the fact that vitamin D_3 has a protective effect in that it regulates the cellular intake of calcium. However, the evidence for the existence of this mechanism in embryonic brain cells is weak.

3. The Effects of Vitamin D_3 on Dopamine

Limited data show that vitamin D_3 has a neuroprotective effect on the neurons constituting the brain's dopaminergic system[14]. In a study by Cass et al., rats were repeatedly exposed to methamphetamine in neurotoxic doses, which decreased the dopamine and serotonin levels in the striatum and nucleus accumbens. Upon introduction of vitamin D_3, these levels improved significantly, suggesting that vitamin D_3 has a protective effect on the dopaminergic system[34].

Another effect of vitamin D_3 in the dopaminergic pathways is the increase in dopamine synthesis. A study on adrenal medulla tissues of rats also demonstrated that vitamin D_3 increases dopamine through tyrosine hydroxylase, one of the enzymes involved in dopamine synthesis[35]. In a study in which the post-mitotic factors crucial for dopaminergic neuron development were examined, it was found that there was a decrease in the Nurr1 and p57kip2

phenotype in the mesencephalic embryonic brains of rats with vitamin D_3 deprivation[9,36]. In another study that measured dopamine levels in the forebrain of newborn rats with vitamin D_3 deprivation, it was demonstrated that there was a reduction in the conversion of dihydroxyphenylacetic acid (DOPAC) to homovanillic acid (HVA), and that vitamin D_3 deficiency affected dopamine turnover in the developmental process even when there was no change in dopamine levels[37]. In addition, rats born to mothers with vitamin D_3 deficiency have been shown to have symptoms of hyperactivity[38].

4. Anti-Inflammatory Effects of Vitamin D_3

The anti-inflammatory effect of vitamin D_3 on the developing brain is another area of research. Vitamin D_3 is an important immune modulator[39]. Garcion et al. revealed that vitamin D_3 suppressed induced nitric oxide synthase (iNOS) expression and caused a six times increase in the number of macrophages and a decrease in the number of apoptotic cells at the lesion site during inflammation of the brain induced by lipopolysaccharides[40]. In another study, inflammatory mechanisms simulated in an experimental autoimmune encephalitis model were found to decrease with vitamin D_3 levels[41]. Furthermore, vitamin D_3 metabolites have been found to suppress the stimulant effect of epidermal growth factor on vascular smooth muscle cells and thus inflammation[42]. In a study conducted by Tiims et al., vitamin D_3 deficiency was found to be related to an increase of circulating matrix metalloproteinase 2 (MMP2) and C-reactive protein (CRP) which could be reversed with vitamin D_3 support[43]. This study demonstrated that there was an inverse relationship between C-reactive protein, an effective factor in inflammation, and vitamin D_3[43]. It has also been found that NF-jB activity, one of the factors in inflammation, is suppressed by vitamin D_3[44].

Although several mechanisms have been proposed, the hypothesis that vitamin D_3 achieves this effect through T-cell function has gained the most recognition[45]. Macrophages and dendritic cells have VDR ligands, 1-alpha hydroxylase enzyme is up-regulated by active macrophages, and activated macrophages are able to synthesize and secrete 1,25(OH)2D3. These findings provide further evidence of the role of vitamin D_3 in reducing inflammation[46,47] and support the role of vitamin D_3 in anti-inflammatory processes; however, more studies are needed to determine how vitamin D_3 affects brain functions related to psychiatric disorders and behavioral processes.

All these findings support the hypotheses that vitamin D_3 levels have a critical effect on brain development and that vitamin D_3 deficiency might have detrimental effects on mental development and may cause behavioral problems. Possible mechanisms linked to the effects of vitamin D_3 on brain development were summarized in Table 1.

