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REVIEWS

The Neurosteroid Hormone Vitamin D: Modern Prospects

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Abstract—Vitamin D (calciferol) is a key vitamin playing an important role in the regulation of the musculoskeletal, immune, cardiovascular and nervous systems. Vitamin D deficiency is a risk factor for multiple brain disorders. Mounting evidence shows robust neuroprotective properties of vitamin D, as well as its ability to improve neuronal function and reduce brain disorders. Here, we focus on the latest clinical and preclinical (rodent and zebrafish) data on the role of vitamin D as a neurosteroid hormone, including its role in regulating the synthesis and functions of neurotransmitters and neurotrophic factors. A better insight into the role of vitamin D in brain function may lead to novel approaches to the treatment and prevention of vitamin D deficiency-related brain disorders.

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INTRODUCTION

The secosteroid vitamin D (calciferol, Fig. 1) is an important vitamin in the body [1–4] that regulates cell proliferation, blood calcium and phosphorus levels [5–7], as well as functioning of the musculoskeletal, immune [8–11], cardiovascular [12], and nervous [13–15] systems. Recent decades have witnessed a growing interest in the physiological role of vitamin D in the body (Fig. 2). Vitamin D is synthesized in the human skin from 7-dehydrocholesterol following exposure to ultraviolet radiation [16], and the main mechanism of its action involves binding the active form (calcitriol) of this hormone to the nuclear vitamin D receptor (VDR), followed by the induction of expression of >1000 target genes [18, 19, 20–22]. The *VDR* gene is highly conserved across vertebrates [23] and is widely expressed in human and animal tissues, including virtually all brain regions (Fig. 3). Rapid (nongenomic) effects of vitamin D on its membrane receptors (mVDRs) have also been described (Fig. 3) [24, 25], although the molecular identity and signaling mechanisms of these receptors remain poorly understood [26–29].

Over the past decades, extensive evidence has accumulated showing robust positive clinical effects of vitamin D in the brain [30–33] (Fig. 2) and the risks of developing brain disorders due to vitamin D deficiency and/or *VDR* genetic mutations [34–38] (Tables 1, 2). Preclinical data (Table 3) also support the critical importance of vitamin D and VDR signaling in the brain [3, 39, 40]. However, despite the growing interest in the role of this vitamin in the brain, many aspects of its neurobiology remain

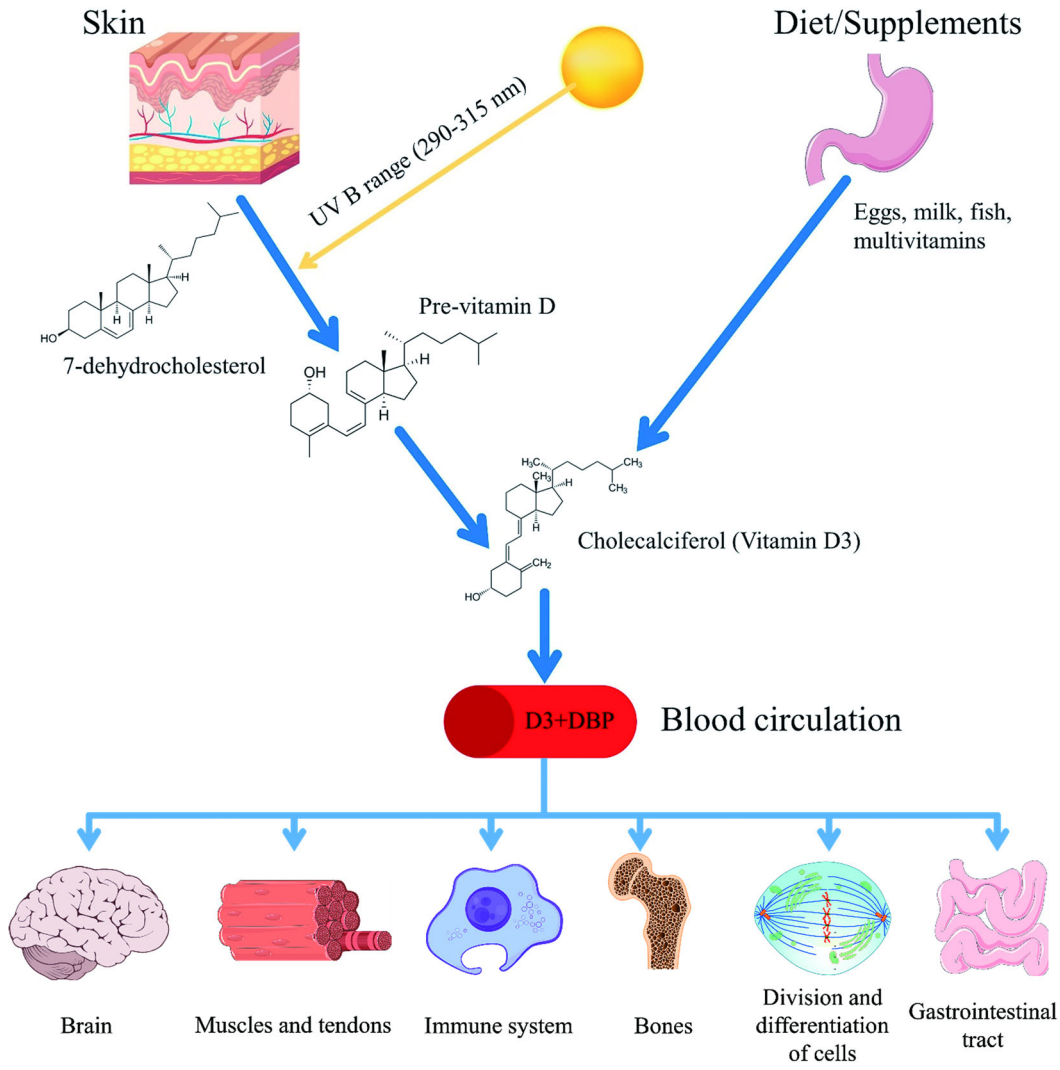

Fig. 1. A diagram illustrating vitamin D synthesis and biological action. DBP—vitamin D-binding protein. Further vitamin D metabolism proceeds via its hydroxylation followed by the excretion with bile [17].

unclear. Here, we summarize clinical and preclinical evidence on vitamin D effects in the brain, accumulated over the last 10 years, aiming to provide a deeper insight into its role in the central nervous system (CNS), and highlight promising research trends in this area.

