Vitamin D as a Neurosteroid Affecting the Developing and Adult Brain

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Abstract

Vitamin D deficiency is prevalent throughout the world, and growing evidence supports a requirement for optimal vitamin D levels for the healthy developing and adult brain. Vitamin D has important roles in proliferation and differentiation, calcium signaling within the brain, and neurotrophic and neuroprotective actions; it may also alter neurotransmission and synaptic plasticity. Recent experimental studies highlight the impact that vitamin D deficiency has on brain function in health and disease. In addition, results from recent animal studies suggest that vitamin D deficiency during adulthood may exacerbate underlying brain disorders and/or worsen recovery from brain stressors. An increasing number of epidemiological studies indicate that vitamin D deficiency is associated with a wide range of neuropsychiatric disorders and neurodegenerative diseases. Vitamin D supplementation is readily available and affordable, and this review highlights the need for further research.

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INTRODUCTION

Vitamin D deficiency is prevalent throughout the world, particularly in high-risk groups including pregnant woman, infants, dark-skinned migrants, and the elderly (115). In Australia, a recent study showed that 31% of the population has vitamin D deficiency, which is defined as a serum concentration of 25-dihydroxyvitamin D [25(OH)D] below 50 nmol/L (44). Although vitamin D is essential for calcium homeostasis and bone metabolism, it also has a role in other physiological functions, such as an immune modulator (9) and in cell proliferation and differentiation (16). Research over the past 15 years has revealed many functions of vitamin D in brain development and adult brain function. More recently, evidence has accumulated that suggests low vitamin D levels during adulthood may also be associated with adverse brain-related outcomes. A growing body of evidence from epidemiology and neuroscience links vitamin D deficiency with a range of neuropsychiatric disorders and neurodegenerative diseases (53). If low vitamin D is associated with adverse brain outcomes, this could have important public health implications because the treatment of vitamin D insufficiency (i.e., supplementation) is safe, cheap, and publicly acceptable.

This review has three broad aims: (*a*) to summarize the role vitamin D plays within the healthy developing and adult brain, (*b*) to highlight the impact that vitamin D deficiency has on brain function in health and disease, and (*c*) to provide up-to-date evidence supporting the links between vitamin D deficiency and neuropsychiatric disorders and neurodegenerative diseases.

Vitamin D Synthesis

Vitamin D is synthesized from 7-dehydrocholesterol within the skin via UVB radiation. The amount of synthesis is dependent on a wide range of factors including latitude, season, atmospheric conditions, skin pigmentation, and age as well as personal habits including type of attire worn during exposure to sunlight (84a), sunscreen use, and time spent outdoors (36). Importantly, at high latitudes during winter and spring months, it is not possible to synthesize sufficient vitamin D from sunlight, and therefore dietary intake and supplementation are vital to maintain adequate levels of vitamin D (49).

The conversion of 7-dehydrocholesterol in the skin of humans and animals forms vitamin D_3, whereas the conversion of ergosterol in plants, yeast, and fungi forms vitamin D_2 (112). Both forms can be converted to the biologically active vitamin, but they may not have equal nutritional value in people (81), although this is likely to vary in different species, such as rodents (84, 88). Vitamin D_3 is reported to be 87% more potent in raising and maintaining serum 25(OH)D levels compared to vitamin D_2 in people, and it provides two- to threefold greater storage capacity of vitamin D in adipose tissue (81). Additionally, vitamin D_2 supplementation may even suppress endogenously formed vitamin D_3 (176).

Vitamin D is converted to its biologically active form via two enzymatic steps, the first of which occurs in the liver. Vitamin D is hydroxylated to 25(OH)D via either the microsomal (CYP2R1) or the mitochondrial (CYP27A1) P450 25-hydroxylase enzymes (171). 25(OH)D is then converted to the biologically active 1,25 dihydroxyvitamin D (vitamin D) in the kidney via 1α-hydroxylase (CYP27B1). This enzyme is tightly controlled via feedback mechanisms from parathyroid hormone, calcium, phosphate, calcitonin, fibroblast growth factor 23, and vitamin D itself (112).

Although the main expression of 1α-hydroxylase is within the kidney, a variety of other tissues also express this enzyme, including the skin, immune cells, placental tissue, and pancreas (54, 203). The presence of extrarenal 1α-hydroxylase suggests that an autocrine/paracrine mechanism plays a role in localized effects of vitamin D (82).

Genomic Versus Nongenomic Pathways of Action

Vitamin D exerts its effects via both genomic and nongenomic pathways (18). The genomic pathway begins with vitamin D binding to the vitamin D receptor (VDR), which is a member of the steroid/thyroid superfamily of nuclear transcription factors (184). VDR is present throughout the body in almost all tissue types (13, 54, 72, 195).