Pathophysiology of Autism Spectrum Disorder (ASD) and Its Relationship with Vitamin D_3

Vitamin D_3 deficiency and autism show many similarities in their etiopathogenesis. Findings on autism indicate that this condition is more common in urban areas, in climates with less sunlight, at higher elevations and in areas with high air pollution, all of which coincide with the etiology of vitamin D_3 deficiency[48-50]. In the few studies where plasma vitamin D_3 levels of autistic children were compared with a control group, contradictory results were obtained[51-53]. In a study by Meguid et al., it was determined that children with autism spectrum disorder (ASD) had lower serum calcidiol and calcitriol levels compared to the healthy control group[51]. On the other hand, there is also research that shows similar or lower vitamin D_3 levels in children with ASD compared to control groups[52,53]. A study carried out in Turkey compared children with ASD and developmental delay, and children with only developmental delay (DD), and no difference in their basal vitamin D_3 levels was observed. In the next phase of that study, vitamin D_3 replacement was provided with special training for the cases of vitamin D_3

Table 1. The Effects of Vitamin D on Brain Development

Potential Effect	Effect Mechanism	References
Neurotrophic effect (factors that affect neuronal differentiation, maturation and growth)	NGF mRNA increased NT-3 mRNA increased NT-4 mRNA down regulated GDNF mRNA increased	Neveu et al., 1994a; Neveu et al., 1994a; Neveu et al., 1994a; Naveilhan et al., 1996
Neuroprotective effect	Increase of glutathione through the increase of gamma-glutamyl transpeptidase	Garcion et al., 1999
Antioxidant effect	Neuronal protection against neurotoxicity induced by oxygen free radicals such as hydrogen peroxide	Ibi et al., 2001
	Decrease in iNOS	Garcion et al., 1997
Intracellular calcium regulation	Down-regulation of voltage-sensitive Ca+2 paths	Brewer et al., 2001
	Increase in intracellular calcium-linking proteins	Alexianu et al., 1998
Effect on dopaminergic system	Neuroprotective effect on dopaminergic paths	Cass et al., 2006; Puchacz et al., 1996
Effect on neurotransmission and neuroplasticity	Morphologic changes in the brain in developmental vitamin D deficiency	Féron et al., 2005; Eyles et al., 2003
	Neurite outgrowth increases	Brown et al., 2003
	Changes in apoptosis, mitosis and neurogenesis in vitamin D deficiency	Ko et al., 2004; Féron et al., 2005; Brown et al., 2003
Anti-inflammatory effect	Suppressed inflammatory response	Garcion et al., 1998; Nataf et al., 1996; Carthy et al., 1989; Cantorna et al., 2005; Garcion et al., 1997;

deficiency. The results showed that in both groups, vitamin D_3 growth values were normal for children who received replacement and significantly better than the values for the children who did not receive treatment[26]. Molecular systems in which vitamin D_3 plays a role and which have also been suspected in ASD pathophysiology will be discussed in subsequent sections.

A. Neurogenesis and Neurotrophic Factors

Congruencies between the biological mechanisms thought to take part in ASD and the mechanisms in which vitamin D_3 plays a role are striking (Table 2). There are overlaps between neural growth steps in which vitamin D_3 takes part and the pathways implicated in the development of autism spectrum disorders[9,54,55]. Halicka et al. have argued that vitamin D_3 plays a role in decreasing DNA damage by acting as an agent in DNA repair[54]. Genetic mutations resulting from DNA damage are also implicated in the pathogenesis of ASD[55]. In a study in rats conducted by Taniura et al., vitamin D_3-specific DNA response element (VDRE) was shown to have high levels of activity in the cerebellum, an area of the brain that is frequently linked to ASD[56].

There is a striking relationship between neurotrophic factors, vitamin D_3, and autism. In a prospective study conducted with blood samples, neurotrophin levels from newborns with autism, mental retardation and cerebral palsy were compared with healthy control groups; a significant increase in neurotrophin-4 (NT-4) levels was detected in the subjects with autism and mental retardation, while no significant difference in neurotrophin-3 (NT-3) levels was found[57].

In a similar study by Miyazaki et al., subjects with autism and mental retardation were compared with a healthy control group, and it was determined that NT-4 levels were higher in subjects with mental retardation. Higher levels were also identified in autistic subjects, but no statistical significance was found[58]. Nelson et al.