Since many brain diseases are associated with hypovitaminosis D [59–61], vitamin D therapy reduces the risk of the three most common CNS disorders—anxiety [44], depression [62], and dementia [63]. Genetic variations of *VDR* are linked to Alzheimer's (AD) [35] and Parkinson's [37] diseases and cognitive impairments [36], as well as depression and autism (Table 2). It is believed that vitamin D effects may be mediated by the protection of neurons from oxidative stress and neuroinflammation [8], including the action of this hormone as an antioxidant that reduces the risk of neurodegenerative diseases [33, 60, 65]. Vitamin D also promotes synthesis of neurotrophic factors (e.g., the nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF) [66–68]), regulates calcium and phosphorus levels in the brain [69, 70], and protects the myelin sheath of nerve fibers. In contrast, its deficiency leads to myelin destruction and the development of multiple sclerosis [42] and neuromyelitis optica (Devic's disease) [43]. In addition to its action on neurons, vitamin D affects glia, reducing the pro-inflammatory M1 phenotype of microglia [21]. Activated astrocytes demonstrate high expression of genes encoding

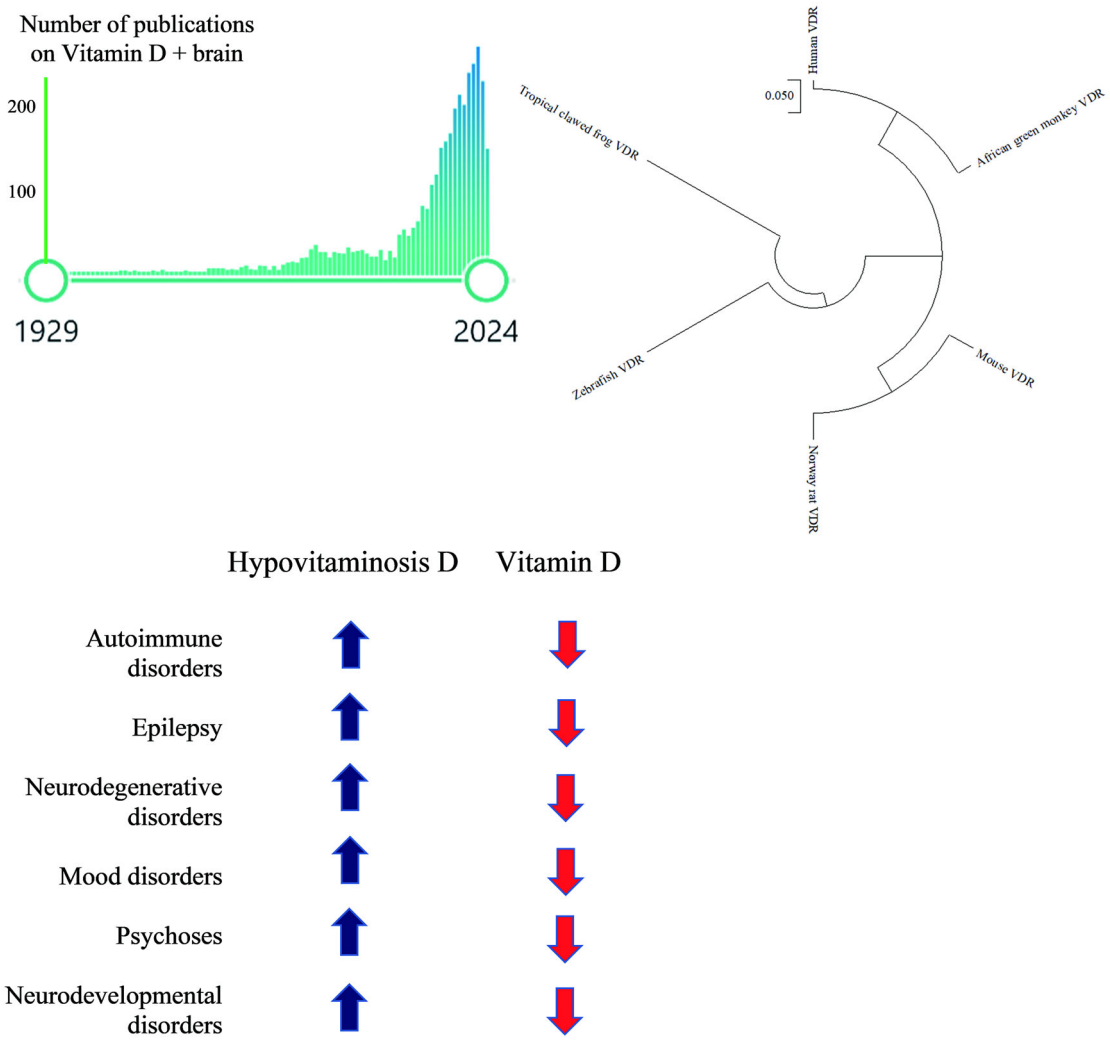

Fig. 2. Relevance of research on vitamin D in the central nervous system, as seen from the increase in the number of publications on vitamin D + brain in the Pubmed database (www.Pubmed.gov, accessed August 2024). Left panel illustrates the overall conservation of *VDR* genes in humans, primates, rodents, amphibians, and zebrafish (*Danio rerio*), as analyzed by their nucleotide sequences in CDS FASTA format using the Ensembl database (www.ensembl.org/index.html, accessed August 2024) and presented as a phylogenetic tree generated using the MEGA 11 software. Bottom panel illustrates major groups of CNS disorders influenced by hypovitaminosis D and vitamin D therapy (see further details in text and Table 1).

