

Vitamin D and Serotonin's Role in Neuropsychiatric Disorders

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Abstract

Vitamin D is known to play an active role in the development of nerve cells, as well as regulating the expression of one of the important genes in serotonin metabolism, namely THP2. Vitamin D and serotonin play an important role in the development of various neuropsychiatric diseases, Autism spectrum disorder (ASD), schizophrenia, bipolar disorder, and depression. **Method:** An article review was carried out by tracing various scientific literature relating to theories regarding the relationship of vitamin D and Serotonin, as well as neuropsychiatric disorders related to metabolic disorders and the production of vitamin D and serotonin. **Results:** The biological activity of vitamin D is mediated by the vitamin D receptor (VDR). The bonding complex between VDR and VDRE in the promoter of a gene will initiate the transcription process, one of which is TPH2, which plays an active role in the synthesis of brain serotonin. Serotonin has an important role as a neurotransmitter, hormone and morphogen for the brain. This neurotransmitter have important functions in the brain in controlling appetite, energy expenditure, sleep, body temperature, mood, and social cognition. **Conclusion:** Vitamin D plays an active role in the transcription of TPH2, which plays an active role in the synthesis of brain serotonin. Vitamin D facilitate tryptophan metabolism by increasing TPH2 to synthesize serotonin. Disruption of vitamin D levels will change serotonin levels and function in the brain, resulting in impaired behavior and executive brain function.

Keyword: *Vitamin D, Serotonin, Autism, Autism Spectrum Disorder*

INTRODUCTION

Vitamin D is a neuroactive hormone that has a very varied role both in brain homeostasis, neuronal development, immunological modulation, aging, and gene regulation. Vitamin D has been known to bind to more than 2700 genes and regulate the expression of more than 200 of these genes, one of which is THP2 which plays an

important role in serotonin synthesis.(Patrick and Ames, 2015; Saad *et al.*, 2015; Anjum *et al.*, 2018; Lee *et al.*, 2019) Serotonin has an important role as a neurotransmitter, hormone, and morphogen for the brain, which has an important function in controlling appetite, energy expenditure, sleep, body temperature, mood, and social cognition.(Nordquist and Orelan, 2010; Patrick and Ames, 2015; Sabir *et al.*, 2018).

In patients with Autism Spectrum Disorder (ASD), Attention Deficit and Hyperactivity Disorder (ADHD), bipolar disease, schizophrenia, or impulsive behavior disorder, low brain serotonin levels are found. There is also an important role for vitamin D in some of these neuropsychiatric disorders. (Patrick and Ames, 2015) This literature review is carried out to examine the link between Vitamin D and serotonin in the process of neuropsychiatric abnormalities.

METHODS

The literature review was carried out by tracing various scientific literature relating to theories about the relationship of vitamin D and Serotonin, as well as tracing the latest research on neuropsychiatric disorders related to metabolic disorders and the production of vitamin D and serotonin. Then an analysis was carried out by linking various research results to get the right conclusions and outlined in a scientific text.

FINDINGS AND DISCUSSION

Vitamin D Production and Metabolism

The production of vitamin D₃ (cholecalciferol) in the skin is not an enzymatic process but is produced from 7-dehydrocholesterol (7-DHC) which is initiated by the breakdown of the B ring by UV light (on the 280-320 UVB spectrum) of the sun, then forms pre-D₃. UVB intensity and skin pigmentation contribute to the speed of this process. Melanin in the skin can inhibit UVB reaching 7-DHC thereby minimizing D₃ production, as well as clothing and sunscreen application on the skin. Vitamin D can also be obtained from food, where most foods contain vitamin D. (Christakos *et al.*, 2010, 2016; Bikle, 2014; Shi, Wang and Xu, 2017)

Vitamin D is metabolized by the enzyme cytochrome P450 mixed-function oxidases (CYPs) through 3 main steps namely 25-hydroxylation, 1 α -hydroxylation,

