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**REVIEW**

# Molecular Regulation of the CNS by Vitamin D

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**Summary**

Vitamin D is a lipid-soluble vitamin that can be found in some foods. It is also produced endogenously (in the presence of ultraviolet light), transported through the blood to the targets organs and this is the reason to consider vitamin D as a hormone. It is known that vitamin D has genomic and non-genomic effects. This review is focused mainly on the vitamin D receptors, the importance of vitamin D as a neuromodulator, the role of vitamin D in the pathophysiology of devastating neurological disorders such as Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease and the benefit of vitamin D and its derivates in alleviating these disorders.

**Keywords**

Vitamin D • Neurosteroids • Brain • Neuroprotection • Neuroinflammation

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## Introduction

It has been observed that the sunlight and warm weather have always been associated with good mood and subjectively better feelings and conversely, the lack of sunshine with physical and mental decline. Without detailed knowledge of the mechanisms of action, some neurological disorders have been treated in the past with phototherapy and vitamin D, by e.g., Aretaeus as early as in the 2$^{nd}$ century AD.

It was later revealed that besides its archetypal role in bone health, vitamin D has been shown to have positive pleiotropic effects on various levels of human health [1]. Twenty years ago, vitamin D was firstly proposed as a neurosteroid [2] and since then, researches have been amazed at the complexity of molecular mechanisms interacting between vitamin D and neural cells. Developmental, anticancer, antiepileptic, neuro-protective, neuro-immunomodulating, anti-calcification, psychotropic and other observed effects demonstrate the significant role of vitamin D for the brain function and mental health. In animal studies, targeted vitamin D deficiency has led to morphological changes in the brain, in particular a larger volume of lateral ventricles and a smaller cortex thickness [3]. Despite the ever-increasing number of studies concerning the importance of vitamin D in the pathophysiology of neuropsychiatric disorders, the exact cellular mechanism of action remains still unknown. The review focuses on the current knowledge in the field of molecular processes and clinical manifestation that links vitamin D levels and neurological functions.

## Genomic and non-genomic effects of vitamin D

*Vitamin D synthesis - Location, enzymatic apparatus*

Since the discovery of photosynthesis of pre-vitamin D in human skin in the eighties [4], the major metabolic pathway leading to biologically active vitamin D has been described in detail many times, e.g. [5]. In brief, there are two sources of vitamin D: cholecalciferol (vitamin D3) produced in the cutaneous tissue of animals, and ergocalciferol (vitamin D2) synthesized in plants. In liver, they both undergo first hydroxylation at position 25 to create calcidiol (25(OH)D). Then, in the kidney, the second hydroxylation at position 1 is performed by the

action of 1alpha-hydroxylase (CYP27B1) to produce hormonally active calcitriol ($1,25(OH)_2D$). However, other tissues, including the brain are known to express CYP27B1 and other apparatus necessary for the local production of calcitriol [6]. Since both calcidiol as well as calcitriol can cross the blood-brain barrier [7], autocrine and paracrine regulation of calcitriol production from circulating calcidiol has been suggested [8]. It appears that the major calcitriol production and production in non-renal tissues may be significantly independent processes.

*Vitamin D receptors*

In terms of structural properties, vitamin D belongs to the group of steroid hormones with all the analogies that this entails. It is synthesized in endocrine tissue, from where it is transported in cooperation with binding proteins (vitamin D binding protein-VDBP or albumin) through the blood stream to target organs. The effects of vitamin D are mediated through the vitamin D receptor (VDR), which belongs to the nuclear steroid/thyroid receptor superfamily.

Vitamin D exerts biological action *via* both genomic and non-genomic actions. "Classic" genomic effects (in the order of hours to days) act through nuclear VDR, which, after the activation and formation of a heterodimeric complex with the retinoid-X-receptor (RXR), binds to promoter sequences in DNA called Vitamin D response elements (VDREs) and serves as modulator of gene transcription. It has been discovered that thousands of VDR binding sites and hundreds of genes are modulated in this way [9]. In contrast, rapid non-genomic effects of vitamin D alter numerous membrane-mediated signaling pathways involving opening of ion channels, the induction of second messengers ($Ca^{2+}$, cyclic AMP, fatty acids and phosphatidylinositol 3-phosphate) and activation of signaling molecules, such as phospholipase C (PLC) and phospholipase A2 (PLA2), phosphatidylinositol-3 kinase (PI3K) and p21 ras protein, together with protein kinases, specifically protein kinase A (PKA), tyrosine-protein kinase Src, mitogen-activated protein kinases (MAPK), protein kinase C (PKC) and $Ca^{2+}$-calmodulin kinase II (CaM kinase II) and others as discussed in detail elsewhere [10].