VDR and Cyp27B1 (a cytochrome P450 superfamily enzyme involved in vitamin D synthesis) [71], while the hormone itself reduces the levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β), and Toll-like receptor 4 (TLR4) in these glial cells [71]. Possessing all key features of a classic neurosteroid hormone [72–76], vitamin D also interacts with other steroids [30]. For example, the therapeutic effect of progesterone in neurotrauma is manifested clinically only at an adequate level of vitamin D, while in an animal model of neurotrauma, there was noted a decrease in neuroinflammation (a reduction in both the number of injured neurons and astrocyte activity) after co-administration of these two steroids [77].

BRAIN DISEASES ASSOCIATED WITH VITAMIN D DEFICIENCY

Vitamin D deficiency has long been associated with a high risks of AD [78], a severe neurodegenerative pathology caused by beta-amyloid aggregation and neurofibrillary tangles with astro- and microgliosis [79]. AD is also the most frequent cause of

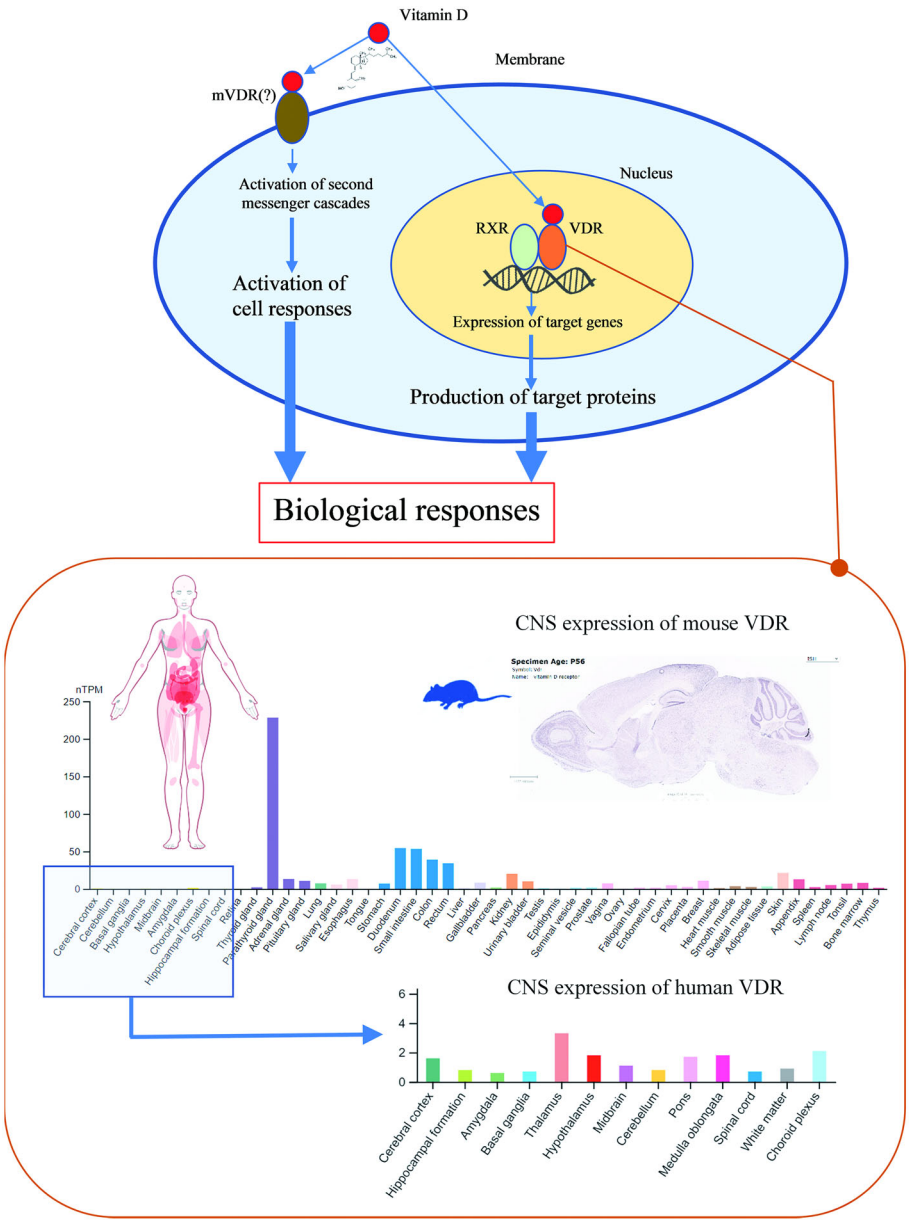

Fig. 3. Effect of vitamin D on its specific nuclear (VDR) and membrane (mVDR) receptors. Bottom inset summarizes VDR distribution across various tissues and different brain regions in humans (based on the Human Protein Atlas, www.proteinatlas.org/ENSG00000111424-VDR/, accessed August 2024) and in the mouse brain (Allen Brain Atlas, www.mouse.brain-map.org/experiment/show/100144119, accessed August 2024). RXR—retinoid receptor (forms a heterodimer with VDRs upon binding vitamin D in the nucleus).

dementia [80, 81]. There is a direct relationship between vitamin D status and AD, as both patients and APP and PS1 mice (two genetic models of AD) demonstrate reduced blood calciferol levels [82]. In rodents, chronic hypovitaminosis D leads to neuronal senescence, neurodegeneration, and beta-amyloid accumulation in the brain [40, 83]. AD is also associated with *VDR* whose genetic variation may double the risk of AD [84] and related cognitive impairments [41]. In addition to improving AD, vitamin D has a positive effect on cognitive function in general. For example, elevated blood calciferol levels correlate with lower risks of dementia [46], while vitamin D deficiency correlates with a worsening of neuropsychological functions [85], especially in elderly patients [86].