Once vitamin D is bound to the receptor, VDR is phosphorylated to induce a change in conformation to release corepressors and allow VDR to heterodimerize with the retinoid X receptor (18). This heterodimer then recruits coregulatory protein complexes and binds one of many vitamin D response elements within the genome to influence gene transcription. The vitamin D response element is composed of two hexameric binding sites on DNA, arranged as either direct repeats interspaced with a small but varying number of nucleotides or as inverted palindromes interspaced by nine nucleotides (80, 170).

The ability of this heterodimer to influence gene transcription is dependent upon the range of coregulatory protein complexes, such as steroid receptor coactivators and VDR-interacting

protein, which determines whether repression or activation occurs (57). The recently established genome-wide map of VDR binding identified over 2,700 genomic positions occupied by the VDR, showing the pleiotropic nature of vitamin D (163).

Like other neurosteroid hormones, vitamin D initiates nongenomic rapid responses via either a membrane-bound VDR (130) or a protein-disulfide isomerase-associated 3 (PDIA3) protein (35). The variety of signal transduction systems that are rapidly activated by vitamin D include influx of Ca^{2+}; intracellular release of Ca^{2+} stores; modulation of adenylate cyclase, phospholipase C, and protein kinases; and alteration of the phosphorylation states of cellular proteins (35, 55).

Rapid nongenomic effects of vitamin D may therefore play a role in a variety of cellular processes, with evidence supporting the role of vitamin D in proliferation and immune function (102). Importantly, both the VDR and PDIA3 receptors are present in the adult brain (51, 150).

Vitamin D Metabolism in the Brain

The activating enzyme of vitamin D, 1α-hydroxylase, is found in a wide variety of tissues throughout the body, including the brain (54, 203), along with 25-hydroxylase (68) and the enzyme required for the degradation of the biologically active form of vitamin D, 24-hydroxylase (CYP24A1) (11). Animal studies have shown that the VDR is also found within specific brain regions, including the hippocampus, amygdala, hypothalamus, thalamus, cortex, and cerebellum (159, 191).

The distribution of the VDR and 1α-hydroxylase has also been elucidated in the adult human brain and is similar to that found in the rat (54). The VDR and the 1α-hydroxylase enzyme are colocalized and are found in both neurons and glial cells. The VDR seems to be exclusively nuclear in mature neurons, whereas 1α-hydroxylase is located within the cytosol (54). One recent study showed some immunohistochemical staining of VDR in the soma of mature dopaminergic cells; however, western blots confirmed that the VDR was restricted to the nucleus of both the developing and mature midbrain (43). In contrast, previous studies have shown that unliganded VDR constantly shuttles between nucleus and the cytoplasm (158).

The VDR is present early in the development of the rat, between embryonic day (E)12 and E15, with levels of VDR increasing until weaning (postnatal day 21) and still present in the adult brain (25, 43, 190). The time-dependent expression of VDR in the brain during fetal development supports a role for vitamin D in brain development. The initial VDR expression in brain corresponds within the appearance of dopaminergic neurons within the mesencephalon. Additionally, VDR is present within dopaminergic neurons in the adult substantia nigra (43).

THE ACTIONS OF VITAMIN D WITHIN THE BRAIN

Growing evidence shows that vitamin D has many functions in both the developing and adult brain, including maintaining calcium balance and signaling, regulating neurotrophic factors, providing neuroprotection, modulating neurotransmission, and contributing to synaptic plasticity.

Vitamin D and Calcium Signaling Within the Brain

A high level of calcium in the brain leads to neurotoxicity, and one action of vitamin D within the brain is associated with a reduction in calcium levels. Vitamin D has been shown to downregulate or modulate L-type voltage-gated calcium channels (L-VGCCs) (202, 205). This occurs through downregulation of L-type voltage-sensitive calcium channel (L-VSCC)-A1C subunit mRNA and protein, mediated by VDR mechanisms (71). Vitamin D treatment has also been shown to downregulate L-VSCC-A1D subunit mRNA, but this does not occur via VDR (71). In mice

lacking vitamin D, L-VGCCs are shown to be upregulated, leading to increased Ca^{2+} influx (205). Evidence suggests that vitamin D can directly provide neuroprotection against excitotoxic insults in vitro by its downregulation of L-VGCCs (19).

Vitamin D also regulates the gene expression of a number of calcium-binding proteins, including parvalbumin and calbindin D28k (46, 187), and proteins associated with Ca^{2+} homeostasis (51). The evidence suggests that the effects of vitamin D on Ca^{2+} occur via both genomic and nongenomic actions (51, 144, 202).

