Vitamin D and the Pathophysiology of Parkinson's Disease

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Abstract

The relationship between vitamin D and Parkinson's disease (PD) is a complex and evolving area of research. While not definitively established as a causative factor, accumulating evidence suggests a potential association between vitamin D deficiency and increased risk, severity, or progression of PD. This relationship likely operates through multiple interconnected pathways, highlighting the need for further investigation. Several studies have reported an inverse correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and the risk of developing PD. Lower 25(OH)D levels have been associated with an increased incidence of PD, suggesting a protective role for adequate vitamin D status. This association might be explained by vitamin D's pleiotropic effects, impacting various systems implicated in PD pathogenesis. One proposed mechanism involves vitamin D's influence on neuroinflammation. Vitamin D receptors are widely distributed in the brain, including regions vulnerable in PD, such as the substantia nigra. Vitamin D modulates the immune response, potentially reducing neuroinflammation, a key contributor to dopaminergic neuronal loss in PD. Furthermore, vitamin D may exert neuroprotective effects by influencing oxidative stress, mitochondrial function, and apoptosis, all processes implicated in the neurodegenerative cascade of PD. Its role in calcium homeostasis, crucial for neuronal function, is another potential avenue for its impact. However, the evidence is not without limitations. Observational studies demonstrating associations do not establish causality. Confounding factors, such as age, lifestyle, and other dietary deficiencies, may influence both vitamin D levels and PD risk. Furthermore, the optimal level of vitamin D for PD prevention or management remains unclear. While some studies suggest that supplementing vitamin D may improve motor symptoms or slow disease progression, the results are inconsistent, and more rigorous, large-scale, randomized controlled trials are needed to confirm these findings and clarify the appropriate dosage and duration of supplementation. In conclusion, while the precise role of vitamin D in PD remains to be fully elucidated, compelling evidence points towards a potential link between vitamin D deficiency and PD risk or severity. Further research, particularly well-designed clinical trials, is essential to determine the clinical significance of vitamin D supplementation in PD management and to unravel the complex mechanisms underlying this association.

Keywords: Vitamin D, Parkinson's Disease

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Introduction

Vitamin D is a fat-soluble secosteroid, traditionally considered a key regulator of bone metabolism, calcium and phosphorous homeostasis, supplied with the diet or produced by skin exposure to ultraviolet light [1, 2]. Vitamin D can also be synthesized by humans in skin, during sunlight exposure, by the effect of ultraviolet B (UVB) realizing the conversion from the steroid precursor, 7-dehydrocholesterol in activated vitamin D3 [1, 2].

Two forms of vitamin D exist, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Its action is made possible through the binding to the vitamin D receptor (VDR), after which it directly and indirectly modulates the expression of thousands of genes. Vitamin D is important for brain development, mature brain activity and associated with many neurological diseases, including Parkinson's disease [3].

Vitamin D Sources

Vitamin D intake is a poor predictor of serum 25OHD concentrations in subjects with an intake between 2 and 20 μ g/day [4]. It is difficult to obtain adequate vitamin D from a natural diet. Vitamin D can be obtained from some dietary sources. Two forms of dietary vitamin D exist in nature: vitamin D3 (25-OH-D3) or cholecalciferol which derives from the consumption of some foods of animal origin (oily or bluefish, egg yolk, and meat are particularly rich in vitamin D3) and vitamin D2 (25-OH-D2) or ergocalciferol, which is mainly contained in nuts (almonds, walnuts), mushrooms, beans, and green leafy vegetables. Similar to cholecalciferol, ergocalciferol must be hydroxylated at positions 25 and 1α to become maximally active [4].

Vitamin D levels

Blood 25-(OH)D concentration of 75 nmol/L (30 ng/mL) is needed for optimal bone mineral density in younger and middle-aged adults [5]. Deficiency of vitamin D in serum is very common with an approximately 32% of the healthy population in the United States. It has been associated with various health disorders such as cardiovascular diseases, cancer, bone health, neuropsycologic, infectious and reproductive disorders [6]. Increasing evidence suggests that high levels of 25-(OH)D serum concentration may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease and infectious disease [7].

Vitamin D receptors

The vitamin D receptor (VDR) is present in several types of tissue including intestine, immune cells, and parathyroid hormone, but it is not expressed in skeleton tissue [8]. In the CNS, vitamin D can activate different pathways, genomic and non-genomic [9, 10]. Indeed, in the CNS there are two different types of vitamin D receptors: a nuclear receptor (VDR) and a membrane-associated rapid response steroid binding receptor (MARRS). VDR is a member of the nuclear receptor family of transcription factors, a steroid/thyroid hormone superfamily of transcription regulation factors that, when complexed with calcitriol, binds vitamin D to specific genomic sequences, inducing gene transcription (genomic pathway) [11]. Vitamin D also binds a membranous receptor, the surface receptor MARRS, with different effects in calcium and phosphates homeostasis, molecular chaperoning, immunomodulation and activation of the protein kinase C pathway, cAMP pathway, as well as the MAP kinase pathway (non-genomic pathway). However, the 1,25D3-MARRS receptor has also been found to have genomic effects, binding DNA and regulating gene transcription [12].

