



Review

Vitamin D and the central nervous system

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Abstract:

Vitamin D is formed in human epithelial cells *via* photochemical synthesis and is also acquired from dietary sources. The so-called classical effect of this vitamin involves the regulation of calcium homeostasis and bone metabolism. Apart from this, non-classical effects of vitamin D have recently gained renewed attention. One important yet little known of the numerous functions of vitamin D is the regulation of nervous system development and function. The neuroprotective effect of vitamin D is associated with its influence on neurotrophin production and release, neuromediator synthesis, intracellular calcium homeostasis, and prevention of oxidative damage to nervous tissue. Clinical studies suggest that vitamin D deficiency may lead to an increased risk of disease of the central nervous system (CNS), particularly schizophrenia and multiple sclerosis. Adequate intake of vitamin D during pregnancy and the neonatal period seems to be crucial in terms of prevention of these diseases.

Key words:

vitamin D, central nervous system

Abbreviations: CNS – central nervous system, DBP – vitamin D binding protein, DVD – developmental vitamin D, GDNF – glial cell line-derived neurotrophic factor, iNOS – inducible nitric oxide synthase, MARRS receptor – membrane associated, rapid response steroid-binding receptor, NGF – nerve growth factor, SOCE – store-operated calcium entry, TH – tyrosine hydroxylase, 25(OH)D₃ – 25-hydroxyvitamin D₃

role in the development of cardiovascular disease, diabetes, and various cancers, less attention has been paid to the effects of vitamin D on the development and function of the nervous system. This paper seeks to highlight the neuroprotective and neurohormonal effects of this vitamin.

Introduction

The discovery of the systemic role of vitamin D opened a new area of research on the role of this vitamin in the modulation of physiological and pathological processes, as well as the prevention and treatment of many diseases. While a number of reports exist describing the pleiotropic effects of vitamin D and its

The physiological role and sources of vitamin D

The major role of vitamin D in the human body is commonly related to calcium metabolism and bone structure, and vitamin D deficiency is associated with the development of rickets in children and osteoporosis

sis in adults. However, scientific evidence clearly indicates that the biological importance of this vitamin greatly exceeds these aspects. Currently, there is no doubt that vitamin D is involved in a number of processes, that it constitutes an important factor in maintaining health, and that its deficiency is associated with the development of various pathological processes. Low levels of vitamin D are considered to be an important factor contributing to the development of cardiovascular diseases, metabolic syndrome and type 2 diabetes mellitus, inflammatory or immune disorders, as well as common cancers [8, 50, 64].

In humans, a natural source of vitamin D is its synthesis in the skin upon exposure to sunlight [ultraviolet B (UVB) radiation with a wavelength of 290–315 nm]. The level of exposure to sunlight determines the rate of synthesis of vitamin D in the skin. This depends on such environmental factors as geographic latitude, season, time of day, cloud coverage as well as personal characteristics, such as skin pigmentation, age, clothing, typical amount of time spent outdoors, and the use of anti-UV protection. Low exposure to sunlight is associated with a low rate of vitamin D biosynthesis. However, excessive exposure does not result in a further increase in synthesis of vitamin D due to its rapid photodegradation into a variety of biologically inactive photoproducts [29, 68]. Vitamin D is also obtained from the diet. The main dietary sources of cholecalciferol are fatty fish (such as eel, herring, salmon, mackerel), fish oil, and egg yolk, as well as margarines and other products fortified with vitamin D. The presence of vitamin D in foods other than these is limited.

A specific protein that binds vitamin D, vitamin D binding protein (DBP), transfers it through the circulatory system primarily to the liver, where the first step in the metabolic activation of vitamin D takes place. This involves the enzymatic hydroxylation of carbon 25. The resulting 25-hydroxyvitamin D (25(OH)D) is the main circulating metabolite of vitamin D, with a typical half life of 2 to 3 weeks. This is why the level of 25(OH)D is considered to be an indicator of vitamin D status in the body. Next, 25(OH)D is transported to the kidneys (and to some other tissues, e.g., the skin, and cells of the immune system), where calcitriol ($1\alpha,25\text{-(OH)}_2\text{D}_3$) is formed *via* the enzyme 1α -hydroxylase (CYP27B1). This is a biologically active form of vitamin D₃, considered a hormone. Calcitriol molecules are transported to the cells of various organs, where they influence a number of

biological processes by activating receptors for the active form of vitamin D. Moreover, some organs have the ability to produce locally the steroid hormone $1\alpha,25\text{-(OH)}_2\text{D}$, which generates cell-specific actions, e.g., proliferation, differentiation or immune regulation [57].