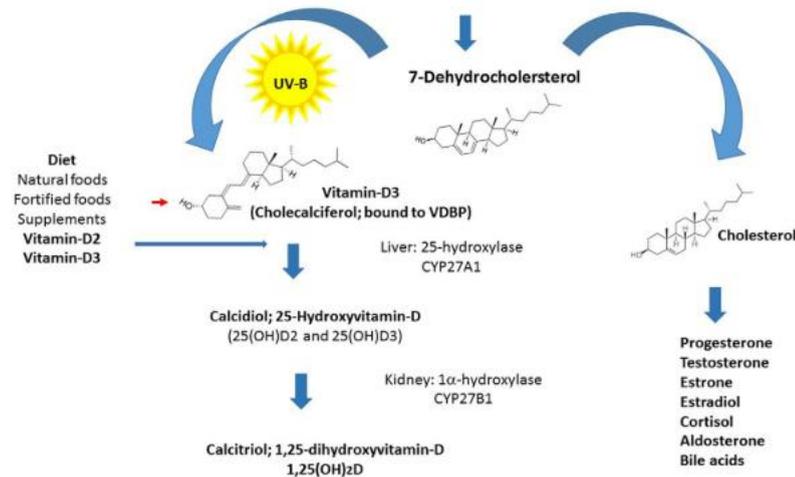
and 24-hydroxylation. These enzymes are located in cell organelles, namely the endoplasmic reticulum (RE), for example, CYP2R1 or in the mitochondria (for example CYP27A1, CYP27B1, and CYP24A1). Although CYPs are involved in vitamin D metabolism, only CYP2R1 and CYP24A1 are crystallized. CYP2R1 contains 2 extra helices that form substrate channels in the RE bilayer layer. (Christakos et al., 2010, 2016; Bikle, 2014)

The liver has been known as the main organ that produces 25OHD from vitamin D. The activity of the 25-hydroxylase enzyme is found in mitochondria and microsomal fractions of liver cells. CYP27A1 is the only mitochondrial 25-hydroxylase, which has been identified as 27-hydroxylase sterols involved in the synthesis of bile salts and does not hydrolyze D2. This enzyme is distributed in all cells of the body, not only in liver cells. Meanwhile, another CYPs, CYP2R1 are identified in the microsomal fraction of rat liver cells. This enzyme hydrolyzes D2 and D3, and acts as the main 25-hydroxylase. (Christakos et al., 2010, 2016; Bikle, 2014)

The kidney is the main organ as a source of circulating 1,25(OH)₂D₃. There is only one enzyme that has 1 α -hydroxylase activity, CYP27B1. Mutations in this enzyme coding gene are known to be a cause of pseudovitamin D deficiency conditions caused by reduced production of 1,25(OH)₂D₃. 1 α -hydroxylase in the kidneys is regulated by three hormones, namely parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and 1,25(OH)₂D₃. PTH stimulates CYP27B1, while FGF23 and 1,25(OH)₂D₃ inhibit it. An increase in circulating calcium levels will suppress CYP27B1 activity through suppression of PTH secretion, while an increase in phosphate levels will suppress the enzyme through the FGF23 stimulus. Meanwhile 1,25(OH)₂D₃ can inhibit CYP27B1 expression in the kidneys through a complex mechanism involving vitamin D receptors (VDR) and vitamin D inhibitory receptors (VDIR), thereby resulting in histone deacetylation and activation of DNA methyltransferase in CYP27B1 promoters and inhibiting transcription of the gene. (Christakos et al., 2010, 2016; Bikle, 2014)

Another enzyme involved in the main pathway of vitamin D metabolism is CYP24A1, which is the only 24-hydroxylase known to be involved in vitamin D

metabolism. This enzyme has 24-hydroxylase and 23-hydroxylase activity. The regulation of the expression of this enzyme has a reciprocal relationship with CYP27B1, especially in the kidneys. In almost all cells, CYP24A1 is induced by 1,25 (OH) 2D3 and is often used as a 1.25 (OH) 2D3 response marker in these cells. (Christakos et al., 2010, 2016; Bikle, 2014)



Picture 1. Vitamin D's Metabolism(Koc and Meier, 2017)