Table 1. Neurological and mental diseases associated with vitamin D

Neurological diseases	Mental illnesses
Parkinson's disease [40] Alzheimer's disease (AD) [41] Multiple sclerosis [42] Devic's disease [43]	Depression [33] Anxiety disorders [44] Bipolar disorder [45] Schizophrenia [32] Attention deficit hyperactivity disorder (ADHD) [46] Autism [47] Epilepsy [48]

Table 2. Neurological and mental diseases associated with *VDR* gene polymorphisms

Neurological diseases	Mental illnesses
Parkinson's disease (*BsmI*, *ApaI*, *FokI*) [37, 40]	Depression (*FokI*, *BsmI*, *ApaI*, *TaqI*) [49]
Alzheimer's disease, AD (*Cdx-2*, *FokI*, *BsmI*, *ApaI*, *TaqI*) [50]	Schizophrenia (*rs10741657 AA*, *rs10877012 TT*, *rs6013897 AA*) [51]
Multiple sclerosis (*ApaI*, *BsmI*, *FokI*, *TaqI*) [52]	Autism (*Cdx-2*, *FokI*, *BsmI*, *TaqI*) [53]

Table 3. Approaches to studying vitamin D using animal models

Models	General characteristics
Vitamin D-free diet [55, 56] (rodents)	Decreased blood calcidiol and calcitriol levels, altered neuroanatomy, hyperlocomotion, increased exploratory activity, decreased learning ability, decreased size of the lateral ventricles
Paricalcitol* administration [55] (rodents)	Decreased blood calcidiol and calcitriol levels
VDR gene knockouts [39, 57] (mice)	Prepulse inhibition deficit, anxiety, decreased activity in the open field and Y-maze, motor dysfunctions
Vitamin D-free diet [5] (zebrafish *Danio rerio*)	Reduced swimming near the surface (anxiety-like behavior), overall hypoactivity
Administration of various doses and forms of vitamin D (larval zebrafish) [58]	Changes in zebrafish fry activity depending on tank illumination

*A drug used for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure, a 1,25-dihydroxyergocalciferol analog, the active form of vitamin D2 (ergocalciferol).

Depression is another severe and highly prevalent brain disorder [87], manifesting as lowered mood, inattention, and general hypoactivity [88, 89]. However, although positive effects of vitamin D intake or sunlight therapy on mood, as well as the seasonal nature of depression, are well known, their relationship to vitamin D is not fully understood. One of putative mechanisms of vitamin D action may be related to the hippocampus [90], whose structure is disrupted in patients with chronic depression [59, 91] and which is rich in VDRs [92]. Likewise, vitamin D deficiency in rodents provokes its atrophy during development [59, 93]. Monoamine deficiency in the brain is also linked to the pathogenesis of depression [94], and hypovitaminosis D reduces dopamine and serotonin synthesis [59]. VDRs are expressed in dopaminergic neurons of the hippocampus, substantia nigra, and prefrontal cortex that all play a key role in depression, while VDR expression in the substantia nigra in rodents can delay the differentiation of dopaminergic neurons and cause behavioral deficits in hypovitaminosis D [95].

Bipolar disorder is yet another mental health condition characterized by abrupt swings from depres-

sion to mania, whose relationship to vitamin D is poorly understood [21]. For example, while patients with bipolar disorder are indistinguishable in calciferol and 24,25-dihydroxyvitamin D levels from controls [45] or groups with other mental illnesses [96], most studies nevertheless reveal lower vitamin D levels than normal [97].

Anxiety spectrum disorders are presently most prevalent CNS illnesses worldwide and present as anxiety/excessive worries [98] accompanied by the hypothalamic-pituitary-adrenal (HPA) axis dysfunction, impaired glucocorticoid production, and the imbalance of inhibitory and excitatory neurotransmission [99]. A negative correlation has been shown between vitamin D levels and anxiety disorders, whereas regular vitamin D intake promotes a decrease in these diseases [44] (see also increased anxiety in *VDR* mutant mice, Table 3, and HPA axis disorders in rodents with hypervitaminosis D [44]).

Multiple sclerosis is a severely debilitating neurological disease [100] whose symptoms (spasticity, fatigue, pain) are caused by a nonselective autoimmune brain lesion [101, 102]. Vitamin D deficiency [103], as well as *VDR* ApaI, TaqI, and BsmI polymorphisms [104], are linked to the risk of this disease, while the *VDR* FokI polymorphism is associated with higher vitamin D levels in both controls and multiple sclerosis patients [105] (Table 2). Patients with another autoimmune disorder, Devic's disease, also have reduced calciferol levels [43], but it is unclear whether it is causative or consequential for this pathology [43].

Autism spectrum disorder (ASD) represents a severe psychiatric disorder characterized by social behavior deficits, stereotypies, cognitive impairments [106], and hypo- or hypersensitivity [106]. Autistic children and adolescents have lower vitamin D levels than their healthy peers [47, 107], while children born to mothers with low vitamin D levels are more likely to develop autism [47]. On the contrary, vitamin D supplementation can correct autism symptoms in infant children [107, 108].