Vit. D and nervous system

Vitamin D metabolites could pass through the blood–brain barrier and the presence of 1,25(OH)2D3 in the cerebrospinal fluid (CSF) suggests the existence of a catabolic pathway in the CNS [13]. Not only is 1α-hydroxylase expressed in the brain (especially cerebellum, cerebral cortex and substantia nigra) but it was also observed that different neuronal populations could inactivate 1,25OH2D3 to 25OHD3 [14]. Vitamin D could also regulate the differentiation and proliferation of neurons and microglia, and dopamine signaling transduction [15]. The effects of vitamin D, including regulating synaptic plasticity and molecular transport in cell organelles, and maintaining the cytoskeleton, are sufficiently proved, which implies the important roles of vitamin D in brain development and synaptic plasticity [16].

Vitamin D assists in anti-oxidation by up-regulating the expression of glutathione and superoxide dismutase and down-regulating the expression of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) [17]. Moreover, vitamin D enhances neuronal survival by regulation of neurotrophins, including neural growth factor (NGF), glial-line derived neurotrophic factors (GDNF), and brain-derived neurotrophic factors (BDNF) [18]. The synthesis of neurotransmitters, including acetylcholine (ACh), dopamine (DA), serotonin (5-HT), and gamma-aminobutyric acid (GABA) is also under the control of vitamin D [19]. Vitamin D could protect neurons by altering glutamate levels and reducing excitotoxicity caused by long-term increases in extracellular glutamate levels and hyperactivation of the N-methyl-d-aspartate receptor (NMDAR) [20].

There was very little knowledge about how vitamin D could exert its genomic effects in brain cells and a complete absence of any understanding about whether, like other neurosteroids, vitamin D would also have more rapid non-genomic actions. Over the last two decades, research on neurons, non-neuronal brain cells, in both human and animal brains, has confirmed not only does the brain possess the molecular machinery for vitamin D's actions, but also that VDRs are functional, that liganded VDRs directly regulate the expression of target genes and that vitamin D in the form of 1,25-hydroxyvitamin D3, 1,25(OH)2D3 can rapidly alter ion channel function [21]. Moreover, new epigenetic mechanisms have been revealed as gene regulatory pathways that vitamin D targets to affect gene expression in the developing brain [22].

As a result of all this research, vitamin D can now be considered an important steroid in brain development [23]. There was a strong focus on vitamin D and neurotrophic factors important for dopaminergic neurons, such as glial cell line-derived neurotrophic factor (GDNF) [24] and now brain-derived neurotrophic factor (BDNF) [25]. 1,25(OH)2D3 increases, and the developmental dietary absence of vitamin D reduces the expression of these crucial neurotrophic factors in neurons and glia in developing and adult brains. Vitamin D's regulation of neurotrophic factors remains a central feature in brain ontogeny [26].

Neuroprotective actions of vitamin D in the brain.

The effects of vitamin D on the nervous system have been receiving increasing attention. Many vitamin D-related enzymes and vitamin D receptors (VDRs) are widely present in the brain, and the metabolites of vitamin D could interact with neuronal and glial cells to exert various effects [27]. Multiple mechanisms have been proposed for the role of vitamin D in neurodegenerative diseases. Vitamin D may confer neuroprotection through the action of neurotrophic factors, regulation of nerve growth or through protection against cytotoxicity [28]. In several studies, the synthesis of neurotrophic factors, including neurotrophin 3 (NT3) and glial cell line-derived neurotrophic factor (GDF), were upregulated by 1,25(OH)2D3 [29]. [30, 31] showed that vitamin D induced stimulation of neurotrophins was correlated with a neuroprotective effect in rat models. Through the VDR, vitamin D can upregulate nerve growth factor (NGF) [32], and in a rat model of peripheral nerve injury, rats exposed to vitamin D2 demonstrated significantly increased axogenesis and axon diameters [33]. Vitamin D may also modulate the toxicity of reactive oxygen species. Nitric oxide is produced by inducible nitric oxide synthase (iNOS), an enzyme that is induced in CNS neurons and non-neuronal cells as part of an immune response [34]. At high levels, nitric oxide can damage neurons, and vitamin D has been shown to inhibit the synthesis of iNOS, thereby reducing levels of nitric oxide [35].