Table 2: Overlap between the Effects of Vitamin D and Autism in the Brain

Vitamin D_3	References	Autism	References
Increases glutathione and has antioxidant effects on brain	Garcion et al., 1999; Ibi et al., 2001; Garcion et al., 1997	Deficits in glutathione redox systems	Rose et al., 2012; Gu et al., 2013
The regulation of proteins that regulate neuronal differentiation and changes at the cellular level, such as the regulation of cytokine and neurotrophin	Eyles et al., 2005; Féron et al., 2005; Eyles et al., 2003 Brown et al., 2003	In autism, micro-anatomical changes were also reported in the brain	Casanova et al., 2006
Changes in neurogenesis, apoptosis and mitosis	Ko et al., 2004; Féron et al., 2005; Brown et al., 2003		
Decreased iNOS	Garcion et al., 1997	NO increased	Sweeten et al., 2004;
No study		BDNF increased	Nelson et al., 2001; Miyazaki et al., 2004
Increased NGF mRNA	Neveu et al., 1994a;	No significant difference when compared to healthy control group	Nelson et al., 2001
Increased GDNF (mRNA)	Naveilhan et al., 1996	No study	
Increased NT-3 (mRNA)	Neveu et al., 1994a	NT-3 decreased	Nelson et al., 2006
Decreased NT-4 (mRNA)	Neveu et al., 1994a	NT-4 increased	Nelson et al., 2001
Vitamin D_3 deficiency was held responsible for etiology of autoimmune disorder	Zhang et al., 2010; Hamza et al., 2011;	Autoimmune disorders are more common among the families of autistic patients	Sweeten et al., 2003

detected lower NT-3 levels in autistic patients compared to their healthy counterparts[59]. In studies where NGF levels in autism, mental retardation and control groups were examined, no statistically significant differences were found between the groups[57]. Several studies have found that vitamin D_3 increases NGF[15] and GDNF[22] levels.

In our study of patients diagnosed with autism and cognitive development disorders, we found a significant improvement in development scores and autistic symptoms and detected a significant increase in NGF levels, which suggests that NGF could be the prime mediator of vitamin D_3's effects in patients with ASD[26]. On the other hand, patients with cognitive developmental delay have been observed to have an increase in their GDNF that parallels the recovery of their developmental level, particularly in patients who have been given vitamin D_3 replacement therapy. It is thought provoking that there is a higher possibility of this effect taking place via GDNF in patients with cognitive developmental delays. Based on the findings of the research, it was determined that NGF could be used to mark the progress of autistic disorders, and GNDF could be used to mark the progress of cognitive developmental deficits[26].

B. Immune System

The role of vitamin D_3 with respect to the immune system is frequently examined in the etiology of autism. Vitamin D_3 receptors have been detected in lymphocytes, activated B cells and dendritic cells[60]. T cell dysfunctions have been revealed in autism[61]. Furthermore, an increasing number of studies has shown vitamin D_3 playing a role in allergic and autoimmune reactions[60]. Recently, vitamin D_3 deficiency has been thought to be the trigger for some autoimmune disorders, such as multiple sclerosis and systemic lupus erythematosus[62-64]. Similarly, compared to the normal population, autoimmune disorders are more common among families who have children with autism spectrum disorder[62].

A number of studies has been carried out solely on the vitamin D_3/autism/immunity relationship. In a study that examined the relationship between $25(OH)D_3$ and anti-myelin-associated glycoprotein (anti-MAG) in autistic children, lower vitamin D_3 levels were detected compared to the healthy group and, as serum 25-hydroxyvitamin D_3 levels increased, autism symptoms decreased. Further, in nearly 70% of autistic patients, serum anti-MAG auto-antibodies levels were high; a negative correlation was detected between serum 25-hydroxyvitamin D_3 levels and anti-MAG auto-antibodies[62].

C. Antioxidant Systems

Another area where vitamin D_3's effects and the possible pathogenesis of autism overlap is in anti-oxidation systems. In several studies, autistic patients have been found to have deficits in their glutathione redox systems, and this suggests that there could be a connection between systemic disorders and autism[65-66]. Accordingly, it has been determined that vitamin D_3 increases the quantity of antioxidant agents such as glutathione by increasing the enzyme gamma-glutamyl transpeptidase. This enzyme is responsible for glutathione formation in the physiologic formation of vitamin D_3, and thus plays a role in brain detoxification mechanisms[28].

Patients with ASD have also been found to have higher levels of nitric oxide compared to healthy control groups[68]. Nitric oxide is a compound that is produced by iNOS, damaging neurons and oligodendrocytes when produced in high quantities[67]. Vitamin D_3, on the other hand, has been shown to inhibit iNOS[69].