Schizophrenia is a severe, highly heterogeneous mental disorder that encompasses positive (delusions, hallucinations) and negative (anhedonia, social isolation, affect flattening) symptomatology, as well as cognitive impairments [109]. There is evidence of a link between schizophrenia and vitamin D system's activity [110], because *VDR rs10741657 AA*, *rs10877012 TT* and *rs6013897 AA* polymorphisms are associated with schizophrenia [51], while hypovitaminosis D has been reported in 70% of people with schizophrenia, particularly increasing the risk of its development during the first year of life [110, 111].

Attention deficit hyperactivity disorder (ADHD) is a widespread neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity [112]. Low blood calciferol concentrations are associated with the risk of ADHD [97], which may be due to defects in serotonin synthesis by tryptophan hydroxylase 2, whose 'vitamin D response element' (VDRE) activates serotonin production [97]. An association of ADHD with the Intron8 polymorphism of *VDR* has also been found [113]. In contrast, vitamin D intake reduces hyperactivity, impulsivity, and inattention not only in children, but also in adults with ADHD [114].

Epilepsy is one of the most common neurological diseases, presenting as CNS hyperarousal and seizures [115]. Interestingly, the seasonal nature of epilepsy reproduces that of hypovitaminosis D [116], whereas vitamin D intake reduces the occurrence of epileptic seizures by 40% [117]. The vitamin also exerts acute anticonvulsant effects in a rodent model of pharmacogenic epilepsy [118], whereas the disruption of vitamin D signaling in *VDR* knockout mice causes increased seizure sensitivity [119]. Analyses of various *VDR* polymorphisms show that the *FokI AC* genotype less, and the *ApaI AA* genotype more frequently, occur in people with epilepsy [120] (Table 2).

Finally, linking CNS diseases to vitamin D status inevitably raises the question of its threshold blood concentrations [121] (30–40 ng/mL [122–124]). It is generally considered that vitamin D deficiency is 12–20 ng/mL [125], insufficiency—20–30 ng/mL [126], sufficiency—50 ng/mL, and hypervitaminosis—above 100 ng/mL [121]. Notably, posing a serious biomedical problem [127–129], hypovitaminosis D affects 60–70% of the world population [130].

EXPERIMENTAL MODELS TO STUDY VITAMIN D IN THE CNS

Experimental (animal) models are important tools to explore the role of vitamin D and its receptors in the pathogenesis of CNS diseases [76, 131]

(Table 3). The main approaches to animal modeling of hypovitaminosis D include artificial vitamin D deficiency and engineering of genetically modified animals by targeting the genes of its synthesis or signaling. For example, a dietary model of vitamin D deficiency in female rats deprived of ultraviolet light and dietary vitamin D supplementation leads to decreased blood calcidiol and calcitriol levels and brain alterations in newborn rat pups, whose cortex proves to be longer and thinner, and whose lateral ventricles are enlarged [55]. Dietary vitamin D deficiency affects differentiation and proliferation of brain cells during the neonatal period [132], also causing animal hyperlocomotion [56], impaired learning, and a reduction in the size of lateral ventricles [133]. Thus, even short-term prenatal vitamin D deficiency affects brain development and function, leading to cognitive and behavioral disorders in adult individuals, which may be important in terms of translating these results to humans.

Another approach to studying vitamin D is based on the depletion of its reserves through the administration of paricalcitol [55], a cytochrome CYP24A1 inducer that incites rapid calcidiol and calcitriol catabolism (Table 3). As soon as three weeks following the administration of several paricalcitol doses to rats, the serum levels of both hormones proved to be below detection limits [55]. Owing to this model, various vitamin D effects (e.g., bone and mineral metabolism, hypertension, oxidative stress, and inflammation) have been studied, opening up the possibility of applying this model in brain research as well.

The use of zebrafish (*Danio rerio*), an established model organism in neurobiological research, has a number of advantages specifically for studying CNS diseases [134] and may also be useful for unraveling evolutionarily conserved physiological functions of vitamin D. Firstly, high fecundity and rapid development of zebrafish makes them a convenient model for experiments and collecting big data arrays [135]. Secondly, the transparency of zebrafish embryos and fry allows the in vivo investigation of internal processes with high resolution [136], which is particularly important for analyzing the formation of key brain structures at early stages of embryonic development. In addition, zebrafish have numerous genetically modified strains for studying various aspects of CNS diseases, easily manipulable genetics, and a number of well-developed and effective genome editing techniques [137].

Taken together, this makes zebrafish increasingly applicable for studying the role of vitamin D in the brain. For example, a vitamin D-deficient diet reduces fish swimming near the surface of water in an unfamiliar aquarium (i.e., reveals more anxious behavior compared to controls) and causes overall hypoactivity [5]. Models have also been generated based on zebrafish fry, where vitamin D2 alters behavior depending on light levels, reducing swimming in the dark, but not in the light [58]. Likewise, the VDR agonist lithocholic acid at high concentrations suppresses swimming activity during both light phases in this model, while at low concentrations it does so only in the light [58].

The effects of vitamin D on CNS conditions are also studied using zebrafish models of other diseases. For example, vitamin D administration to zebrafish with artificially induced hyperglycemia, a characteristic feature of diabetes mellitus, reduces blood sugar levels and restores memory and learning abilities in the T-maze [138]. This is particularly significant given that in humans, hyperglycemia reduces cognitive functions and even causes AD. Thus, vitamin D normalizes zebrafish cognitive functions impaired by artificially induced hyperglycemia, further supporting the conserved mechanisms linking these two disorders.