In hippocampal neurons, the presence of vitamin D was associated with downregulation of the L-type voltage-sensitive Ca2+ channel and was correlated with a neuroprotective effect at physiologic doses [36]. Also, vitamin D may exert a neuroprotective effect through reducing oxidative stress. In a study in which dopaminergic and non-dopaminergic neurons were exposed to glutamate, pretreatment with vitamin D protected both cell types against cytotoxicity in a dose-dependent manner [37]. Apart from augmenting the presence of the GDNF gene and activating the mechanisms, neuroprotection is also offered by 1,25-dihydroxyvitamin D3 by exerting anti-oxidant effects since GDNF has the capacity to scavenge free radicals via augmentation of catalase and glutathione peroxidase enzymes in the striatum nigra [38].

The Relationship between Vitamin D and Cognitive Function:

Vitamin D can exert its effect on neurocognition through a number of mechanisms such as induction of neuroprotection, modulation of oxidative stress, regulation of calcium homeostasis, and inhibition of inflammatory processes [10]. The distribution of VDR in humans is strikingly similar to that observed in rodents. Its presence in the hippocampus, cerebral cortex, and limbic system of humans and rodents reinforces the role of vitamin D in regulating learning and memory; however, VDR is also localized in the olfactory, visual, and auditory systems, so it may also play a role in somatosensory functions, which could contribute to better cognitive task performances [39]. Moreover, neuroprotective effects of cholecalciferol have been shown in young rats [40].

Analyzing the development of the whole brain, they described an increase in the volume of lateral ventricles accompanied by a decrease in the hippocampal volume [40]. This finding has not been confirmed in adult mice nor in rats [41, 42], but it has been described in patients with mild cognitive impairment [42]. In another study, vitamin D deficiency has also been associated with a 28% increase in lateral ventricles in aged humans [43]. Vitamin D deficiency has been linked with the dysregulation of dopamine and serotonin neurotransmission. In developing brains, the VDR appears exactly when the dopaminergic system starts to develop [44, 45]. VD3 showed neuroprotective actions on brain mitochondria injured by toxins and should stimulate translational studies focusing on its use as a therapeutic strategy for the treatment of neurodegenerative diseases such as PD [46].

Vitamin D and the Pathophysiology of Parkinson's Disease

The presence of a high concentration of VDR and 1-α-hydroxylase in the substantia nigra (SN) provides evidence of a possible relationship between PD and vitamin D [47]. There is evidence that vitamin D is implicated in dopaminergic neurotransmission and cellular events such as neurogenesis and neurite development [48]. Vitamin D has been shown to increase the expression of the tyrosine hydroxylase enzyme in the chromaffin cells of the adrenal medulla, which display vitamin D receptors on the surface, increasing production of catecholamines [49]; furthermore, vitamin D seems to have a role both in the synthesis of dopamine in the CNS and in its storage [50]. It was also found that vitamin D attenuates neurotoxicity induced by 6-hydroxydopamine (a toxic compound) in rats, protecting against dopamine depletion in SNpc, and vitamin D may upregulate the expression of the glial cell line-derived neurotrophic factor (GDNF), specifically in the striatum, suggesting its protective role in PD [51]. Moreover, vitamin D may display an important role in counteracting oxidative stress in the brain, since it reduces reactive oxygen species by different mechanisms, including PARP1 inhibition [52].

Another study has reinforced the neuroprotective role of vitamin D, which seems able to inhibit aggregation of α-synuclein, through the expression of calbindin-D28k, a calcium-binding protein [53]. Another report showed that VDR-knockout mice have a behavioral phenotype similar to human PD, exhibiting muscular and motor impairments, albeit with no detrimental effect on cognitive function [54]. Few studies have assessed the relationship between vitamin D status and non-motor symptoms, such as cognition, depression, anxiety, insomnia, and orthostatic hypotension. According to several investigations, vitamin D levels influence cognitive function; however, to date, the impact of vitamin D on cognition in PD has been poorly explored [55, 56]. In mice, a low postnatal vitamin D status compromises processes such as learning and hippocampal-dependent memory, suggesting that an adequate vitamin D intake is essential for efficient hippocampal function [57]. The role of vitamin D in Parkinson's disease has been widely studied. Lower 25(OH)D levels might be responsible for dopaminergic neuronal death contributing to PD development, due to the lack of its protective function [49].

