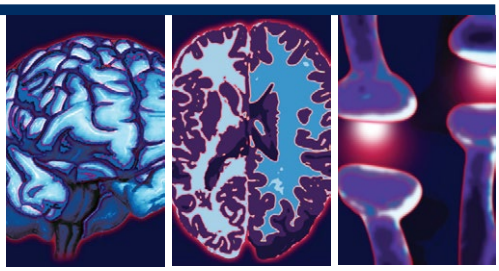
Review



Antidepressant Effect of Vitamin D: A Literature Review

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Abstract

Depression is a common chronic psychiatric disorder that often reappears in sufferers. However, the cause of depression is still not clear. It is generally considered to be a complex cause. An increasing number of studies have shown that vitamin D deficiency plays an important role in the occurrence and development of depression. In this review, the role and possible mechanisms of vitamin D as a potential antidepressant are discussed.

Keywords

Depression; Vitamin D; Vitamin D receptor; Antidepressant

Introduction

The incidence of depression was 4.4 %-20 % in the general population, which increases yearly, significantly affecting individuals, their families and society. The World Health Organization (WHO) predicts that depression will become the world's second most common disease by 2020 [1]. China has more than 26 million people with depression. Although the cause of depression is still unclear, it is generally considered to be caused by a combination of factors, including genetics, personality traits, endocrine imbalances, changes in the external environment and physical diseases.

At present, the following are the most common hypotheses explaining the etiology of depression: (1) the neurotransmitter hypothesis holds that lower levels of serotonin, and other neurotransmitters, cause depression. Clinical treatment consists of antidepressants that increase serotonin levels in the synapse to alleviate symptoms [2]. (2) The stress in the hypothalamic pituitary adrenal (HPA) axis function damage theory, states that stress stimulates the release of corticotropin releasing hormone (CRH), and promotes adrenal cortisol release, which interferes with healthy HPA axis function [3]. (3) The neurotrophic factor and nerve regeneration dysfunction hypothesis argues that depression is caused by decreased expression of brain-derived neurotrophic factor (BDNF) and neurotrophic factors, in addition to atrophy of the hippocampus and other brain areas [4-8]. (4) The nutritional etiology of depression model suggests that folic acid, vitamin D, and some essential trace elements play an important role in the pathogenesis of depression [9-13]. Findings show folic acid, vitamin B, zinc, selenium, iron and fatty acids play key roles in depression. Low folate and homocysteine, but not low vitamin B12 levels, were associated with increased depressive symptoms [12]. A growing body of evidence also suggests that vitamin D is a key factor in the pathogenesis and development of depression [14,15]. Here, we discussed the metabolism of Vitamin D and antidepressant effect of Vitamin D.

Vitamin D source and metabolism

Vitamin D is a fat-soluble vitamin essential in the body. Common forms are vitamin D2 (ergo calciferol) and vitamin D3 (cholecalciferol). The main source of vitamin D is produced when skin is exposed to the sun's ultraviolet rays (290 nm-315 nm), which is converted to 7-dehydrocholesterol into vitamin D3. Speed of synthesis depends directly amount and intensity

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of sun exposure which is affected by latitude, season, skin protection, age, and the time of day [16-18]. The second important source of vitamin D is dietary intake. Foods rich in vitamin D include deep-sea fish, animal liver and milk. In addition, special supplements like vitamin D pills also serve as a reliable source [18]. The classically described role of vitamin D is the regulation of calcium and phosphorus metabolism, and bone development; regulating calcium and phosphorus absorption, calcium metabolism and calcium reabsorption in the kidney. Recent attention has focused on the role of vitamin D in cell differentiation, oxidative stress, inflammation and immune response, influence on cognitive and emotional health [19,20]. Some studies have also found vitamin D plays an important role in treating depression [21,22].

After absorption of vitamin D, it reaches the liver via the circulatory system with the help of vitamin D binding protein (DBP). In the liver, vitamin D is transformed by 25- hydroxylase into 25-hydroxy-vitamin D_3, the major circulating metabolite of vitamin D in the body with a half-life of up to 2-3 weeks. Therefore, the serum level of 25-hydroxy-vitamin D_3 is used to evaluate vitamin D level in the body. 25-hydroxy-vitamin D_3 is transported to the kidneys and converted by 1-alpha-hydroxylase into 1, 25-(OH) $_2D_3$, the biologically active form of vitamin D. Some organs are capable of producing 1, 25-(OH) $_2D_3$ to regulate cell proliferation, differentiation or immune function [19]. 1, 25-(OH) $_2D_3$ regulates gene expression through binding to vitamin D receptors. 1, 25-(OH) $_2D_3$ combines with the membrane associated rapid response steroid binding protein (MARRS) and regulates the non-genomic effects of vitamin D [23-28]. 1, 25-(OH) $_2D_3$ is translated into 1,24,25-$(OH)_3D_3$ by 24-hydroxylase in the kidney and inactivated [29]. Vitamin D receptors and 1-alpha-hydroxylase exist in the brain, particularly the hypothalamus and dopaminergic neurons. Thus, vitamin D plays an important role in the synthesis of neurotransmitters, inflammatory reaction and calcium balance process.