It remains a matter of debate which form of vitamin D receptors is involved in non-genomic actions. Nemere and colleagues identified a specific membrane binding protein for 1alpha,25-dihydroxyvitamin $D_3$ (biologically active form of vitamin D) that rapidly triggers $Ca^{2+}$ transport across the membrane [11]. This receptor was later described as a membrane-associated rapid response steroid (MARRS) binding protein and detailed structural characteristics revealed that this protein was already known from other systems and names e.g., protein disulfide isomerase, family A, member 3 (Pdia3), thioredoxin-like protein or glucose responsive protein 58 kDa (GRP58) and endoplasmic reticulum protein 57/60 kDa (ERp57 or ERp60) [10,12,13]. Intensive molecular studies on the regulation of the genomic and non-genomic effects of vitamin D show that these mechanisms are complex on many levels. The nuclear VDR is likely to be also involved in non-genomic effects, at least for some signaling pathways. It has been revealed that nuclear VDR occurs not only in the cell nucleus but also in caveolae-enriched plasma membranes and perinuclear area. Both Pdia3 and nuclear VDR bind caveolin-1, a scaffolding protein whose knocked down expression led to the loss of genomic as well as non-genomic actions of vitamin D [14].

The VDR is present in numerous brain cells such as oligodendrocytes, astrocytes, microglia, and neurons [6]. Furthermore, the extensive Genotype-Tissue Expression (GTEx) project revealed the expression of the VDR in all 11 studied regions within human brain including cerebral cortex, cerebellum, amygdala, anterior cingulate cortex, caudate (basal ganglia), hippocampus, hypothalamus, nucleus accumbens, putamen, spinal cord, and pituitary gland, with the highest abundance in the hypothalamus [15]. Receptor localization indicates responsive regions of its effector, so it is possible to deduce significant roles of vitamin D in areas where VDR is expressed.

## Vitamin D as a mediator

In the following paragraphs, factors that participate in the proper functioning of the nervous system are mentioned. They have been reported to be modulated by active vitamin D and their dysregulation may lead to the development of neuropathological conditions.

***Neurotransmitters***

*Catecholamines*

Vitamin D deficiency is often associated with altered neurotransmission, while dopamine (DA) being the most commonly reported. DA plays several regulating

roles especially as a major component of reward-motivated behavior but also in motor control, executive and arousal functions mediated *via* activation of dopaminergic receptors in substantia nigra, ventral tegmental area, and arcuate nucleus of the hypothalamus within the human brain. The importance of vitamin D on the dopaminergic system was discovered in the 1980s [16] and has been evidenced by several observations. First, the VDR expression has been detected in both rodent as well as human developing dopamine neurons [17]. Second, a study on experimental neuronal model has shown that VDR and 1,25(OH)2D3 are directly involved in regulating the expression of dopaminergic-associated genes resulting in increasing DA neuron differentiation, tyrosine hydroxylase (TH) expression (the rate-limiting enzyme in dopamine synthesis), increasing DA production and decreasing the expression of NEUROG2 a marker of immature DA neurons [18]. Vitamin D has been also shown to alter the gene expression of key factors necessary for the physiological differentiation and maturation of DA neurons such as Nurr1 or p57Kip2 [19,20]. Furthermore, maternal vitamin D treatment increased the expression of factors Lmx1a, Nurr1 and TH in individual mesencephalic DA cells, restored normal DA positioning and thus prevented the development of abnormal dopaminergic phenotypes in mouse offspring [21]. Third, the developmental vitamin D deficiency (DVD) has been shown to directly modulate metabolic pathways resulting in reduced DA biosynthesis and turnover [22].

It is of note that developmental changes in dopaminergic signalization due to vitamin D deficiency did not occur equally in all parts of the neonatal rat brain, which may produce inconsistent results [23].

*Glutamate/GABA–glutaminergic system*

Another signaling system affected by vitamin D uses the major excitatory and inhibitory neurotransmitters - glutamate and GABA (γ-aminobutyric acid) - and their common precursor glutamine. Vitamin D deficient adult mice produced a reduction in glutamate decarboxylase 65/67, the enzymes involved in GABA synthesis. In addition, immunodeficient laboratory mice reported decreased brain levels of glutamate and glutamine and elevated levels of GABA when fed by a vitamin D deficient diet [22]. Another study by the same research group confirmed that developmental deficiency of vitamin D induces decreased levels of glutamine ubiquitously across the brain supporting impairments in glutamate signaling and/or energy metabolism [23].

It is not yet known whether vitamin D directly binds and modulates N-methyl-D-aspartate (NMDA) receptors, a ligand-gated calcium channels regulated by glutamate. However, a study on neurotransmitter receptors revealed reduced expression of the NMDA receptor subunit after vitamin D administration, which contributes to the protective effect of vitamin D against neurotoxicity [24]. Vitamin D partially inhibited NMDA and kainate receptor mediated actions as demonstrated on juvenile gonadotrophin-releasing hormone (GnRH) neurons [25].

In fetal growth restriction rats (FGR) the cognitive function was effectively perfected after 30 days of vitamin D supplementation and the learning and memory ability was also significantly improved. Moreover, the mRNA and protein relative expression of NRI subunit of the NMDA receptor in hippocampus of FGR rats was significantly higher after vitamin D administration than that in the control group [26].