Action mechanism of vitamin D

An active metabolite of vitamin D, 1,25-dihydroxycholecalciferol, affects target cell function by regulating gene expression and *via* non-genomic action. In the former, an intracellular vitamin D receptor (VDR), belonging to the family of nuclear receptors, acts as a transcription factor, modifying the expression of a number of genes associated with various metabolic pathways [66]. The other, non-genomic effect of $1,25\text{-(OH)}_2\text{D}_3$ involves membrane-associated rapid response steroid-binding (MARRS) receptors for vitamin D located in plasma membrane caveolae [38, 49]. *Via* these receptors, the hormonal form of vitamin D regulates cytosolic calcium concentration by releasing calcium (Ca^{2+}) ions from intracellular stores and the influx of calcium ions through calcium channels. It also affects the activity of phospholipase C (PLC), adenylate cyclase as well as Raf and MAP kinase pathways [18, 65]. Vitamin D receptors have been found in cells of various tissues, not only those directly responsible for calcium metabolism. These include pancreas β cells, stomach cells, the ovaries, the testes, the thymus, white blood cell precursors, parathyroid tissue, and brain cells [50]. These findings indicate an important role for these receptors, and for vitamin D itself, in regulating various metabolic processes, and underscore the vitamin's pleiotropic effects.

The vitamin D receptor gene (*VDR*) is located on the long arm of chromosome 12 (12q13.1), and has several polymorphisms, for example FokI, BsmI, Tru9I, EcoRV, ApaI, TaqI, and Cdx2, which might have biological effects resulting in susceptibility to different diseases. Currently, data are available describing an association between VDR gene variants and risk of diabetes, cancer (cancer of the prostate, colon), osteoporosis, autoimmune disorders (lupus, cirrhosis, hepatitis, Crohn's disease, Graves' disease), and kidney diseases [62, 63]. Specific VDR polymor-

phisms have also been considered as possible risk factors for developing schizophrenia as well as multiple sclerosis, but this relation still awaits confirmation [26, 33, 42].

The neuroprotective effects of vitamin D

There is evidence indicating the role of vitamin D in regulating the development and function of nerve cells and the potential ramifications of vitamin D deficiency in this respect.

The involvement of vitamin D in the function of the central nervous system is supported by the presence of the enzyme 25(OH) D_3 -1 α -hydroxylase, responsible for the formation of the active form of vitamin D, as well as the presence of vitamin D receptors in the brain, mainly in the hypothalamus and dopaminergic neurons of the substantia nigra [17]. Vitamin D is believed to play a similar role to that of neurosteroids. Due to its interaction with the MARRS receptors, the hormonal form of vitamin D affects various intracellular metabolic pathways [38, 49]. Moreover, the enzyme 1 α -hydroxylase and the nuclear VDRs are also present in the microglia, i.e., non-neuronal cells of the central nervous system (CNS). This suggests both autocrine and paracrine effects for calcitriol on nerve cells [4].

The influence of the active form of vitamin D on the nervous system is associated with modifying the production and release of neurotrophic factors such as nerve growth factor (NGF), which is essential for neuron differentiation, as well as increasing the levels of glial cell line-derived neurotrophic factor (GDNF). In addition, vitamin D has been shown to significantly increase the rate of neurite outgrowth when added to hippocampal explants [4]. Moreover, 1,25-(OH) $_2D_3$ is an important factor modifying the synthesis of such neuromediators as acetylcholine *via* increased gene expression of the enzyme choline acetyltransferase (CAT) [24, 60]. Vitamin D has also been found to affect the expression of genes associated with GABA-ergic neurotransmission [22] and to stimulate the expression of tyrosine hydroxylase (TH), responsible for catecholamine biosynthesis [52, 56].