PROBLEMS AND PROSPECTS

Studying the effects of vitamin D on human and animal nervous systems is a dynamically developing and promising area of research [131, 139, 140], yet not without relevant but still unresolved problems. For example, the behavior of rats and mice exposed to dietary vitamin D deficiency during development differs under distinct conditions [55]. In rats, hypovitaminosis D impairs latent, but not prepulse, inhibition and working memory. Electrophysiological studies of vitamin D-deficient rats reveal increased hippocampal long-term potentiation and learning in the Y-maze behavioral test [141]. Unlike rats, vitamin D-deficient mice demonstrate impaired learning with a paradoxical increase in exploratory and motor activity [132]. Moreover, a positive correlation between maternal calcidiol levels during pregnancy and the mental and psychomotor

Table 4. Analyses of genetic homology of the main vitamin D system's genes in humans, mice and zebrafish, based on coding nucleotide sequences in the BLAST database (www.blast.ncbi.nlm.nih.gov/Blast.cgi, accessed August 2024)

Genes	Biological functions of encoded proteins	Human vs. mice, %	Human vs. fish, %	Mice vs. fish, %
VDR	Nuclear vitamin D receptor	84.92	78.53	78.21
CYP2R1	25-vitamin D hydroxylase (synthesis enzyme)	89.63	69.01	66.98
CYP27B1	1α-Vitamin D hydroxylase (synthesis enzyme)	82.55	64.57	89.13
CYP24A1	1,25-hydroxyvitamin D3-24-hydroxylase	82.89	67.16	75.00
Average homology, %	85.00	85.00	67.32	77.32

development of infants up to one year of age [142, 143] and older has been reported in the clinic [144], suggesting that vitamin D deficiency during different developmental phases may differentially affect neurobehavioral syndromes and have species- and perhaps lineage-specific differences.

Vitamin D-induced stimulation of neuro- and gliogenesis is also of interest here. For example, the vitamin D-induced enhancement of adult neurogenesis in various models [145, 146] matters in terms of the neuroprotective properties of this hormone-like vitamin, as discussed above. Meanwhile, vitamin D-induced enhancement of astro- and microgliogenesis may have opposite effects under certain conditions, raising the possibility of probably more complex nature of vitamin D action on different cells of the nervous system, clearly meriting further investigation.

Unraveling genetic and physiological causes of vitamin D-associated CNS diseases in animals is an important line of research [55]. In addition to rodents, a relatively novel model object, the zebrafish, is increasingly being used in this field (Table 3). Recent findings generally indicate the evolutionarily conserved nature of vitamin D involvement in CNS regulation, since the behavioral and cognitive alterations it evokes in fish resemble those seen in clinical patients (Table 1) and in rodent models (Table 3). Sequence analyses of the main genes of the vitamin D system, encoding receptors and enzymes of its synthesis and metabolism, indicate their high homology in humans, mice, and fish (Table 4, Fig. 2). At the same time, the well-known elevated neuroregeneration level in zebrafish (compared to humans and rodents) may require a more specific interpretation of data on vitamin D effects, accentuating the importance of further cross-taxon translational studies of its role in the brain.

Data on the possible link between vitamin D and gamma-aminobutyric acid (GABA) are also interesting. For example, vitamin D has a rapid anticonvulsant effect in a mouse model of seizures induced by the GABA-lytic agent corazol (pentylenetetrazole) [147], while *VDR* knockout mice in the same model show increased seizure sensitivity [4]. Thus, further studies are needed to elucidate the relationship between vitamin D and GABA in the CNS, including both vitamin D-induced indirect modulation of the GABAergic system and its direct impact on $GABA_A$ receptors. Since many neurosteroids have allosteric modulation sites on the $GABA_A$ receptor [148], and the rapid effect of vitamin D on corazol-induced seizures rules out VDR-mediated genomic effects, this possibility deserves comprehensive investigation, as does the possible involvement of mVDRs in these processes. An indirect vitamin D–GABA interaction through vitamin D effects on other neurotransmitters (e.g., monoamines) and gliotransmitters, which in turn may mediate the modulation of GABAergic neurons, is also possible.

An analysis of the known molecular partners of human VDRs (Fig. 4) using the KEGG (Kyoto Encyclopedia of Genes and Genomes) database revealed 100 major pathways, including steroid-related processes of transcription/translation, immune activity, cellular response to stimuli, oncogenesis and cell growth, as well as CNS-related processes, such as the regulation of gliomas, synaptic plasticity, Huntington's disease, oxytocin and GABA receptors (the latter again supporting a possible biological link between vitamin D and the GABAergic system).