*Serotonin*

Neurotransmitter serotonin (5-hydroxy-tryptamine) affects numerous physiological processes in human body including sleep, learning, memory, pain, mood, social behavior, parenting and many others. Selective serotonin reuptake inhibitors are a class of drugs that are broadly used as antidepressants when treating major depressive and anxiety disorders, and other psychological conditions. The synthetic pathway of serotonin derives from the amino acid L-tryptophan and the rate-limiting enzyme of the biosynthesis is tryptophan hydroxylase (TPH) when type 1 (TPH1) is localized in peripheral “non-brain” tissues and tryptophan hydroxylase type 2 (TPH2) is neuron-specific [27]. It has been revealed that vitamin D affects serotonin metabolism by potentiating TPH2 gene expression in human as well as experimental model [28] and inhibit expression of peripheral TPH1 so that less serotonin outside and more serotonin in brain is produced [29,30]. In addition to TPH, vitamin D also alters the expression of the enzyme responsible for the serotonin breakdown - monoamine oxidase (MAO), which increases the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the key degradation metabolite of serotonergic pathway [31]. The 5-HIAA was significantly increased in brains of vitamin D deficient mice compared to controls. Also, the serotonin/5-HIAA ratio pointed to increased serotonin turnover in connection with vitamin D deficiency [22].

The impacts of vitamin D deficiency on serotoninergic system explains some pathophysiological conditions such as autism [32], sleep and mood disorders [33].

*Acetylcholine*

The cholinergic system in the brain plays a key role in modulating sensory and motor functions along with cognitive behavior through the regulation of acetylcholine receptors. Two enzymes, choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), are essential in assessing cholinergic transmission. Whereas ChAT is an enzyme responsible for the synthesis of the neurotransmitter acetylcholine, AChE is an enzyme that catalyzes the breakdown of acetylcholine and some other choline esters that function as neurotransmitters.

The importance of vitamin D in the regulation of the cholinergic system has been confirmed in several studies, especially in experimental animals with a previous disorder of cholinergic signaling. In diabetic animal models, the ChAT activity has been observed to be significantly decreased while the AChE activity has been significantly increased compared to non-diabetic control. Diabetes-induced alterations in enzyme activity were mitigated by vitamin D3 supplementation and the neuroprotective effect of vitamin D supplementation on cognitive function in diabetic animals was attributed to the enhancing prefrontal cortex cholinergic transmission [34]. In another study, a six-month vitamin D substitution reversed neuropathological processes caused by a high-fat diet in Wistar rats and supported the potential effect of vitamin D on recognition memory and cholinergic transmission [35]. Additionally, the administration of vitamin D to animals with streptozotocin-induced sporadic Alzheimer's type dementia resulted in the prevention of increased AChE activity [36]. As hypothyroidism was significantly associated with an overactivity of AChE, treatment with vitamin D alleviated the enzymes activity and recovered hypothyroidism-induced cognitive impairment and improved memory performance [37].

In addition to affecting the enzymatic activity involved in acetylcholine metabolism, vitamin D has also been shown to restore altered cholinergic receptor gene expression towards normalization in diabetic rats [38].

***Ion channels***

Calcium ion ($Ca^{2+}$) is an essential intracellular agent for communication and triggering signaling pathways. Inside the cell, the calcium ion functions as an allosteric modulator of proteins and enzymes or as a second messenger in signal transduction. In neurons, in addition to the role of an intracellular signaling mediator, calcium also plays the role of a charge carrier. Calcium signaling is involved in various physiological processes such as neurotransmitter release, apoptosis and maintenance of membrane excitability. Calcium homeostasis is crucial for proper neuronal function, and dysregulation toward elevated intracellular calcium leads to calcium-induced brain neurotoxicity [39] and can be the cause of various neurological disorders including amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and others [40].

*L-type voltage-gated calcium channels (L-VSCCs)*

One type of calcium channel reported to be modulated by active vitamin D is the L-type voltage-gated calcium channel. Evidence indicates that several mechanisms are involved in the regulation of calcium balance by vitamin D in terms of reduces $Ca^{2+}$ signaling.

Treatment with vitamin D reduces both L-VSCC activity and expression of subunits forming the L-type channel in brain neurons [41]. On the contrary, vitamin D deficient rats exhibits dysregulated calcium regulating genes expression, including a voltage dependent anion channel 1 (VDAC-1) which is the major calcium ion transport channel [42]. Calcitriol deficient mice with knockout 1α-hydroxylase showed an increase in the expression of L-type voltage-gated calcium channel [43]. Moreover, the expression of LVSCC-A1C protein was enhanced when VDR was down-regulated, again providing evidence for vitamin D's ability to regulate calcium ion channels [44].

Recent studies show that in addition to the aforementioned genomic actions vitamin D also affects calcium ion channels by means of fast actions non-genomically, without the participation of gene expression. 1,25(OH)2D is able to non-genomically modulate L-VGCC activity in a subset of neurons in the developing mouse brain [45].