The neuroprotective role of vitamin D_3 involves the synthesis of proteins binding calcium (Ca^{2+}) ions (e.g., parvalbumin) and thus maintaining cellular calcium homeostasis, which is very important for

brain cell function [9, 20, 61]. Moreover, 1,25-(OH) $_2D_3$ administration was shown to down-regulate L-type voltage-sensitive Ca^{2+} channel expression in rat hippocampal cultures. This indicates the protective effect of the hormonal form of vitamin D on the brain *via* a reduction in the influx of calcium ions into neurons [3]. It has also been shown, based on studies on immature rats, that vitamin D modulates L-type calcium channel opening *via* nongenomic effects through various kinase pathways and enzyme activities in the cerebral cortex [70]. It is worth emphasizing that maintaining the appropriate level of calcium ions in nerve cells is especially important for their normal function. Physiologically, an increase in calcium (Ca^{2+}) ions in nerve cells contributes to an increased release of glutamic and asparaginic acids that stimulate the N-methyl-D-aspartate (NMDA) receptors to open the calcium channels, which results in nerve cell depolarization and increased influx of Ca^{2+} ions through the voltage-dependent calcium channels. Increased levels of these ions in cytosol lead to the fusion of synaptic vesicles with the presynaptic membrane and the release of transmitters. Excess calcium in nerve cells can contribute to excitotoxicity because it leads to an increased release of stimulating amino acids and other neurotransmitters, the activation of nitric oxide synthase (NOS), and the formation of reactive oxygen species (ROS), as well as the activation of proteases and lipases, leading to plasmic and mitochondrial membrane damage. A disruption in calcium ion transport and high calcium levels triggers the arachidonic acid cascade and enhances lipid peroxidation [11].

Vitamin D also stimulates the influx of Ca^{2+} ions through store-operated calcium entry (SOCE) channels, located in cells such as skeletal muscle cells or lymphocytes. This involves stromal interaction molecule (STIM) proteins that play the role of calcium level sensors in these cells and regulate the SOCE process [40, 65]. Recently published data by Gruszczyńska-Biegąła et al. [25] indicate that neurons replenish their internal calcium stores with this mechanism. It has not been established yet whether vitamin D's involvement in the regulation of these recently discovered paths of calcium influx extends to the nerve cells.

Rat neuron culture studies showed that 1,25-(OH) $_2D_3$ increases glutathione levels in these cells. The reduced form of glutathione (GSH), supplied into nerve cells by astrocytes, is a fundamental antioxidant

protecting cells against ROS and apoptosis caused by oxidation. This suggests an important neuroprotective effect for the active form of vitamin D₃, by counteracting oxidative damage to the CNS [27, 58]. In addition, vitamin D inhibits the synthesis of inducible nitric oxide synthase (iNOS). In a hypoxic environment, this enzyme becomes activated in neurons, which yields a substantial amount of nitric oxide (NO), high levels of which initiate a cascade of neurotoxicity and neuron death. This is due to the fact that NO is a precursor of peroxynitrite ONOO⁻, which in turn leads to the deactivation of a series of enzymes by reacting, for example, with sulfhydryl (-SH) groups as well as by injuring mitochondria and disturbing cellular energy processes [51, 54]. As an iNOS inhibitor, vitamin D protects the brain from peroxynitrite-mediated neuronal damage. Limiting this enzyme's activity may play a role in nerve tissue protection from such neurodegenerative conditions as Parkinson's, Alzheimer's, or Huntington's disease [61].