Neurotrophic Properties

The first evidence to support the role of vitamin D in neuronal differentiation, maturation, and growth came from in vitro studies showing that treatment with vitamin D led to changes in several neurotrophic factors, with increased synthesis of nerve growth factor (NGF) (146, 198), glial cell line–derived neurotrophic factor (GDNF) (143), and neurotrophin 3 (NT-3), and with decreased synthesis of NT-4 (145). Vitamin D treatment was also shown to increase levels of the low-affinity neurotrophin receptor ($p75^{NTR}$) in vitro (142). Depletion of vitamin D during rat fetal development leads to a reduction in NGF, GDNF, and $p75^{NTR}$ in newborn pups (52).

NGF is essential for the survival and differentiation of sensory and sympathetic neurons as well as the cholinergic basal forebrain neurons (108), and GDNF is integral to the development of dopaminergic (183) and noradrenergic systems (161). Although NT-3 stimulates the production of neurons and has widespread effects on their function and survival (120), the $p75^{NTR}$, along with NGF, is essential for necessary programmed cell death in the brain (34).

Initial in vitro work in several cancer cell lines, including mouse myeloid leukemia cells and melanoma cells, showed that the addition of vitamin D inhibited cell growth, led to a reduction in proliferation, and increased differentiation (153). Vitamin D's ability to induce differentiation was shown to be extended to normal bone marrow progenitor cells in vitro (133), and its antiproliferative effects were confirmed in vivo against malignant cancers (48). Furthermore, the addition of vitamin D to cultured embryonic hippocampal cells was shown not only to increase NGF but also to increase neurite outgrowth and decrease mitosis (22).

Neuroprotection

Evidence indicates that vitamin D provides neuroprotection by regulating NGF and GDNF. In vitro studies have shown that NGF protects against glutamate toxicity and Ca^{2+} ionophore and nitric oxide (NO) donor toxicity (109). Animal studies have shown that NGF is able to protect against excitotoxic injury (63), and in an animal model of Parkinson's disease, GDNF is neuroprotective against ischemia (194), 6-hydroxydopamine (6-OHDA) toxicity (96), and injury (69).

Vitamin D itself has also been shown to provide neuroprotection against excitotoxic injury from 6-OHDA, both in vitro and in vivo (192), which may occur by its downregulation of L-VGCCs (19). Pretreatment with vitamin D ameliorated the locomotor deficits seen with 6-OHDA lesions into the medial forebrain bundle. In addition, pretreatment protected against 6-OHDA-mediated depletion of dopamine and metabolites within the substantia nigra (192). Injection of vitamin D into adult rats leads to an increase in GDNF mRNA and protein expression within the striatum (165), and pretreatment with vitamin D has also been shown to significantly increase GDNF protein expression and TH immunoreactivity in the substantia nigra after 6-OHDA lesioning (166).

It is well known that vitamin D has an effect on the immune system and directly affects immune cells (134). Within the CNS, vitamin D exerts immunomodulatory effects directly on infiltrating

macrophages and parenchymal microglia (141). Treatment of microglia in vitro with vitamin D inhibits the production of tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and NO by activated microglia, which suggests an anti-inflammatory role for vitamin D within the brain (111). Vitamin D has been shown to downregulate the expression of inducible nitric oxide synthesis (iNOS) (66) and to regulate the expression of gamma glutamyl transpeptidase (65), an enzyme important in the glutathione pathway; these findings suggest that vitamin D has an important role in antioxidant metabolism. Vitamin D–deficient animals have elevated inflammatory proteins in the brain, including TNFα and IL-6, indicating that baseline brain inflammation may be increased even without injury (11, 33).

A recent animal study showed elevated levels of vitamin D metabolism enzymes, VDR, and 25(OH)D in the hippocampus following a chronic unpredictable mild stress paradigm in rats when compared to controls (90). Vitamin D is known to be neuroprotective, and therefore it may be that upregulation of vitamin D can protect against the damaging effects of stress within otherwise-healthy subjects.

Neurotransmission

Vitamin D has been shown to regulate a number of neurotransmitter systems. For example, vitamin D treatment leads to increased choline acetyltransferase activity in specific brain regions, which may impact on cholinergic neurotransmission (175). In rats, vitamin D has been shown to protect against methamphetamine-induced reductions in dopamine and serotonin in both the striatum and accumbens (32). Vitamin D treatment has also been shown to increase both potassium- and amphetamine-evoked overflow of striatal dopamine as well as increase substantia nigra tissue levels of dopamine and its main metabolites (31).