*Transient receptor potential cation channel subfamily V member 1 (TRPV1)*

TRPV1, also known as capsaicin receptor or vanilloid receptor 1 plays a role in nociception and belongs to the group of ion channels with the ability to control intracellular calcium. Both 25OHD and 1,25(OH)2D can directly (but weakly) activate TRPV1

yet antagonize the stimulatory effects of the capsaicin and oleoyl dopamine. The physiological manifestation of vitamin D effects may result in TRPV1-mediated calcium entry into neurons suggesting vitamin D may temper nociceptive pain signaling pathways [46].

*Plasma membrane pumps and exchangers*

Another mechanism of action of vitamin D is an increase in the expression of the plasma membrane $Ca^{2+}$ pump (PMCA) and the sodium/$Ca^{2+}$ exchanger 1 (NCX1) *via* the activated VDR [47].

*Voltage-gated chloride channels*

To date, a handful of studies have described triggering voltage-gated chloride channel by calcidiol and calcitriol. Sertoli and kidney cells were used in these studies [48,49]. However, it remains to be clarified whether a similar mechanism also operates in human neurons.

The aforementioned findings confirm that calcium homeostasis is crucial for the proper development and functioning of the nervous system. As vitamin D interferes with calcium signaling, vitamin D deficiency may disrupt calcium signaling and may result in various neurodegenerative disorders [32].

*Calcium-binding proteins*

Vitamin D treatment may protect against neurotoxicity and calcium-mediated destruction also through the upregulation of calcium-binding proteins. In vivo study, vitamin D increased expression of calbindin-D28K and parvalbumin [50].

***Neurotrophins***

The neurotrophins and neurotrophic factors includes a family of proteins that regulate neural development, survival, function and plasticity as reviewed e.g. by Huang and Reichardt [51]. Since the early 1990s, when 1,25(OH)2D3 was first described as a possible inducer of nerve growth factor [52], it has been shown that vitamin D significantly interferes with the function of the nervous system through the modulation of diverse neurotrophins.

*Nerve growth factor (NGF)*

Nerve growth factor is well recognized as a regulatory protein facilitating cell differentiation and survival, neurite outgrowth, and apoptosis prevention in target neurons. In the aforementioned study [52], 1,25(OH)2D3 was revealed to increase the expression of NGF in murine fibroblasts, which resulted in an increased concentration of this biomolecule in the culture cells medium. Papers that were subsequently published demonstrated a similar stimulating effect of active vitamin D on the NGF expression in primary cultures of glial cells [53], astrocytes [54], Schwann cells [55], neurons [56] or even *in vivo* in animal brains [57]. Accordingly, reduced NGF production was observed in 1,25(OH)2D3 lacking mice brains [43] and the disruption of NGF production that may result in higher vulnerability to aging and neurodegeneration was observed when VDR was suppressed [44].

*Brain-derived neurotrophic factor (BDNF)*

The brain-derived neurotrophic factor is a key protein involved in neuronal growth and maintenance, a regulator of neurotransmitters and neuroplasticity related to memory and learning. Available studies have shown that vitamin D supplementation significantly raised BDNF in non-differentiated neural stem cells [58], in adult [59,60] as well as aging [61] experimental brains. Prenatal vitamin D deficiency leads to reduced BDNF [62]. In addition, a direct positive association between serum vitamin D and BDNF concentrations has recently been observed in humans [63].

However, it should be noted that the effect of vitamin D on BDNF production is not consistent across all neural cell types. Increased BDNF expression after vitamin D application could not be demonstrated, for example, in astrocyte cells [64].

*Neurotrophin 3 (NT-3) and Neurotrophin 4 (NT-4)*

Neurotrophins are protein-based agents supporting the survival and differentiation of existing neurons and stimulating neurogenesis. Both NT-3 and NT-4 can be regulated by active vitamin D. After vitamin D stimulation, increased expression of the NT-3 was observed in multiple nerve cell types and tissues [58,64,65], while NT-4 was down-regulated, at least in astrocytes [64].

*p75 neurotrophin receptor (p75NTR)*

The p75NTR receptor was first described as a nerve growth factor receptor fifty years ago [66]. It was much later that p75NTR was shown to function as a receptor for other neurotropic factors including NGF, BDNF, NT-3 and NT-4 [67,68].

In addition to regulating the expression of

neurotrophins, alone vitamin D also interferes with the expression of the receptor for neurotrophins. The active hormone raised the abundance of the mRNA the low-affinity neurotrophin receptor (the p75NTR protein) in rat oligodendrocytes [69] and on the contrary, reduced expression of p75NTR was observed in newborn rats of vitamin D-deficient mothers [3]. However, it has also been shown that such modulation by vitamin D is most likely site and cell type specific [70].