The results of many studies suggest an impact of vitamin D on immune system function as well as on the development of inflammation. Suppressive effects of calcitriol on interferon γ (IF- γ) or interleukin-2 (IL-2) production by stimulating the synthesis of interleukin-10 (IL-10), also known as the cytokine synthesis inhibitory factor (CSIF), have been demonstrated [1, 13, 50]. Additionally, administration of 1,25(OH)₂D₃ was shown to inhibit the production of tumor necrosis factor- α , interleukin-6, and NO in the EOC13 microglial cell line, indicating direct anti-inflammatory properties for calcitriol on microglia [41]. At the same time, depression and autoimmune diseases, including multiple sclerosis, are believed to be associated with overproduction of pro-inflammatory cytokines that disrupt normal brain cell metabolism. Thus, vitamin D, with its immunomodulating effects, may decrease the risk of these processes [20].

There has been growing interest in the potential effect of calcitriol on human glioma cells. Induction of steroidogenic genes by vitamin D was observed in human GI-1 cells [69]. In glioblastoma multiforme (GBM) cell lines (Tx3095, Tx3868, U87, U118, U373), no influence of vitamin D₃ on cell growth regulation was found indicating resistance of these cells against antiproliferative effect of calcitriol [53]. However, multidirectional action of calcitriol in glioblastoma multiforme, depending on cell environment, and possibly depending on the various molecular pro-

files involved in metabolizing vitamin D₃, was suggested [10]. Therefore, the potential role of vitamin D in human glioma therapeutical concept is still under discussion.

Vitamin D as a neurohormone

Animal studies have shown that vitamin D deficiency may increase the risk of brain dysfunction. It was reported that vitamin D deficiency significantly affects brain cell differentiation and proliferation during the neonatal period. The timing of correction of vitamin D intake and levels was found to influence persistence of some of these changes and animal behavior [for review see 16]. At this point, it is worth mentioning the studies by Harms et al. [28] conducted on rat dams fed a diet depleted in vitamin D and exposed to no UVB radiation for 6 weeks prior to conception, and then throughout the entire pregnancy. Ten weeks after birth and already receiving a diet enriched with vitamin D, the young rats underwent a series of behavioral tests that measured social behaviors, anxiety levels, behavior during a forced swimming test, and motor activity. In comparison to control animals, those deprived of vitamin D during the prenatal period were shown to exhibit a more pronounced hyperlocomotor behavior after being introduced to a new environment. The symptoms observed in these animals are consistent with animal models of schizophrenia. This is supported by a positive response to antipsychotic drugs (haloperidol) in enhanced locomotor activity induced by developmental vitamin D (DVD) depletion, as demonstrated by Kesby et al. [37]. In a similar study, conducted by Fernandes de Abreu et al. [21], the offspring of dams fed a diet deficient in vitamin D underwent an olfactory learning test. In comparison to control animals, the mice with DVD deficiency exhibited learning disability at week 30 after birth. Moreover, magnetic resonance imaging scans revealed that the cerebral lateral ventricles were reduced in size (which is, in fact, inconsistent with reports of an increased lateral ventricular volume in patients with schizophrenia). Furthermore, a significant loss in hippocampal volume in DVD-deficient mice was observed as late as at week 70 after birth. This confirms the hypothesis that the effect of vitamin D on brain function takes place mainly at the molecular,

rather than cellular, level. The authors suggest that the learning disability found in the tested animals may be a result of vitamin D deficiency altering the expression of factors involved in neurotransmission and synaptic plasticity.

In 1999, McGrath stipulated that low prenatal vitamin D (especially during the third trimester) may be a risk factor for development of schizophrenia in offspring [47]. This assumption was based on the fact that the majority of people who develop this condition were born in winter or spring, i.e., in the period when there is typically insufficient sun exposure to induce vitamin D₃ synthesis in the skin. Among those suffering from schizophrenia, a relatively large proportion is made up of people of dark complexion who have migrated to regions of high latitude, as well as people who live in great metropolises, where the duration of sun exposure and outdoor activity are limited by lifestyle [27, 47]. Studies in African Americans showed a relationship between low levels of vitamin D in mothers during the third trimester of pregnancy and an increased risk of schizophrenia in their children [46]. Similarly, a lack of vitamin D supplementation during the first year of life in Finnish boys correlated with an increased risk of developing schizophrenia [44]. However, both low and high concentrations of neonatal vitamin D in Danish studies were associated with an increased risk of schizophrenia [45].