■ Correlation between vitamin D and depression

Recent studies have found that depression is associated with vitamin D deficiency [30-32]. There are a number of studies that show vitamin D affects brain development and healthy function [33,34]. During late pregnancy, vitamin D deficiency in the mothers is associated with reduced energy levels when newborns reach young adulthood [35-37]. In animal experiments, vitamin D receptor knockout mice showed increased grooming, irritability, and reduced nesting and maternal behaviors compared with normal mice [38]. Vitamin D deficiency in mice also causes behavioral alterations similar to depression and anxiety in humans [39,40]. In fact, vitamin D receptor knockout mice exhibited behavioral abnormalities including anxiety and emotional stress in adulthood [41,42]. Clinical studies show vitamin D levels significantly lower in patients with schizophrenia and major depressive disorder compared with healthy controls [43,44]. Many more studies also have shown that vitamin D deficiency is associated with increased depression and other mental disorders [10,45-49]. Indeed, vitamin D deficiency is common among psychiatric patients in general [50].

Studies also show the serum levels of 25-hydroxy-vitamin D_3 in patients with mental disorders are significantly lower compared with healthy controls [36,51-58]. Clinical studies show that people with high levels of vitamin D have a lower risk of depression [53,59]. However, these findings are difficult to interpret, as reduced vitamin D could be a consequence of depressive behaviors. Vitamin D supplementation has been shown to relieve depressive symptoms in patients with low levels [60]. It is important to note that these studies evaluated the effects of vitamin D supplementation alone, not compared with antidepressants. It is reported that many of the published studies assessing vitamin D supplementation included patients who were already receiving antidepressant medication. Vitamin D is, in fact, recommended for use with antidepressant medications in effectively treating depression [61]. However, further studies are needed to elucidate the underlying biological mechanism connecting vitamin D, antidepressants and depression.

■ The mechanisms of vitamin D and depression

The exact mechanism of how vitamin D is associated with depression is unclear. Most

scholars believe low levels of 25-hydroxy-vitamin D_3 lead to a variety of mechanisms involved in the pathogenesis. These include the vitamin D receptor and 1-alpha-hydroxylase and vitamin D pathway components in neural differentiation, neuron function, neurotransmitter synthesis and inhibition of apoptosis and regulation of cell membrane formation [62,63]. In the human body, the distribution of vitamin D receptors is similar to rodents, which is mainly distributed in hypothalamus, closely related to neuroendocrine function [64]. Many researchers have found that the hypothalamus plays important roles in the occurrence and development of depression. In patients with depression, neuropeptide and gene expression levels in the hypothalamus are changes, but the relationship between hypothalamus and depression needs further study to fully describe.

Chemical research animal autoradiography and immunohistochemistry data show the glands in target tissues of 25-hydroxy-vitamin D_3 correspond with exocrine and endocrine systems and promote cell growth processes related to calcium metabolism [65,66]. In addition, 25-hydroxy-vitamin D_3 can affect nerve growth factor, acetylcholinesterase, tryptophan, testosterone, thyroid hormone and tyrosine hydroxylase messenger RNA synthesis, which are associated with depression [67,68]. The classic monoamine neurotransmitter hypothesis suggests depression is associated with 5-HT, dopamine (DA) and norepinephrine (NE). The commonly used clinical monoamine reuptake inhibitors, monoamine oxidase inhibitors and other antidepressant drugs are based on a mountain of strong research and clinical data. Studies have shown that the expression of genes involved in the transfer of vitamin D affects nerves and stimulates the release of tyrosine hydroxylase, which plays a role in catecholamine biosynthesis [69]. Clinical trials showed serum peroxide and oxidized markers in patients with depression were higher compared with control subjects [70,71]. Previous studies showed that vitamin D improved the activity of glutathione in the cerebral cortex and striatum, and also increased glutamate cysteine ligase (GCLM), glutathione reductase, which improved glutathione synthesis and played an important role in anti-oxidation [72,73]. Goudarzvand et al. found that vitamin D improved the acute oxidative damage in dentate gyrus mice [74]. Taken together, the research shows vitamin D improves depression via ameliorating antioxidant injury. Depression is a nerve immunity disorder; many diseases that modulate the immune system are associated with depression. The biological characteristics of depression are often stress induced, including activation of the immune system, cytokine release, and abnormal metabolism of neurotransmitters. Given that vitamin D plays a role in immune regulation, the link between vitamin D and depression is becoming clearer. Studies have shown vitamin D mediates immune regulation via the vitamin D receptor, inhibiting macrophage activity [75]. These studies indirectly suggest that vitamin D regulates immunity plays an indirect role in depression. Some studies have demonstrated that adult dentate gyrus subgranular zone in new neuron generation is closely related to vitamin D [76]. Successful antidepressant treatment and appropriate emotional control require neuron regeneration. Vitamin D plays a role in promoting neuronal differentiation and maturation by regulating the levels of neurotrophic factors and mitosis [77]. Importantly, vitamin D plays an important role in the differentiation of brain cells [78].

■ Prospects studying vitamin D

Although a strong association exists between vitamin D and depression, the underlying biology needs further study. Vitamin D signaling may be involved in the occurrence of depression [79]. While the understanding of the basic physiological function of vitamin D in the brain is improving, more research is needed on the complex process, especially vitamin D ligand distribution and receptor function. Studies from human MRI brain scans and animal modeling will likely advance this understanding [33]. Given that vitamin D plays a significant role in physical and mental health, accurately detecting the level of vitamin D in patients with depression is key. And supplementation may be the most convenient and low-cost treatment method to improve the quality of life. Based on the currently available literature vitamin D is a leading choice as an adjuvant drug to improve clinical efficacy in any treatment modality.

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