The biological activity of 1,25 (OH) 2D3 is mediated by its receptors namely vitamin D receptors (VDR), a nuclear receptor that belongs to a family of steroid receptors (including receptors for retinoic acid, thyroid hormones, sex hormones and adrenal steroids). In humans, the gene that codes for VDR is located on chromosome 12q13 with 9 coding exons and 8 noncoding exons. (Christakos et al., 2016; Zhang et al., 2018) Vitamin D receptors (VDR) can be found in almost all body tissues, and there are thousands of VDR-binding sites in the genome that regulate hundreds of genes. This VDR consists of three domains, namely (1) N-terminal DNA binding domain with 2 zinc fingers that bind to DNA curves in different regions (vitamin D response elements / VDREs); (2) C-terminal ligand binding domain; and (3) regions that connect the two domains together. VDR binds to its VDRE which will then recruit the co-regulator complex needed for its genomic activity. (Bikle, 2014; Christakos et al., 2016; Shi, Wang and Xu, 2017) The complex bonding between VDR and VDRE in the promoter of a gene will initiate the transcription process. (Kesby et al., 2016) Place of binding of VDR and activation of related genes VDR activity varies from one cell to another. As well as this binding site VDR can be found anywhere in the genome and

can be far from the genes that it regulates. (Bikle, 2014; Christakos et al., 2016; Shi, Wang and Xu, 2017)

In the human brain, quite a lot of VDR is found, especially in the hypothalamus region and nerve cells found in the substantia nigra. Besides, VDR is also expressed in oligodendrocytic cells, microglia, and astrocytes. Microglia cells play an important role in the central nervous system and play a role in overcoming infections in the brain, and brain development. Activation of these cells is associated with several diseases such as schizophrenia and autism. Microglia cells play an important role in the process of neuroinflammation and neurodegeneration, so that the decrease in the production of cytokines that can activate these cells by vitamin D activity, plays a role in the protection of nerve cells. (Koc and Meier, 2017; Eyles and Mcgrath, 2018)

Vitamin D's Roles

Good nutrition early in life is very important for the development of neurons. Vitamin D is a neuroactive hormone that has a very varied role both in brain homeostasis, neuronal development, immunological modulation, aging, and gene regulation. Vitamin D has been known to bind to more than 2700 genes and regulate the expression of more than 200 of these genes. In children aged 1-18 years, it is recommended that vitamin D be given in the range of 200-600 IU per day. 90% of vitamin D is synthesized in response to skin exposure to UV-B light. (Saad et al., 2015; Anjum et al., 2018; Lee et al., 2019)

Vitamin D receptors can be found in the nucleus of various brain areas that are known to regulate behavior such as the cortex, cerebellum and limbic system. These receptors also often have the same location in cells with 1α -hydroxylase I, the final enzyme of the vitamin D activation pathway. It has been known from previous studies that vitamin D acts as a neurotrophic and neuroprotector, and vitamin D is also called to function as neurosteroid. Low serum vitamin D levels are associated with low cognitive test results among Alzheimer's patients, as well as adults who perform memory tests found a positive correlation between vitamin D levels and scores with a Mini Mental State Examination examination. Research conducted by Lee et al in 2009 states that low serum vitamin D levels are significantly related to the slow

process of psychomotor, which shows the importance of vitamin D in cognitive and psychomotor processes. (Lee et al., 2009)

1,25(OH)₂D₃ functions in brain development, by regulating neurotrophic signaling pathways which are very important in the defense and migration of nerve cells, which are in the developmental stage. 1,25(OH)₂D₃ regulates two molecules in the brain, glial-derived neurotrophic factor (GDNF) and nerve growth factor (NGF), by increasing the synthesis of GDNF, and regulation of NGF signals. GDNF is important for modulating the development, defense, and function of dopamine nerve cells. While NGF is important in the growth and survival of developing neuron cells, especially cholinergic nerve cells that extend to the hippocampus (Kesby et al., 2016; Eyles and Mcgrath, 2018)

Besides being important in the development of the nervous system, there are various roles of vitamin D in the body, including:

1. Bone

Vitamin D has a direct or indirect effect on bone development and remodeling which is very important for preventing rickets in developing bone, as well as osteoporosis and bone fractures in aging bones (Lee et al., 2009; Bikle, 2014)

2. Skin

Vitamin D analogs have been widely recognized as a therapy for hyperproliferative skin diseases such as psoriasis. This relates to the ability of 1,25 (OH) ₂D₃ and its analogs to inhibit proliferation, stimulate cell differentiation, and suppress immune activity that is closely related to these diseases. (Bikle, 2014)