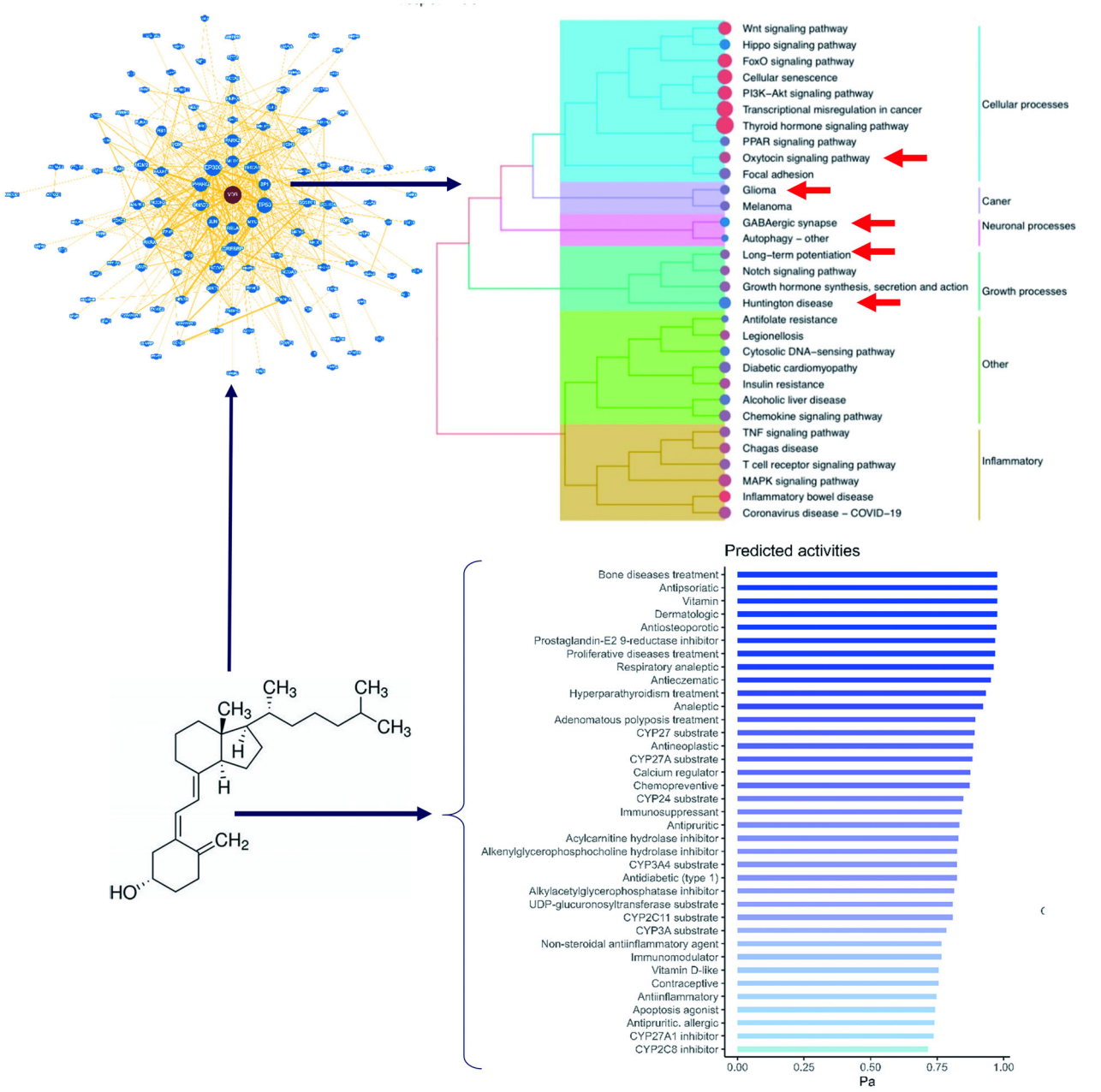

Fig. 4. Analyses of vitamin D molecular pathways through its receptors (VDR) according to the BioGRID (www.thebiogrid.org/, accessed August 2024, left) and KEGG (www.genome.jp/kegg/, right) databases; arrows denote brain-related processes. Bottom panel summarizes predicted biological activities (Pa) for calcitriol according to the PASS Online database (www.way2drug.com/passonline/, accessed August 2024) with high probability Pa > 0.7 (also see text for details).

Another important question concerns the very nature of vitamin D. Calcitriol is traditionally viewed as the main physiologically active form of vitamin D in the body [149]. However, there is evidence for the biological effects of calciferol, previously thought to be a low-activity circulating form of vitamin D [17]. Thus, the role of this and other VDR ligands in the CNS remains poorly understood and requires further research. To gain a deeper insight into the biological activity of vitamin D, we analyzed calcitriol in silico using the PASS Online database [150] that allows predicting the functional properties of small molecules by their chemical structure taken from a library of more than 250000 known properties as of August

2024 (Fig. 4). Interestingly, among the predicted biological activities of calcitriol, widely represented are its traditional effects, such as anti-osteoporotic and calcium-regulating, immunomodulating, as well as antidiabetic and antiproliferative (which confirms its potential for the therapy of diabetes [151] and some cancers [152]). The high probability of substrate-specific and inhibitory interactions with enzymes involved in vitamin D metabolism (CYP27, CYP3A4, CYP2C8 and CYP24) may suggest potential interactions between vitamin D and other drugs [153].

Studying the relationship between CNS diseases and vitamin D levels in the body can also shed light on the issue of comorbidity of a number of such diseases. For example, there is a well-known frequent comorbidity of depression with AD, anxiety disorders, schizophrenia, and other psychiatric diseases [154–156]. Since correlations with the vitamin D system's activity are observed for all of them (Fig. 2), a detailed analysis of this issue may lead to a better insight into the link between vitamin D and the leading psychiatric diseases, and probably to the emergence of new vitamin D-based multi-target therapies (Table 5).

Another important aspect relates to blood concentrations of active forms of vitamin D and, accordingly, the choice of doses to be prescribed for vitamin D deficiency. A significant part of vitamin D is synthesized in the skin under the influence of ultraviolet radiation, the degree of exposure to which is difficult to standardize, so it is as difficult to assess the vitamin D intake rate. Moreover, the very process of determining blood levels of vitamin D active forms in the clinic is associated with multiple difficulties. It is also important that vitamin D (D3) can trigger a negative feedback in the body, leading to a compensatory increase in the degradation of its active form and causing a parallel disruption of a number of physiological processes. An important role is also played by the proteins that specifically bind various forms of vitamin D (vitamin D-binding proteins, DBPs) and thus directly influence its blood concentrations (Fig. 2). Therefore, the level and physiological activity of these proteins, as well as their possible individual variability, should also be considered when selecting doses for vitamin D therapy.