Apart from risk of schizophrenia, there is evidence, coming from human studies, linking vitamin D deficiency to increased risk of developing major depression [35]. The US NHANES III study, conducted in 7,970 subjects aged 15 through 39, showed that the risk of depression was higher in those with low vitamin D levels [23]. Moreover, in studies by May et al. [43] involving 7,358 subjects with cardiovascular disease (coronary artery disease, myocardial infarction, congestive heart failure, stroke, atrial fibrillation, or peripheral vascular disease), low levels of vitamin D were associated with episodes of depression. In a similar study, conducted in a group of elderly subjects (65–95 years old), the severity of depression also correlated with low serum 25(OH)D levels [31].

Clinical studies indicate a possible association of vitamin D deficiency with the development of Alzheimer's and Parkinson's diseases [12, 14, 20, 61]. In addition, poor vitamin D status has been implicated in the pathogenesis of dementias [5, 19]. It has been shown that 25(OH)D insufficiency (≤ 20 ng/ml) was associated with a higher risk of all-cause dementia

(AD, stroke with dementia, and other) [5]. Recently, it has been demonstrated that vitamin D modulates progesterone protection of the brain from traumatic injury. The protective effect of progesterone was reduced in vitamin D deficient animals, and combined vitamin D and progesterone therapy, more effectively than progesterone alone, increased the extent to which spatial and reference memory were safeguarded following bilateral contusions of the medial frontal cortex [32]. These findings correspond to data reporting that vitamin D induces progesterone synthesis and progesterone-responsive gene expression in cell cultures [69]. This and other lines of evidence suggest that vitamin D treatment might be critically important for preserving neurocognitive functions among the elderly. However, this hypothesis is still under discussion and need to be confirmed by larger studies.

Moreover, a small pilot study investigating vitamin D deficiency and seizure control in epilepsy found that administration of vitamin D₃ in patients with pharmacoresistant epilepsy, and with low (< 30 ng/ml) serum 25(OH)D level, resulted in a median seizure number reduction of 40% [30]. Animal studies also support an anticonvulsant effect for vitamin D, as administration of cholecalciferol enhances the anticonvulsant effect of conventional antiepileptic drugs [2], and increased seizure severity was present in vitamin D receptor knockout mice [36].

Adequate vitamin D supply may also lower the risk of multiple sclerosis (MS). This chronic demyelinating disease of the central nervous system leads to multifocal nervous tissue damage (axonal demyelination and disintegration) that may lead to spasticity and motor weakness. Seasonal vitamin D deficiency was observed to lead to symptom exacerbation [59]. On the other hand, it was found that physical activity secondary to outdoor exercise and sunlight exposure in patients with relapsing-remitting MS was positively correlated with 25(OH)D serum levels which were higher than in inactive MS patients [67]. In addition, patients with established MS and lower vitamin D levels are at higher risk for subsequent relapse [7, 48]. The influence of high treatment doses of vitamin D on MS patients was also studied. Twelve patients in an active phase of multiple sclerosis were given progressively increasing doses of vitamin D₃: from 700 to 7,000 μ g/week (from 28,000 to 280,000 IU/week) along with 1,200 mg elemental Ca/day [39]. After 28-weeks of treatment, the number of gadolinium-enhancing lesions per patient (assessed with a nuclear

magnetic resonance brain scan) was found to decrease significantly. It has been postulated that the neuroprotective effects of vitamin D₃ and its impact on the immune system may inhibit processes that lead to CNS damage, or act indirectly by activating restorative processes [7].

Conclusion

Adequate vitamin D status may play a very important role in terms of appropriate brain development and function [15, 22]. Therefore, adequate supply of vitamin D in specific periods of life, including the prenatal period, seems to be of particular importance, because it may reduce the risk of CNS diseases whose treatment is difficult and which represent a heavy burden both for the affected individuals and their society [6]. What becomes particularly important in light of these reports is continued study of the effects of vitamin D₃ on CNS function aimed at establishing a recommendation of vitamin D dietary intake, which is a key element in averting its deficiency, and making tests determining serum 25(OH)D concentration [34, 55] generally available.

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