Not only can vitamin D act to transiently alter neurotransmitters upon exposure, but there is also evidence to suggest that hormonal imprinting that occurs during the neonatal period permanently alters biogenic amine levels in adulthood. For example, male rats treated with vitamin D at birth showed altered brain stem dopamine and striatal and hypothalamus homovanillic acid (HVA) levels three months later (179). In addition, hormonal imprinting with vitamin D that occurred during the neonatal period in female rats was shown to alter biogenic amine levels in two-month-old offspring. Alterations included increased norepinephrine, dopamine, and serotonin levels in the brainstem; decreased serotonin levels in the hippocampus; and decreased serotonin and HVA levels in the frontal cortex. These changes most likely occurred as a result of epigenetic mechanisms (180).

Synaptic Plasticity

Long-term potentiation (LTP) is a long-lasting enhancement of signal transmission between neurons. LTP is one of the mechanisms underlying synaptic plasticity and is important in learning and memory. Prenatal vitamin D deficiency has been shown to alter many genes involved in synaptic plasticity (51), and evidence suggests that prenatal vitamin D deficiency induces an enhanced LTP in adult rats. Treatment with haloperidol, a high-affinity dopamine D_2 receptor antagonist, reverses the enhanced LTP (74).

Optimal levels of vitamin D were shown to be required for the induction of LTP within the adult rat brain (164). Vitamin D–deficient adult rats showed a reduction in serum calcium, which may have led to the impaired LTP (164), as increased postsynaptic intracellular calcium is necessary for the induction of LTP (23).

RODENT MODELS OF VITAMIN D DEFICIENCY

In rodents, vitamin D deficiency from weaning, during adulthood, or throughout life has produced a range of significant impairments, including reduced body weight, musculoskeletal deficits, impaired prepulse inhibition of the acoustic startle response, and spatial learning deficits (3, 27, 178). Neurochemical changes have also been noted, with significant increases in NE, dopamine, dihydroxyphenylacetic acid (a breakdown product of dopamine), and γ-aminobutyric acid (GABA) (10, 181). However, all of these studies (3, 10, 27, 178, 181) found a reduction in serum calcium levels with vitamin D deficiency, which suggests that the impairments may have been due to altered calcium metabolism. This demonstrates the importance of maintaining normal serum calcium levels and appropriate musculoskeletal function.

Developmental Vitamin D Deficiency

A developmental vitamin D (DVD)-deficient model was first created in Sprague-Dawley rats, in which vitamin D is removed from the diet for six weeks prior to and throughout conception. Under these conditions, dams have a serum concentration of 25(OH)D at the lower limit of detection (<5 nmol/L), which represents a frank vitamin D deficiency seen in less than 4% of the Australian population (44). However, dams are placed back on normal rat chow at the birth of the pups, and 25(OH)D concentrations return to control levels within two weeks (53). Use of this model of transient prenatal vitamin D deficiency in rodents has provided compelling proof-of-principle evidence for the association between DVD deficiency and a wide range of alterations in neuroanatomical, neurochemical, and behavioral measures while normal serum calcium levels are maintained. The DVD-deficient rodent model is reviewed in detail elsewhere (77, 99).

Neurogenesis. Vitamin D deficiency has been shown to alter the gene expression of many cell cycle genes and apoptotic genes during fetal development, leading to changes in cell proliferation and apoptosis (107). Cells dissociated from neonatal rat subventricular zone following vitamin D deficiency during gestation showed increased neurosphere production, which suggests that the absence of vitamin D leads to greater proliferation of neuroprogenitor cells (41). One study looked at the effects of maternal vitamin D deficiency on adult hippocampal neurogenesis and found that the prenatal vitamin D deficiency resulted in decreased neurogenesis in adult rats and that the decrease in neurogenesis could be reversed by treatment with haloperidol, a dopamine inverse agonist (97).

The 1α-hydroxylase knockout mouse lacks the ability to make $1,25(OH)_2D$, and this is associated with increased cell proliferation in the hippocampal dentate gyrus and a reduction in the survival of newborn neurons at 8 weeks of age (205). The $1,25(OH)_2D$ deficiency also significantly increased apoptosis in the hippocampal dentate gyrus, which suggests that this deficiency may be responsible for the loss of the newborn neurons. These results were independent of extracellular calcium (205).

Proliferation, differentiation, and apoptosis. In the rat model of DVD deficiency, the vitamin D–depleted pups had brains that were larger and longer, with larger ventricular volume and a thinner neocortex, than brains from control pups. It was shown that the changes in brain morphology were at least in part due to an increase in cell proliferation (52). Moreover, analysis of genes involved in the regulation of apoptosis found that the DVD-deficient pups had a significant reduction in apoptosis during gestation compared with control pups (107). Lack of vitamin D during development also led to a multitude of changes in gene expression of proapoptotic and cell

cycle genes, which corresponded to observed changes in apoptosis and increased cell proliferation (107). These studies confirmed that loss of vitamin D leads to alterations in cell proliferation, differentiation, and apoptosis during critical periods of brain development.