Potential sex differences in the effects of vitamin D also merit attention. For example, in a mouse model of obesity, a decrease in the number of VDRs in the paraventricular zone alters brain electrophysiological activity and glucose tolerance in males, but not in females [163]. Therefore, further dissection of this problem may provide a better understanding of the vitamin D action profile in terms of personalized medicine. At the same time, despite the predominantly positive effect of vitamin D on the brain (Fig. 2), this interplay does not appear to be entirely linear. For example, apart from the direct toxicity of vitamin D overdose, there is interesting evidence that postnatal hypo- and hypervitaminosis D equally impairs spatial learning and hippocampus-dependent memory in mice, being accompanied by changes in the expression of a number of genes in brain tissues [164]. Vitamin D deficiency in rats also causes a paradoxical improvement of memory [141], which may be due to its action during CNS development, but in general does not fit into the commonly accepted paradigm of vitamin D action in the brain. One of the important factors in these processes may be the established powerful proapoptotic potential of vitamin D, which may account for the contradictory data on the effect of vitamin D on the functional state of neurons and glial cells in the brain and some negative effects on the brain structures, especially in the case of its overdose.

CONCLUSION

In general, further study of vitamin D effects on the nervous system represents a promising field of neurobiology and may lead to the development of new methods to treat and prevent vitamin D-associated neurological and psychiatric diseases. The use of experimental (animal) models is an important translational approach to studying pathophysiological CNS mechanisms related to the vitamin D system's dysfunction. Thus, the expanded use of both traditional (rodents) and alternative (e.g., zebrafish) model organisms is therefore essential in this field in terms of seeking for evolutionarily conserved mechanisms and targets for this critical neurosteroid. It is important, however, for the therapeutic approach to be balanced, and to ensure that possible adverse effects of vitamin D in the CNS also receive due scrutiny. Finally, there are multiple open questions in this area (Table 5), whose solution will provide a

Table 5. Selected open issues on the role of the vitamin D system in the central nervous system

• Vitamin D has neuroprotective properties [157]. Can taking vitamin D be effective in preventing neurodegenerative changes that occur as a result of aging?
• What is the nature of mVDR? What are its gene, structure and molecular partners? What are the possible interactions between mVDR and the classical nuclear genomic effects of vitamin D mediated by VDR? Can new ligands act on both types of vitamin D receptors simultaneously?
• Do vitamin D deficiency disorders have comorbidity? What role can vitamin D play in it as a common link?
• Can increasing vitamin D levels cause negative effects by increasing the concentrations of its steroid metabolites such as calcidiol and calcitriol?
• Vitamin D regulates the synthesis of a number of neurotrophic factors and neurotransmitters [33]. Can it, directly or indirectly, influence intelligence and other cognitive characteristics of the human and animal brain?
• Vitamin D modulates the activity of microglia [158] and also regulates the synthesis of neurotrophic factors that promote the renewal and repair of neurons [66, 67]. Will it be an effective tool to combat the consequences of strokes and traumatic brain injuries?
• What are the neurotranscriptomic and neurometabolomic profiles of hypo- and hypervitaminosis D?
• What are the mechanisms of epigenetic and epigenomic modulation of the vitamin D system?
• Attacks of psychosis in schizophrenia are often treated with antipsychotics. Given the association between schizophrenia and vitamin D [159], can there be side effects from the simultaneous use of antipsychotics and vitamin D (for example, in the correction of manic symptoms in bipolar disorder, as well as psychosis and a number of other central nervous system disorders)?
• What types of neurons are most affected by vitamin D, and how does this affect their function? Is there a predominance of the neuronal effects of vitamin D depending on specific neuronal regions or functions?
• Vitamin D is able to reduce the concentration of glial-derived neurotrophic factor (GDNF) [76]? What is the contribution of vitamin D to the physiological functions of neuroglia—astrocytes and microglia?
• Vitamin D in excess has toxicity that can provoke neuropsychiatric abnormalities—difficulty concentrating, confusion, apathy, drowsiness and depression [160]. What physiological and biochemical mechanisms may be involved in these neurotoxic effects?
• Since vitamin D has neuroprotective properties [157], can it influence neuronal survival during toxic exposures? If yes, then how?
• Vitamin D may influence microglial function [158]. Can vitamin D have different effects on the functions of different populations (e.g., M1 and M2) of microglial cells?
• Are there cross-taxon differences in the effects of vitamin D on the vertebrate CNS?
• Different people respond differently to the same dose of vitamin D [161], which may have a genetic basis [162]. Does it contribute to decreased or increased sensitivity to the effects of vitamin D in the CNS? What is the contribution of vitamin D as a neurosteroid to the modulation of other steroid-dependent processes (e.g., allosteric modulation of the GABA-A receptor) in the brain?
• How does vitamin D interact with other neurosteroid hormones in the brain? Is it possible to create therapeutics based on its hypothetical synergy and other CNS steroids? For example, can vitamin D enhance the therapeutic effects of other steroids?
• How do the stimulating effects of vitamin D on the genesis of new neurons and glial cells affect the brain?
• Given the steroidal nature of sex hormones, as well as vitamin D itself, are there sex differences in the effects of vitamin D on brain and behavior of humans and animals?
• What are the possible negative consequences of vitamin D on apoptosis, neurogenesis and gliogenesis?
• How do the effects of vitamin D vary with age? Are there critical age windows for vitamin action in the brain?
• Does vitamin D have an acute effect on memory? Can new nootropic drugs be created based on vitamin D and other ligands? VDR?

better insight into the physiological role of vitamin D in the human and animal CNS, being also relevant for the development of new therapies based on the vitamin D system, its brain receptors, and related small molecule analogs.

AUTHORS' CONTRIBUTION

Conceptualization, project supervision and coordination (A.V.K.), draft writing (A.S.L.), concept discussion, manuscript editing, final version discussion and approval (A.V.K., A.S.L., A.D.Sh., N.P.I., D.S.G., G.N.I.).

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ETHICS APPROVAL

This work does not contain any experimental animal or human studies.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflict of interest.

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