3. Metabolic Disease and Diabetes Mellitus

VDR is also expressed by adipocytes, and 1,25 (OH) ₂D₃ increases the process of lipogenesis and decreases lipolysis. Pancreatic B cells also express VDR and 1,25(OH)₂D₃ increase the secretion of the hormone insulin. Some studies suggest that vitamin D deficiency is related to the incidence of insulin resistance. So it is recommended for patients with pre-diabetes and diabetes mellitus to consume vitamin D to prevent complications from diabetes. (Bikle, 2014)

4. Cancer

1,25(OH)₂D₃ is known to suppress tumor development by blocking the elements involved in the cell cycle in the process of division or interfering with signals from growth factors, inducing apoptosis, stimulating repair of DNA damage, preventing angiogenesis and inhibiting metastases. (Christakos et al., 2014; Shi, Wang, and Xu, 2017)

5. Cardiovascular

VDR and CYP27B1 are expressed in the heart, both present in myocyte cells and fibroblasts. 1,25 (OH) ₂D₃ and its analogs have been known to suppress cardiac hypertrophy markers, and the deletion of VDR in heart cells can cause cardiac hypertrophy. Similarly, experiments in animals showed that in rats that did not have VDR and CYP27B1 an increase in renin production from the kidneys and heart increased angiotensin II and caused hypertension and atherosclerosis. (Bikle, 2014)

6. Immune System

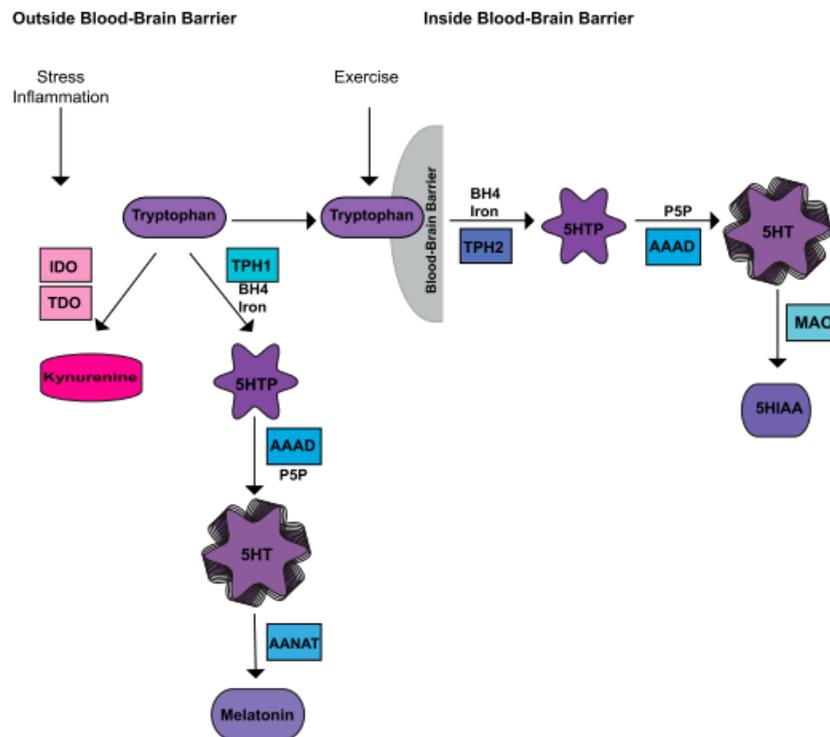
The immune system is divided into innate and adaptive immune systems. The innate immune system is activated by stimulation of Toll-like receptors (TLRs) in polymorphonuclear cells, where this activation will induce antimicrobial peptides such as cathelicidin and reactive oxygen species (ROS) that can kill infectious agents. Cathelicidin expression is induced by 1,25 (OH) ₂D₃ in myeloid cells and epithelial cells. So it can be concluded that adequate levels of vitamin D will be able to support the immune response to infectious agents. (Bikle, 2014)

As was discussed earlier that vitamin D can regulate several neurotrophic factors and influence the inflammatory response. Thus, vitamin D is thought to play a role as a neuroprotector. The protective effect of vitamin D is seen mainly in dopamine cells. Decreased levels of vitamin D are associated with decreased levels of dopamine and serotonin. (Kesby et al., 2016)