Vitamin D and dopaminergic pathways. A consistent finding from the DVD-deficient rat model is altered dopamine signaling. In neonatal rats, DVD deficiency decreases dopaminergic turnover by a reduction in the expression of catechol-O-methyl transferase enzyme, which is responsible for the breakdown of a dopamine metabolite (100). DVD deficiency has also been shown to significantly reduce factors crucial for specifying dopaminergic phenotype, such as Nurr1 and p57Kip2, during fetal development (42). Nurr1 knockout animals have complete agenesis of dopamine neurons (204), and p57Kip2 knockouts have no tyrosine hydroxylase (TH)-positive mesencephalic cells at E18.5 (93).

Adult female DVD-deficient rats have a significantly increased dopamine transporter density in the caudate putamen and binding affinity in the nucleus accumbens compared with controls and are more sensitive to amphetamine, a dopamine-releasing agent (101). It was recently confirmed that the VDR is present in the nucleus of TH-positive neurons in both human and rat substantia nigra (43).

DVD-deficient model and schizophrenia. A wide range of epidemiological findings have pointed to developmental vitamin D deficiency as a risk factor for the development of schizophrenia (126); these findings are discussed in more detail below (see Schizophrenia section). In this section we discuss findings in the DVD-deficient animal model that are relevant to schizophrenia.

The enlarged lateral ventricles and reduced cortical thickness seen in the DVD-deficient pups are frequently reported in schizophrenia patients (79). Adult DVD-deficient C57BL/6 and 129svJ mice (78) and adult DVD-deficient rats had greater spontaneous hyperlocomotion (26) compared with control rats. DVD-deficient rats also show increased locomotion in response to MK-801, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, and a reduction in both MK-801-induced and spontaneous hyperlocomotion with haloperidol, a dopamine receptor antagonist, which was selective for DVD-deficient rats (98). DVD-deficient adult rats also show impaired latent inhibition (14), another feature of schizophrenia (197).

DVD deficiency also led to cognitive impairments in mice (60) and impaired response inhibition in the rodent version of the continuous performance task in rats (186), a key feature of the cognitive deficits seen with schizophrenia. These impairments were reversed by acute treatment with clozapine, an atypical antipsychotic (186). Although the DVD-deficient model does not replicate all of the features of schizophrenia [sensorimotor gating is normal (98)], it is a plausible model that can be used to explore the neurobiological mechanisms in schizophrenia.

Adult Vitamin D Deficiency in Rodents

Vitamin D deficiency has recently been investigated in adult Sprague-Dawley rats to determine whether similar disruptions occur in both the developing and adult brain. In the adult vitamin D (AVD)-deficient model, rats were placed on a vitamin D–deficient diet at 10 weeks of age and at 16 weeks began behavioral testing. They were tested on a wide range of behavioral domains, and overall, AVD deficiency was not associated with an altered phenotype. In a cognitive test of attention and vigilance, the AVD-deficient rats had no learning or attentional deficits but showed a mildly impulsive phenotype. The AVD-deficient rats had increased levels of GABA and an increased dihydroxyphenylacetic acid:HVA ratio in the striatum. The AVD-deficient rats were

shown to be vitamin D deficient and, importantly, had normal calcium levels after eight to ten weeks on the diet (28).

The impact of AVD deficiency on brain function and behavior was also investigated in two strains of inbred mice, C57BL/6J and BALB/c. The mice were placed on a vitamin D–deficient diet at 10 weeks of age for a period of 10 weeks prior to behavioral testing. This procedure resulted in serum calcium levels and body weight in AVD-deficient mice that were not different from those of controls. AVD deficiency was found to result in spontaneous hyperlocomotion in both strains (76). The C57BL/6J strain showed no other behavioral effects of AVD deficiency. However, the BALB/c AVD-deficient mice showed altered behavior on the elevated plus maze, a test used to measure anxiety levels, as well as altered responses to heat, shock, and sound (76).

Brain neurochemistry was also analyzed, and the effects of AVD deficiency in the two strains differed markedly. In the C57BL/6J strain, dopamine and 5-hydroxytryptamine turnover was increased by AVD deficiency, whereas the BALB/c strain showed decreases in levels of glutamate and glutamine and increased levels of GABA and glycine. Of particular interest, both strains showed a small but significant decrease in the level of an enzyme involved in GABA synthesis, glutamate decarboxylase (GAD65/67) (76).