***Neurotrophic factors***

*Glial cell line-derived neurotrophic factor (GDNF)*

A relatively small protein GDNF is highly produced throughout both the central and peripheral nervous system. The main feature of GDNF is the trophic effect especially on dopaminergic and motor neurons. Meanwhile, it is also involved in the processes of survival and differentiation of neurons. Calcitriol has been observed to be a potent inducer of GDNF expression in multiple studies [58,71-73]. In another study, a significant reduction in brain content of GDNF has been also described in rats born to vitamin D-deficient mothers [3]. It should be noted that data were contradictory when taking into account studies of different parts of the brain [74] or *in vivo* studies [75], these studies did not observed a significant effect of calcitriol on GDNF.

For completeness, it would be noted that other members of the GDNF family were hardly examined at all. Vitamin D-deficiency has been shown to reduce neurturtin (NTN)-immunoreactive cells [76], while to the best of authors' knowledge, the effect of vitamin D on the proteins artemin (ART) and persephin (PSP) has not been reported so far.

*Ciliary neurotrophic factor (CNTF)*

In nervous system CNTF instigates neurotransmitter production, neurite outgrowth and is also relevant in neuronal survival. Almost nothing is known about the relationship between vitamin D and CNTF. Only a single study reported that 1,25(OH)2D3 promotes increased expression of CNTF in neural stem cells [58].

***Growth factors and related proteins regulated by 1,25-dihydroxyvitamin D3***

*Insulin-like growth factor 1 (IGF-1)*

This regulatory protein is predominantly produced in the liver with the highest production rate during puberty and the lowest in infancy and elderly. Its main function is to regulate childhood growth and anabolic effects in adults. With regard to vitamin D, the finding that 1,25(OH)2D3 and its analogue enhanced expression of IGF-1 Schwann cells is of key importance [77]. Furthermore, mRNA expression levels of IGF-1 were significantly higher when vitamin D was supplemented to aged rats compared to animals with no vitamin D supplementation [78]. Moreover, the suppression of renal catabolic enzyme vitamin D 24-hydroxylase was observed in IGF-1 treated rats [79]. The reciprocal regulation of IGF-1 and 1,25(OH)2D3 was summarized by Gómez. While 1,25(OH)2D3 has been shown to promote the action of IGF-1 by increasing IGF-1 receptors, IGF-1 increases 1,25(OH)2D3 concentrations by stimulating the hydroxylation of 25(OH)D3 to produce the active 1,25(OH)2D3 hormone [80].

*Fibroblast growth factor (FGF)*

This large family of regulatory proteins is produced in macrophages with effects extending into the nervous system. Active vitamin D significantly interferes with the regulation of fibroblast growth factor-23 (FGF-23). The supply of 1,25(OH)2D increases FGF23 levels [81], subsequently, high levels of FGF23 lead to a reduction in 1,25(OH)2D through a negative feedback mechanism [82]. Additionally, reduced expression of *Fgf-23* gene was observed in VDR-knockout mice [83].

*Klotho protein*

Klotho gene has been recognized as an aging suppressor gene that encodes a multifunctional protein participating in processes of the insulin and Wnt signaling, oxidative stress suppression, and maintaining phosphatase and calcium homeostasis [84]. Three main functions have been recognized in regard to klotho. A hormonal function, an enzymatic and a signaling function as an obligatory co-receptor for FGF23 [85]. 1,25(OH)2D3 induces klotho gene expression in kidney and the loss of klotho protein results in up-regulation of 1,25(OH)2D3 synthesis [86].

*Epidermal growth factor (EGF)*

To our knowledge, the effect of active vitamin D on epidermal growth factor (EGF) levels has not yet been reported. However, an effect on its receptor EGFR has been described. Quantification of changes in protein levels revealed, among other findings, higher expression of the EGFR was induced by vitamin D in human brain

stem cells [87]. Vitamin D regulation of EGFR is likely cell and/or tissue specific as EGFR gene was suppressed by 1,25(OH)2D3 e.g., in human ovarian cancer cells [88].

*Neuregulin (NRG)*

Neuregulins are a group of structurally similar signaling proteins related to the EGF family. They have various functions on the nervous system, especially during the development of neurons and the formation of neuromuscular synapses. Although the molecular mechanism of clinical manifestations has not yet been fully elucidated, it has been observed that vitamin D concentration positively affects NGR1 in the blood samples of schizophrenic patients [89].

*Transforming growth factor (TGF)*

It is a group of relatively small regulatory proteins with cytokine-like function. Changes induced by TGF mainly affect embryonic development, differentiation and proliferation, regulation of the endocrine and immune systems. It has been shown that 1,25(OH)2D3 diminishes the expression of proto-oncogenes and potentiates transforming growth factor (TGF-β2) expression in neuroblastoma cells [90].

***Other signaling proteins***

*Forkhead box protein P2 (Foxp2)*

This protein is crucial for proper development of language and ability to speak in humans [91]. Prenatal vitamin-D deficiency resulted in significant alteration in Foxp2 expression and reduced Foxp2 immunoreactive cells in the developing cortex in vitamin D-deficient rodent fetuses [62].