Serotonin

Serotonin has an important role as a neurotransmitter, hormone, and morphogen for the brain. This neurotransmitter is obtained from tryptophan nutritional essential amino acids, which have important functions in the brain in controlling appetite, energy expenditure, sleep, body temperature, mood, and social cognition. Serotonergic nerve cells innumerable areas in the brain, with projections to the hippocampus, amygdala, hypothalamus, nucleus accumbens, and lateral prefrontal cortex. These neurons also extend to the cortical area where serotonin can modulate behavioral actions through activation of protein-coupled and inotropic G, and ligand-gated ion channel receptors (Nordquist and Oreland, 2010; Patrick and Ames, 2015; Sabir et al., 2018)

Serotonin is known to play a role in planning and making decisions in an individual. The amino acid tryptophan is needed to meet the needs of serotonin in the body. Acute reduction of tryptophan in an individual will reduce serotonin levels, which results in changes in the ability and behavior of an individual in making decisions. Serotonin is also known to have a role in inhibiting impulses that are aggression towards themselves, including suicide and aggression towards others. A decrease in serotonin levels in normal individual results in changes of cooperative behavior and leads to antisocial behavior (Patrick and Ames, 2015) Serotonin production begins with hydroxylation of tryptophan in the central nervous system to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase type 2 (TPH2). The next step is the decarboxylation of 5-hydroxytryptophan which is accelerated by decarboxylation of aromatic amino acids to serotonin (5-hydroxytryptamine; 5-HT). Then after the serotonin packed in vesicles is released from the terminal axon, serotonin is recovered from the synaptic area through the serotonin reuptake transporter (SERT). Serotonin degradation is accelerated by monoamine oxidase-A (MAO-A) and aldehyde dehydrogenase to become a predominant metabolite of serotonin, 5-hydroxyindoleacetic acid. Serotonin concentration is controlled by the vitamin D hormonal metabolite, 1,25-dihydroxy-vitamin D3 through the induction of TPH2 gene expression (Sabir et al., 2018)



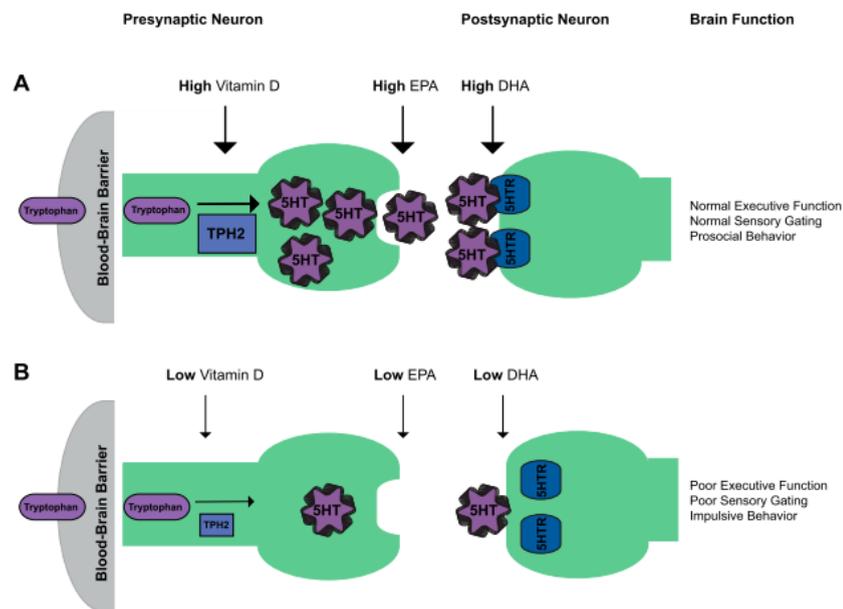
Picture 2. Metabolism pathway of Serotonin (Patrick and Ames, 2015)

Several studies have shown an association between serotonin concentration and behavioral disorders such as Attention Deficit and Hyperactive Disorder (ADHD), autism, bipolar disorder, depression, and schizophrenia as well as in obsessive-compulsive disorder and suicidal behavior. There is a hypothesis that the relationship between vitamin D insufficiency and low central serotonin concentrations is a factor affecting neuropsychiatric disorders. (Patrick and Ames, 2015; Sabir et al., 2018)