These studies show the importance of background strain, with BALB/c mice more susceptible to AVD deficiency than C57BL/6J mice or Sprague-Dawley rats. These general bodies of research also indicate that the timing of exposure to low vitamin D has different impacts on brain outcomes. The absence of vitamin D during development alters the orderly cascade of brain development, which results in a range of neurobiological outcomes as discussed above and reviewed by Kesby and colleagues (99). In contrast, low vitamin D during adulthood is associated with only subtle changes in some behavior and selective changes in neurochemistry that may be related to excitatory/inhibitory systems.

Two-Hit Animal Models

Vitamin D and experimental autoimmune encephalomyelitis: An animal model of multiple sclerosis. The experimental autoimmune encephalomyelitis (EAE) animal model is a model of multiple sclerosis (MS). A range of studies have used this model to look at the effects of both vitamin D treatment and a vitamin D–deficient diet on EAE outcomes (29, 114, 141).

Treatment with vitamin D before or during the induction of EAE is effective in preventing EAE, and treatment with vitamin D after the induction of EAE is effective in decreasing the clinical signs of EAE (29, 114, 141). In addition, vitamin D deficiency increases the susceptibility to EAE and increases the clinical signs of EAE (29, 67). Recently, an animal model of MS pretreated with high-dose vitamin D was shown to have a reduction in demyelination and attenuated microglia activation and macrophage infiltration (196).

Vitamin D is known to be an immune modulator with immunosuppressant activity. Its actions in the EAE animal model and in human MS are most likely to involve, in part, the regulation of inflammatory cytokines. For example, vitamin D decreases the production of proinflammatory cytokines and increases the production of anti-inflammatory cytokines (30, 121). One study showed that vitamin D treatment for MS patients significantly increased serum levels of transforming growth factor-β1, which is an anti-inflammatory cytokine (119). Vitamin D also directly affects cellular immunity. It has been shown to inhibit Th1 cell development in EAE as well as dendritic cell maturation to suppress inflammatory activity (75, 113) and regulate the actions of other T cells (123).

Recently, studies have shown that vitamin D inhibits T-cell proliferation, inhibits the development of IL-6- and IL-17-producing cells, and enhances IL-10 production and the number of regulatory T cells, all mechanisms to promote anti-inflammatory actions (39). It seems clear that

vitamin D can alter the immune response, which is vitally important in autoimmune disorders such as MS.

Unexpectedly, adult offspring of a DVD mouse model showed milder and delayed EAE when compared with control offspring (58). One hypothesis proposed was that mice deprived of vitamin D in utero and subsequently placed on a vitamin D diet from birth actually grew up in an enriched-like environment (58). This hypothesis is supported by epidemiological data showing that a reduced risk of MS is associated with higher sun exposure in children (95, 188). In mice it was shown that offspring born to either a DVD-deficient mother or father displayed early and more severe EAE when compared with control mice (59). More studies are required to examine the molecular basis for the discordant effects between first and second generations.

Vitamin D deficiency and stroke. Studies with animal models of ischemic stroke have also looked at the effects of vitamin D on stroke severity and prognosis (11, 201). For example, a study examined the impact of vitamin D deficiency on stroke severity in the adult rat and found that vitamin D–deficient animals had greater infarct volumes compared with controls, and this corresponded with greater impairments, post stroke, in sensorimotor behavioral testing. Investigations into the mechanism showed that vitamin D–deficient animals had significantly lower plasma, brain, and liver levels of insulin-like growth factor 1 (IGF-1) compared to controls. IGF-1, a neuroprotectant that is usually elevated after injury to protect the tissue, has been attenuated with vitamin D deficiency, which indicates that lower IGF-1 levels may contribute to the greater infarct volume seen with vitamin D deficiency (11).

The inflammatory response was also altered in the vitamin D–deficient rats compared with controls with a reduction in the levels of a variety of cytokines/chemokines including IL-1β, IL-10, and IFN-γ and with an increase in IL-6. These changes could also contribute to the greater infarct volume seen. The same study (11) also looked at the effects of an acute treatment with vitamin D immediately following stroke injury and found no effects on infarct volume or functional capabilities.

Vitamin D deficiency and traumatic brain injury. Vitamin D–deficient rats with traumatic brain injury show increased inflammation and greater open field test behavioral deficits in comparison with controls (33). Although progesterone, a neurosteroid that has been beneficial as a treatment in traumatic brain injury in recent clinical trials (199, 200), was beneficial in injured control animals, there was no improvement with treatment in vitamin D–deficient animals. This suggests that vitamin D deficiency exacerbates traumatic brain injury and diminishes the benefits of progesterone treatment (33).