*Microtubule associated protein (MAP), growth-associated protein (GAP) and synapsin*

While the first two mentioned are involved in the proper growth, maintenance of stability and plasticity of neurons, sinapsins are responsible for the regulation on neurotransmitters from vesicles at synapses. Vitamin D3 administration resulted in increased expression of all microtubule-associated protein-2 (MAP2), growth-associated protein-43 (GAP43) and synapsin-1 in rat cortical neurons suggesting its role in differentiation and maturation processes [92,93]. The tubulin associated unit proteins (Tau) relate to the MAP family. They are mainly present in neurons, where they ensure stability of axonal microtubules. Excessively phosphorylated Tau proteins (p-Tau) are formed to neurofibrillary tangles (NFTs) which are one of the hallmarks of Alzheimer's disease. With respect to vitamin D, treatment with vitamin D or its analogue decreased hyperphosphorylation of tau protein in experimental rats [94,95].

*Amyloid beta protein (Aβ)*

Amyloid beta is a relatively small peptide of 39-43 amino acids, which is formed by cleavage of amyloid precursor protein (APP). Its normal physiological function remains unclear, but the accumulated product Aβ is deposited in amyloid plaques [96], a key pathological feature in Alzheimer's patients.

Vitamin D has been shown to be related to the amyloids in numerous studies. Importantly, even a mild vitamin D hypovitaminosis significantly increased Aβ, which was mainly caused by the regulation of the enzymatic apparatus involved in APP cleavage [97]. Other studies supported the importance of vitamin D by finding that vitamin D administration led to a reduction in Aβ-related biomarkers and induce the clearance in animal models [94,98] as well as Alzheimer's patients [99].

*Alpha-synuclein (α-Syn)*

This neuronal protein is responsible for proper synaptic function and neurotransmitter release. Under pathological condition α-Syn may change conformation to form insoluble aggregates or filaments. Synucleinopathies are manifested in various neurodegenerative diseases, mainly Parkinson's disease but also an α-Syn fragment, known as the non-amyloid beta component (NAC) in Alzheimer's disease.

With regard to alpha synuclein, the neuroprotective significance of vitamin D and its analogues is based in the inhibition of the early α-Syn aggregation [100,101].

*Nuclear receptor related 1 protein (NURR1)*

In humans, NURR1 is critical for DA system in the brain and its disruption results in disorders related to DA dysfunction, including Parkinson's disease, schizophrenia, autism, and manic depression.

Prenatal vitamin D deficiency resulted in reduced Nurr1 expression in developing rat brains [20] and conversely, vitamin D treatment increased the expression of Nurr1 (and TH) in individual mesencephalic DA cells and restored normal positioning [21].

*Neural cadherin (N-cadherin, caherin-2)*

Neural cadherin, like other cadherins, ensures

cell to cell adhesion. In addition, it also ensures interactions between interconnected cells *via* its extracellular domain. In neurons, loss of protein function causes dysregulation of synaptic communication, differentiation DA neurons which clinically manifest which is clinically manifested by learning and memory impairment or hyperactivity.

Whereas developmental vitamin D deficiency decreased N-cadherin expression [75], vitamin D treatment upregulated N-cadherin [102].

***Neuroinflammation markers***

Neuroinflammation is a key process for neurodegeneration and associated neuronal loss which manifest as numerous neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and others. Activated microglia produce diverse pro-inflammatory factors including cytokines and neurotoxic agents.

In numerous reported studies, vitamin D suppresses inflammatory processes by down-regulation of pro-inflammatory interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 1β (IL-1β), interleukin 6 (IL-6), interleukin 17A (IL-17A) and inducible nitric oxide synthase (iNOS) as well as up-regulation of anti-inflammatory interleukin 4 (IL-4), interleukin 10 (IL-10) and interleukin 34 (IL-34) [103-107].

***Markers of oxidative stress***

Oxidative stress is considered an imbalance between arising reactive oxygen species (ROS) and antioxidant capacity of the cell to remove these harmful substances. Oxidative stress causes serious cell damage at the DNA level and accompanies many neurodegenerative and cancer diseases.

Vitamin D protects against oxidative stress by activating the antioxidant enzymes, the superoxide dismutase (SOD) and catalase (CAT) [59,108]. In addition, vitamin D elevates thiol content and decreased nitrite and malondialdehyde (MDA) concentration [59]. Calcitriol also induces upregulation of glutathione (GSH) production, which also contributes to the antioxidant effect of vitamin D rat astrocytes [109].

## Vitamin D deficiency in developing vs. adult brain

As it implied the above, vitamin D deficiency may result in the development of various neurodegenerative diseases. However, the effect depends on the level of maturation of the nervous system.

*Vitamin D deficiency in developing brain*

A number of comprehensive reviews have been published summarizing the effect of vitamin D deficiency on the developing brain. Based on animal models, altered neuronal differentiation, neuroinflammation, neurodegeneration, protein expression and metabolic changes leading to brain structural changes should be mentioned among the main mechanisms [110].

*Vitamin D deficiency in adult brain*

It is supposed that vitamin D deficiency in adulthood does not impact on cell proliferation, differentiation or neuronal apoptosis, but factors such as increased oxidative stress, reduced neuroprotection and disbalance in neurotrophic factors result in disrupted cognition and higher vulnerability to adverse brain conditions [111].