The Role of Vitamin D in Serotonin's Metabolism

Vitamin D has been known to play an active role in the transcription of various genes, one of which is regulating the transcription of TPH2, which plays an active role in the synthesis of brain serotonin. Vitamin D can facilitate tryptophan metabolism by increasing TPH2 to synthesize serotonin. Meanwhile, the presence of other micronutrients such as eicosapentaenoic acid (EPA) will increase the release of serotonin from vesicles in nerve cell presynapses. Another micronutrient, docosahexaenoic acid (DHA) increases the binding of serotonin (5HT) to its receptors (5HTR) in the post-synapse area. So that if there is interference with levels of vitamin

D, EPA, and DHA, it will change the levels of serotonin and its functions in the brain, and result in disruption of behavior and executive brain function. (Patrick and Ames, 2015)



Picture 3. The Role of Vitamin D in Serotonin's Metabolism (Patrick and Ames, 2015)

Neuro-Psychiatric Disorders related to Vitamin D and Serotonin Deficiency

Vitamin D deficiency and insufficiency are very common, especially in pregnant women, populations with dark skin, and urban areas with 4 seasons, winter. (Lee et al., 2019) Vitamin D receptors and 1 α -hydroxylase are known to occur in various areas of the brain and sensory neurons. The active form of vitamin D has an important role in the differentiation of neurons, structure, function, and connectivity in the developing brain. Vitamin D is also known as a substance that affects the synthesis of serotonin and oxytocin, both of hormones play an important role in modulating social behavior (Mazahery et al., 2016; Shi, Wang and Xu, 2017; Sabir et al., 2018)

Besides vitamin D, serotonin also plays an important role in various neuropsychiatric disorders. Several studies mention the involvement of genetic variations in regulating brain serotonin levels, such as polymorphisms in the serotonin transporter (5HTT, SLC6A4) that transport serotonin from the extracellular cavity, and enzymes that play a role in serotonin degradation, namely monoamine oxidase A (MAOA). Polymorphisms in both genes are known to be associated with

psychiatric disorders such as depression, anxiety, aggression, alcoholism, autism, suicidal behavior, and impulsive behavior (Nordquist and Oreland, 2010; Patrick and Ames, 2015)

In patients with ASD, ADHD, bipolar disease, schizophrenia, or impulsive behavior disorder, low brain serotonin levels are found. This explains the existence of impaired executive function, sensory and social behavior in these patients. The presence of polymorphisms in several genes involved in serotonin metabolism, for example, is THP2, related to the possibility of ASD, ADHD, bipolar behavior, schizophrenia, and impulsive behavior which includes aggression in oneself and others. This polymorphism is also associated with other disorders such as depression and anxiety. However, not only is the polymorphism of certain genes, but the vitamin D deficiency also plays an important role here (Patrick and Ames, 2015)

It has been known from several previous studies that vitamin D plays an important role in the etiology of Autism Spectrum Disorder (ASD). In the Australian population, 25OHD insufficiency in mid-pregnancy is known to increase the risk of ASD and language disorders. Similarly, research conducted in the Netherlands showed an increased risk of ASD in fetuses from mothers with low 25OHD levels at a younger gestational age, as well as in newborns. Vitamin D deficiency in middle pregnancy increases the risk of ASD in children about 2.4 times. (Koc and Meier, 2017; Lee et al., 2019)

Various studies have been conducted to identify the causes of impaired vitamin D function in ASD. One way is to look for specific gene variations involved in vitamin D metabolism and its risk in ASD. Genotype variations in TaqI, BsmI, and FokI VDRs are strongly suspected to be related to the risk of ASD. (Koc and Meier, 2017; Zhang et al., 2018) TaqI (rs731236) is located at exon 9, and the polymorphism of this gene causes changes in the structure of VDR. which results in impaired vitamin D binding to VDR. The existence of genetic variations in the nucleotide sequence rs1544410 intron 8 BsmI gene, can affect the stability of VDR mRNA. Meanwhile, the polymorphism at rs2228570 (FokI) which is located at the start codon exon 2, can cause the formation of two proteins of different sizes that change the site of initiation

of this gene. So there is a change in VDR expression. These various polymorphisms are known to be related to the severity of the clinical manifestation of ASD. (Zhang et al., 2018)