A combination treatment of progesterone and low-dose vitamin D after brain injury in vitamin D–sufficient animals was found to preserve spatial and reference memory in comparison with controls, and the combination treatment was more effective than progesterone treatment alone (89). The combination treatment also stimulated astrocytic activity around the injury site, which suggests that the neuroprotective effects are mediated through activated astrocytes (89).

Vitamin D deficiency, aging, and cognition. Aged rats (20 months old) were analyzed for the effects of vitamin D treatment on a spatial memory task and on a spontaneous object recognition task, inflammatory state, and amyloid-β (Aβ) load and clearance. Aged controls demonstrated significant learning and memory impairment compared to young control animals. However, vitamin D treatment significantly improved this age-related decline (20). Age-related changes in inflammatory state were also mitigated by vitamin D treatment, with increased expression of the anti-inflammatory IL-10 and decreased expression of the inflammatory mediator IL-1β

after treatment with vitamin D. The aged control animals showed an increase in amyloid burden compared to young controls. However, this was reduced by vitamin D treatment (20).

Vitamin D deficiency and amyloid-β toxicity. The introduction of Aβ into cortical neuron culture leads to neurodegeneration via upregulation of L-VGCCs and suppression of VDR, whereas additional treatment of vitamin D protected the neurons from cytotoxicity by downregulating L-VGCCs and upregulating VDR (46). Alzheimer's disease (AD) is believed to progress in part from inflammatory processes, including oxidative damage and elevated levels of NO, that occur via iNOS induction. In vitro studies using cortical neurons show that iNOS is elevated following Aβ treatment, whereas vitamin D treatment prevents Aβ-induced cytotoxicity and iNOS upregulation via VDR (47). Previous studies have shown that vitamin D regulates the expression of iNOS (66). Therefore, vitamin D supplementation could lead to a reduction in NO-mediated inflammation in AD, a possibility that should be further investigated.

Furthermore, treatment with a PDIA3 receptor agonist has been shown to significantly improve performance of object recognition memory, reduce amyloid plaques and neurofibrillary tangles, and reduce degenerated axons and presynaptic terminals in a mouse model of AD (182). Vitamin D, a known endogenous agonist of PDIA3, may therefore be important for anti-AD therapy (182).

Polymorphisms in the VDR gene have been shown to be associated with the risk of AD (15, 70). A recent genetic and functional study found that an AD risk allele was associated with lower VDR promoter activity and that overexpression of VDR or vitamin D treatment suppressed amyloid precursor protein transcription in vitro (193). An analysis of mRNA expression following vitamin D treatment of mixed neuron-glia cell culture showed upregulation of genes related to neurodegenerative disorders, including 10 genes that encode proteins that could possibly limit AD development (147). Growing evidence supports a protective role of vitamin D against the progression of AD, which is highly relevant owing to endemic vitamin D deficiency, particularly in the elderly. Randomized controlled trials that examine the benefits of vitamin D supplements in AD subjects are needed.

LINKS WITH NEUROPSYCHIATRIC AND NEURODEGENERATIVE DISORDERS

Recent convergent evidence indicates that vitamin D deficiency has an impact during brain development and on the adult brain, and that it is biologically plausible that vitamin D deficiency would affect human health in terms of neuropsychiatric and neurodegenerative disorders. These disorders tend to have a complex etiology, with both gene and environmental influences. However, vitamin D deficiency seems to be a common risk factor. In this section, we provide the evidence from epidemiology, prospective studies, and clinical trials that links vitamin D to a range of disorders involving the central nervous system. A brief summary of various vitamin D–related pathologies and the strength of evidence that connects vitamin D to a range of disorders is shown in **Figure 1**.

Cognitive Impairment

Many epidemiological studies have found an association between serum 25(OH)D and cognitive function, including memory and orientation (117) and executive function (24, 110). In older adults living independently, low serum 25(OH)D concentrations were significantly associated with cognitive impairment (151). In a recently published systematic review and meta-analysis, lower vitamin D concentrations were significantly associated with poorer cognitive function (12).