## Clinical outcomes of vitamin D deficiency

Many neuropathological disorders share similar pathophysiological mechanisms, e.g., increased inflammation, oxidative stress, neurodegeneration, mitochondrial dysregulation, and apoptosis. These unfavorable conditions also include a vitamin D deficiency as a risk factor for the development of the disease. Such disorders include multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

In the Table 1, we would like to outline the neuropathologies in which vitamin D deficiency has been observed as a significant risk factor. A number of these diseases have already been described in detail, including the role of vitamin D in the disease. For this reason, we do not explain the background and exact mechanism of the disease development in our review. The table merely summaries a brief overview (in alphabetical order) with references to relevant and up-to-date sources where possible.

***Pharmacological application of vitamin D in neurodegenerative diseases***

Considering the pluripotent character of the effects, the use of vitamin D and its artificial analogues are considered to be useful a tool in the treatment of

**Table 1.** Neuropathologies related to vitamin D deficiency.

| Pathology | Involved element | Adverse condition | Reference |
|---|---|---|---|
| *ADHD* | BDNF, DA, serotonin | Neuroinflammation, oxidative stress | [116] |
| *ALS* | IGF-1, GDNF, SOD-1, $Ca^{2+}$ homeostasis | Excitotoxicity, oxidative stress | [117] |
| *ASD* | $Ca^{2+}$ homeostasis, DA, serotonin, GABA/glutamate | Neuroinflammation, mitochondrial dysfunction, oxidative stress | [32] |
| *AD* | p-Tau, Aβ, NGF, BDNF, GDNF, TGF-β, IGF-1, IL-1, IL-6, TNF-α | Neuroinflammation, cholinergic deficits, synaptic loss, and oxidative stress | [118] |
| *Cancer* | Cyclin-dependent kinases, TNF-α, $Ca^{2+}$ homeostasis, p75NTR, NGF, NT-3, GDNF | Oxidative stress, Dysregulated proliferation, apoptosis, migration | [119] |
| *Epilepsy* | GABA/glutamate, NMDA, L-VSCC, $Ca^{2+}$ homeostasis, TGF-β, NO, IL-1β, IL-6, IL-8, TNF-α, IFN-γ | Neuroinflammation, oxidative stress | [118] |
| *(Generalized) anxiety disorder* | GABA/glutamate, serotonin, DA, GSH | Neuroinflammation, oxidative stress | [120] |
| *Huntington's disease* | GABA, BDNF, NGF, CAT | Neuroinflammation, mitochondrial dysfunction, oxidative stress | [121] |
| *Depression* | $Ca^{2+}$ homeostasis, PMCA, L-VSCC, GABA/glutamate, serotonin, DA, TNF-α, IL-1α, IL-1β, IL-6, GSH | Excitotoxicity, neuroinflammation, oxidative stress | [122] |
| *MS* | IFN-γ, IL-1β, IL-2, IL-6, IL-12, TNF-α, NO | Neuroinflammation, oxidative stress, neuronal demyelination | [118] |
| *Neurocognitive decline (mild)* | L-VSCC, NGF, GDNF, NO | Neuroinflammation, oxidative stress | [123] |
| *Neuromyelitis Optica* | IFN-γ, Ig, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17 | Neuroinflammation | [124] |
| *Pain* | TRPV, VDR, NGF, EGFR, GDNF | Cellular signal transduction, activity and survival of proprioceptive neurons | [114] |
| *PD* | L-VSCC, GDNF, NGF, DA, TH, MANF, CDNF, α-synuclein, NO, IL-1β, IL-17, TNF-α, IFN-γ | Neuroinflammation, mitochondrial dysfunction, oxidative stress, excitotoxicity, neurodegeneration of DA neurons | [118] |
| *Seasonal affective disorder* | Serotonin, melatonin, DA | Impaired neurotransmission | [125] |
| *Schizophrenia* | DA, GABA/glutamate, acetylcholine, N-cadherin, NRG1, NF-κB, IL-1β | Impaired neurotransmission, neuroinflammation | [126] |
| *Sleep deprivation and RLS* | Melatonin, serotonin, DA, GABA, N-cadherin | Impaired neurotransmission | [127] |
| *Stress* | Cortisol, melatonin, NE, IL-1β, IL-6, TNF-α, IFN-γ | Neuroinflammation | [128] |
| *Cerebrovascular Diseases* | $Ca^{2+}$ homeostasis, NO, SOD acetylcholine, IL-1, IL-2, IL-6, IL-23, TNF-α, IFN-γ, NF-κB, cadherin | Oxidative stress, neuroinflammation, cholinergic dysfunction | [129] |