However, many mechanisms have been correlated with a neuroprotective effect against excitotoxic insults; 1,25(OH)2D3 stimulates the release of neurotrophin and the synthesis of Ca2+-binding proteins such as parvalbumin, it inhibits the synthesis of inducible nitric oxide synthase (iNOS), macrophage colony-stimulating factor (M-CSF) and tumor necrosis factor α (TNF-α), and it induces downregulation of the L-type voltage-sensitive Ca2+ channel (LVSCC) and upregulation of γ-glutamyl transpeptidase activity [50, 58]. Additionally, a lower concentration of vitamin D correlates with high levels of C-reactive protein (CRP), a marker of inflammation [54]. Overall, the vitamin D role appears fundamental in the prevention of brain aging, considering also its function in the production of growth factors, including nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), glial cell-derived neurotrophic factor (GDNF), glial cell-line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT3) [59, 60].

Vitamin D contributes to intraneuronal calcium (Ca2+) homeostasis and cytosolic Ca2+ glial concentration, acting on the regulation of the L-type voltage-sensitive Ca2+ channel (LVSCC), modifying neuronal function and upregulating the synthesis of parvalbumin and calbindin [3]. Vitamin D also has antioxidant effects, reducing the formation of free radicals and production of reactive oxygen species (ROS), due to the capacity to reduce the synthesis of nitric oxide synthase, reducing activity of NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), and enhancing the activity of the gamma-glutamyl transpeptidase [55].

However, for many authors, there is not sufficient evidence to confirm a function of vitamin D in PD pathogenesis [61]. In a prospective study, [62] found no significant association between serum 25(OH)D and PD risk. While the role of vitamin D as a protective factor in PD is promising, though still controversial, its role in PD symptoms progression is much more complex. Among non-motor symptoms, depression and cognitive impairment seem to be influenced by 25(OH)D3. Better scores in neuropsychiatric testing, especially verbal fluency and verbal memory, are associated with higher 25(OH)D3 serum levels [63], and 25(OH)D concentration was correlated with depression and anxiety scores [64]. [65] assessed the role of VDR polymorphisms in cognitive decline in patients with PD and especially in subjects with FokI polymorphism. Several mechanisms have been proposed for the neuroprotective properties of vitamin D [66].

Vitamin D promotes the expression of insulin-like growth factor 1 (IGF-1), which has neuroprotection capabilities [67]. Also, it has been suggested that vitamin D has antithrombotic and vasodilatory effects which, therefore, improve the blood flow of neurons [68]. Vitamin D, as an antioxidant, with inhibition of reactive oxygen, can prevent blood-brain barrier (BBB) dysfunction after an ischemic stroke [69]. In addition, [62] suggested that the reduced serum vitamin D levels are significantly associated with the risk of developing PD, and this evidence provides the possibility of evaluating the risk of PD by using serum vitamin D levels as a biomarker.

Vit. D and Non-Motor Symptoms of PD:

Various studies have recorded lower levels of vitamin D in PD patients than in healthy controls. Low vitamin D status has also been correlated with the risk for PD and motor severity, whereas less is known about the effects vitamin D has on cognitive function and other non-motor symptoms [70].

Cognition

While many studies have demonstrated an association between vitamin D level and cognition in the general population, the few clinical trials that have been done fail to show improvement with supplementation [71, 72]. Several mechanisms have been proposed for the role of vitamin D deficiency in cognitive decline in the general population that may also apply to the PD population. Vitamin D may be involved in the regulation of acetylcholine and clearing of amyloid beta, both of which are implicated in the pathogenesis of cognitive impairment in PD [73].

Many studies demonstrate that the VDR and enzymes involved in D3 metabolism are expressed in the central nervous system, particularly in the areas of the hippocampus [74], and animal studies have shown that vitamin D deficiency negatively affects hippocampal learning and memory through gene expression and neural development. These studies suggest potential mechanisms for the effect of vitamin D on cognitive impairment in PD, but more work is needed to determine if vitamin D status affects cognition in PD and whether supplementation may help prevent or improve cognitive decline [75].

Mood

The relationship between vitamin D status and depression has been inconsistent in the general population, with some studies demonstrating an increased risk of depression with lower levels of vitamin D [76, 77], while others have shown no association [78]. Limited evidence exists for the association between depression and vitamin D concentration in Parkinson's disease. [64] examined the association between vitamin D levels and various motor and non-motor symptoms. They found that vitamin D level was correlated with depression and anxiety scores after adjusting for age, sex, and BMI [64]. The underlying mechanism by which vitamin D may affect mood is unknown, but several hypotheses exist based on vitamin D's effect on gene expression. The VDR is present in the cingulate cortex and hippocampus, both of which are involved in the pathophysiology of depression [47]. In addition, vitamin D response elements have been detected in the promoter regions of serotonin genes, providing further evidence for a potential role of vitamin D in the development of depression [60].

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