Figure 1 illustrates the possible mechanisms of how vitamin D_3 deficiency might form an 'autistic neuron'.

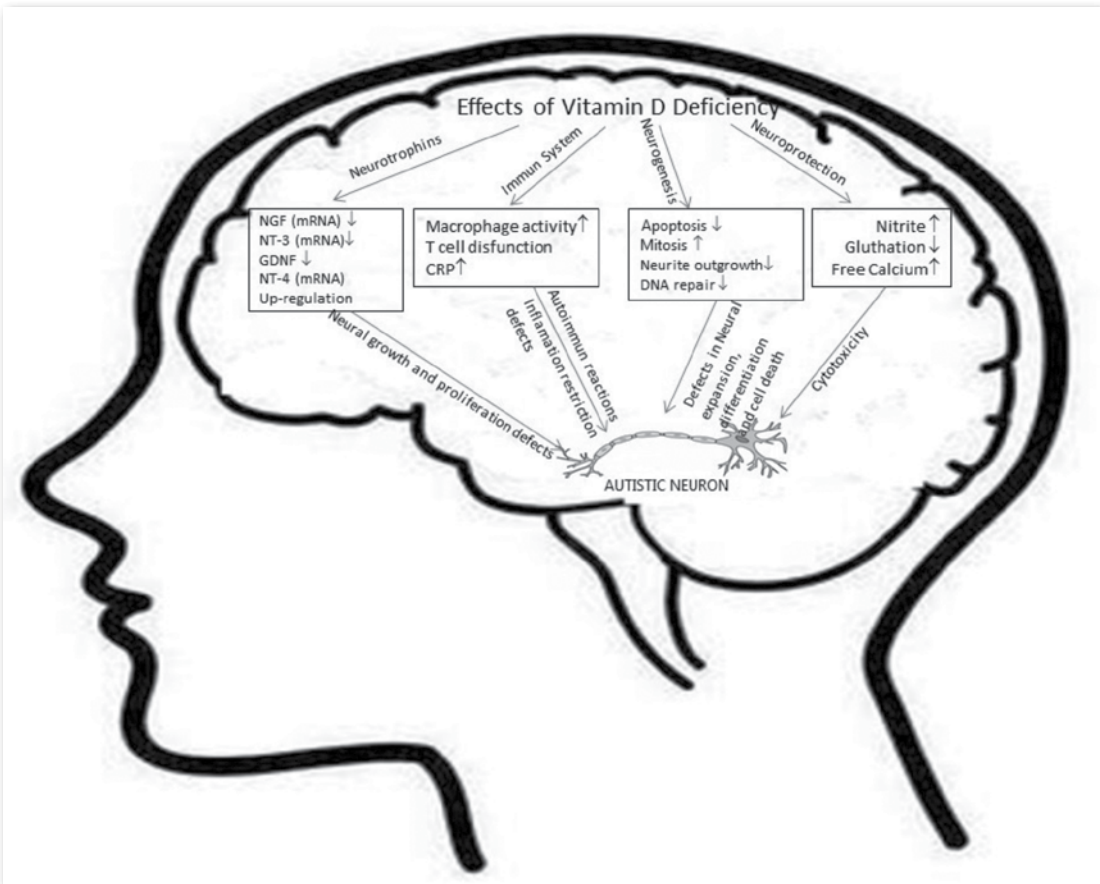

Figure 1: How vitamin D_3 deficiency might form an 'autistic' neuron

Conclusion and Future Directions

It has been shown that vitamin D_3 pathways in the brain might play a role in brain development and autism spectrum disorder pathophysiology. However, the scientific literature in this area has obtained its data based on animal studies, and current data do not seem to be sufficient to draw direct conclusions. Clinical studies need to be carried out to examine the relationship between vitamin D_3 and both brain development and autistic spectrum disorders. Focusing on oxidative stress, biological markers and neurotrophic factors in these studies might generate significant data.

There is also a growing literature regarding the effect of vitamin A (retinol) on brain development and autism. A recent study has shown that CD38 gene transcription is reduced in subjects with autism, and this situation can be ameliorated by a simple treatment with all-trans retinoic acid[70]. Considering the evidence showing the relationship between vitamin D_3 and vitamin A at a cellular level, future research should therefore concentrate on these two vitamins together when examining their effects on autism and brain development[9].

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