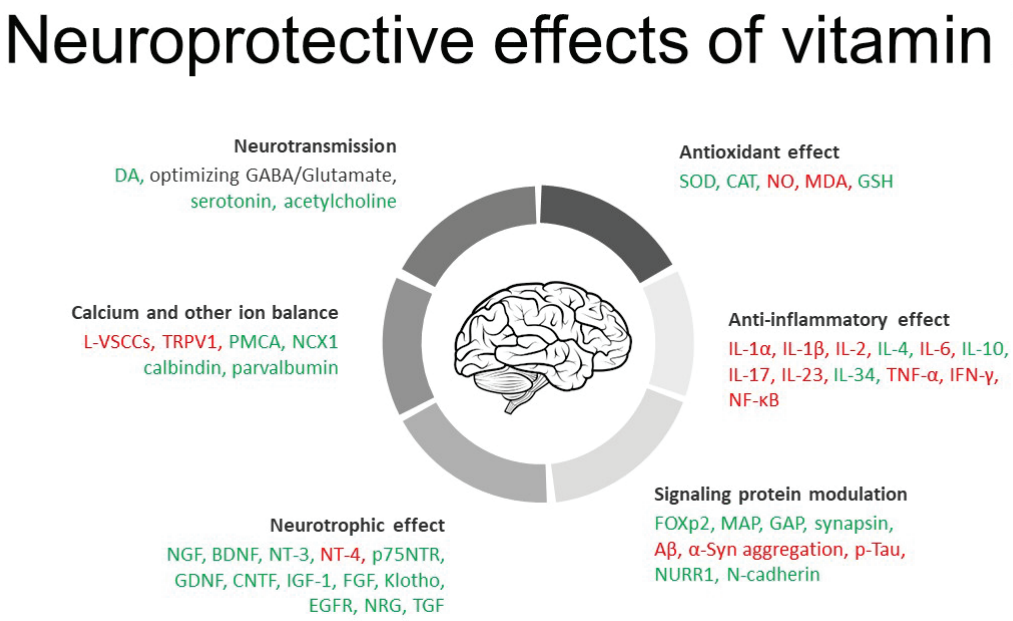


**Fig. 1.** Schematic review of neuroprotective effects of vitamin D. Factors that are up-regulated are marked in green, factors that are down-regulated are in red.

neurodegenerative diseases. One of the prerequisites for effective treatment is determining the optimal dose for the treatment of neurodegenerative disease while simultaneously avoiding hypervitaminosis (and hypercalcemia) due to overdosing. For that reason, vitamin D analogs capable of activating VDR with reduced calcemic effects seem to be advantageous. Vitamin D and its analogs are being considered for therapy in Alzheimer's disease [112], multiple sclerosis [113], chronic pain [114], ADHD [115] and others, but more research is needed to establish effective and safe dosing.

## Concluding remarks

Substantial clinical data reveal that vitamin D may play an important role in the course and amelioration of a number of neuropsychiatric disorders including MS, PD, AD, schizophrenia and more. In the nervous system, 1,25(OH)2D3 reduces oxidative stress and inflammation, induces neuroprotection, and up-regulates a wide variety of neurotrophins and neuro-regulative proteins.

The authors have not aimed to provide a complete review, especially since the topic about the wide role of vitamin D is still developing and on the other hand, some areas of research (vitamin D receptors) have already been extensively covered. The goal of the authors has been to focus on the pathways in which vitamin D can interfere with pathophysiological processes in the nervous system. Some study results reported conflicting data. This may be due to the fact that the regulation by vitamin D is local and tissue specific in many cases. Furthermore, it is shown that both the "classical" genomic way of action with involvement of gene expression and the fast non-genomic pathway work hand in hand, probably synergistically. At the same time, relevant experimental *in vitro* model to study neuropsychiatric condition is yet to be discovered.

## Abbreviations

α-Syn, alpha-synuclein; Aβ, amyloid-β peptide; BDNF, brain-derived neurotrophic factor; CAT, catalase; CDNF, cerebral dopamine neurotrophic factor; CNTF, ciliary neurotrophic factor; DA, dopamine; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; FOXp2, forkhead box protein P2; GABA, γ-aminobutyric acid; GAP, growth-associated protein; GDNF, glial cell line-derived neurotrophic factor; GSH, glutathione; Ig, immunoglobulins; IFN-γ, interferon gamma; IGF-1, Insulin-like growth factor 1; IL, interleukins; L-VSCC, L-type voltage-gated calcium channels; MANF, mesencephalic astrocyte-derived neurotrophic factor; MAP, microtubule associated protein; MDA, malondialdehyde; NE, norepinephrine; NCX1, sodium/calcium exchanger 1; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NRG, neuregulin; NT-3, neurotrophin 3; NT-4, neurotrophin 4; NURR1, nuclear

receptor related 1 protein; PMCA, plasma membrane calcium pump; p-Tau, phosphorylated tubulin associated unit proteins; p75NTR, p75 neurotrophin receptor; SOD, superoxide dismutase; TGF, transforming growth factor; TNF-α, tumor necrosis factor α; TRPV1 transient receptor potential cation channel subfamily V member 1; VDR, vitamin D receptor.

## Conflict of Interest

There is no conflict of interest.

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