Vitamin D markers are 25-hydroxyvitamin D (25(OH)D) levels in serum, which are found to be quite low in the ASD population. (Saad et al., 2015; Mazahery et al., 2016; Lee et al., 2019) Low concentrations of vitamin D can cause an increase in brain size, change its shape, and enlarge the ventricles. This is often found in patients with ASD. (Jia et al., 2019) Other effects are symptoms of autism that are getting worse, and increasing behavior disorders in the ASD population. This is related to the results of previous studies, which mention that there are abnormalities in the concentration of serotonin in the brain and low levels of plasma oxytocin which is associated with low levels of vitamin D in the ASD population (Saad et al., 2015; Mazahery et al., 2016; Altun et al., 2018) The importance of the role of vitamin D in ASD is also supported by several studies, which mention the improvement of the main symptoms of ASD after getting vitamin D supplements. In addition, vitamin D deficiency can contribute to various gastrointestinal diseases, one of which is Inflammatory bowel disease (IBD), and of course this plays a role in gastrointestinal problems in the ASD population (Mazahery et al., 2016; Koc and Meier, 2017; Jia et al., 2019)

Besides ASD, other studies have shown a link between vitamin D deficiency and depression. This is based on the role of vitamin D in brain development and function. At the end of pregnancy, the presence of vitamin D deficiency in the mother is associated with a decrease in the energy level of the child as a teenager. Vitamin D deficiency also affects increasing irritability and behavior change in adult animals, which is also similar to symptoms of depression and anxiety in humans. Clinical research also shows that in patients with schizophrenia and major depressive disorders, vitamin D levels are quite low compared to the control group. In another study, it was mentioned that vitamin D deficiency is closely related to an increased incidence of depression and other mental disorders, and people with sufficient vitamin D levels have a lower risk of experiencing depression (Shi, Wang, and Xu, 2017)

Most researchers believe that the pathogenesis of depressive disorders is related to low levels of 25-hydroxy-vitamin D₃, which also includes VDR and 1-alpha-hydroxylase and other components in the mechanism of neuron differentiation, neuronal function, neurotransmitter synthesis and apoptotic inhibition, and regulation of formation of cell membrane. VDR distribution is most concentrated in the hypothalamus area which has an important role in the incidence and development of depressive symptoms. In depressed patients, there are changes in neuropeptides and levels of certain genes. However, the relationship between the hypothalamus and depression still requires further research. (Shi, Wang, and Xu, 2017)

25-hydroxy-vitamin D₃ can affect nerve growth factors, acetylcholinesterase, tryptophan, testosterone, thyroid hormone, and tyrosine hydroxylase mRNA synthesis which are closely related to depression. As is well known that neurotransmitters such as serotonin, dopamine, and norepinephrine are closely related to depression. Expression of genes involved in the transfer of vitamin D can affect nerves and stimulate the release of tyrosine hydroxylase which plays an important role in the biosynthesis of catecholamines. The study also mentions the activity of vitamin D which can improve glutathione activity in the cerebral cortex and striatum, as well as increase glutamate-cysteine ligase (GCLM) and glutathione reductase which improves glutathione synthesis, so that the anti-oxidant glutathione function can be optimized. The results of this study indicate the important role of vitamin D in preventing depression due to oxidative damage. (Shi, Wang, and Xu, 2017)

Serotonin is indispensable during brain development, as well as in the formation of behavioral attitudes, given its role in shaping mood and behavior in adult individuals. Some studies show the presence of tryptophan depletion can change serotonin levels, and result in mood disorders. Clinical manifestations of tryptophan depletion differ between men and women. In women, there is a decrease in impulsive behavior and decreased mood, while in men there is a decrease in mood and an increase in impulsive behavior. (Nordquist and Oreland, 2010)

CONCLUSION

Vitamin D plays an active role in the transcription of various genes, one of which is regulating the transcription of TPH2, which plays an active role in the synthesis of brain serotonin. Vitamin D can facilitate tryptophan metabolism by increasing TPH2 to synthesize serotonin. Disruption of vitamin D levels will change the level of serotonin and its functions in the brain, resulting in impaired behavior and executive function of the brain.

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