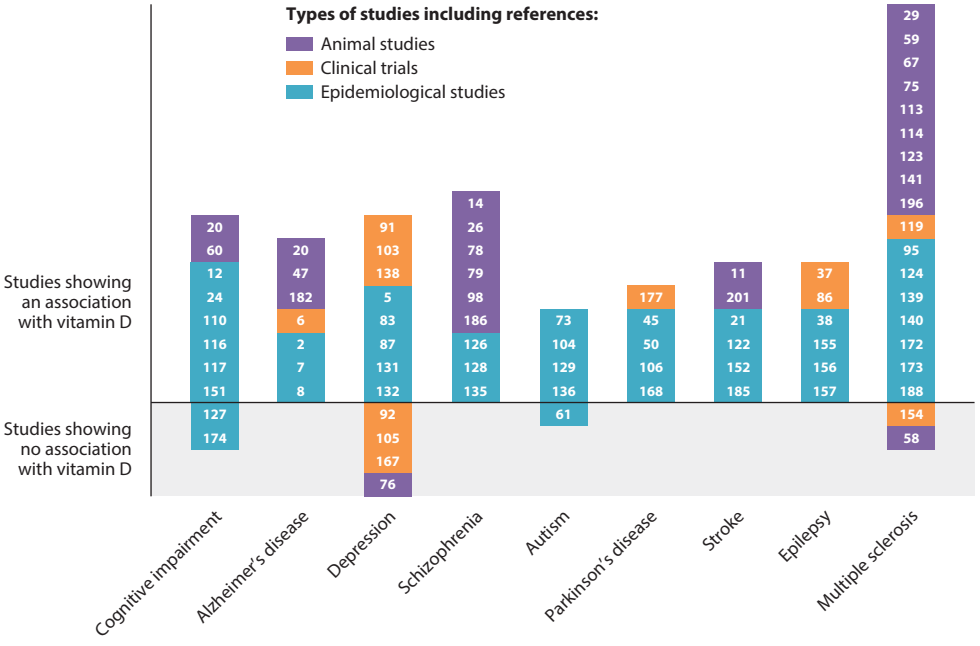

Figure 1

Strength of evidence based on animal studies, clinical trials, and epidemiological studies that show evidence of an association between vitamin D and various disorders. Numbers in boxes correspond to reference numbers.

However, an association is not always found (127, 174), and moreover, from epidemiological studies it is not clear if low vitamin D levels precede the development of cognitive impairments or are a result of poor diet and disability.

A prospective study found that patients identified as vitamin D deficient at initial assessment had greater impairment of cognitive function at baseline and during follow-up three and six years later (116). Cognition was measured using the Mini-Mental State Examination (MMSE), a widely used neuropsychological test of cognitive function, and Trail-Making Tests A and B. At initial assessment, scores on all three tests were significantly worse in subjects who were vitamin D deficient or severely deficient compared to those who were vitamin D sufficient. At the six-year follow-up, subjects who were severely 25(OH)D deficient at baseline were more likely to experience substantial later cognitive decline as assessed by the MMSE and the Trail B, which measures executive functioning, but not on the Trail A, which measures attention (116).

Alzheimer's Disease

AD is a neurodegenerative disorder characterized by progressive and irreversible cognitive deficits and behavioral alterations. The most common symptom is that of memory impairment and loss of spatial memory. A recent meta-analysis (7) looked at the association between low serum 25(OH)D and AD and found that serum 25(OH)D concentrations were overall significantly lower in AD cases than in controls. The meta-analysis revealed a large association of low 25(OH)D concentration with AD. A recent prospective study on the risk of AD in the general population showed an increasing risk of AD with decreasing levels of vitamin D (2).

One study showed an association between higher dietary vitamin D intake and a lower risk of developing AD among older women (8). A small pilot study found that patients who took memantine, an *N*-methyl-D-aspartate receptor antagonist, plus vitamin D for six months had a statistically and clinically relevant gain in cognition, whereas those who took memantine or vitamin D alone showed no effect. This suggests that there may be a synergistic effect in combining the treatments (6).

Depression

Clinical depression is characterized by an all-encompassing low mood and loss of interest in normally enjoyable activities (118). It is generally associated with significant disability, due to an inability to function normally, and with a decreased health status (137). Epidemiological studies have shown a number of risk factors for depression, including gender (higher incidence in females), prior depression, low socioeconomic status, psychiatric comorbidity, medical illness, major adverse life events (94), and, more recently, low vitamin D levels (5).

Many observational and prospective studies suggest an association between low vitamin D levels and depression, particularly in the elderly (83, 87, 131, 132). A recent large systematic review and meta-analysis found that low vitamin D was significantly associated with an increased risk of depression (5); however, from these types of studies, it is not clear whether low vitamin D levels precede depressive symptoms or are a result of having depression.

A randomized, double-blind trial examined the effects of vitamin D supplementation on depressive symptoms in overweight and obese subjects. At the start of the trial there was an association between low serum 25(OH)D and symptoms of depression. Treatment with 20,000 or 40,000 IU vitamin D per week for one year, but not placebo, resulted in significant improvement in depressive symptoms. This study suggests a possible causal link between low vitamin D and depression, at least in the overweight and obese (91).

Treatment with fluoxetine, a serotonin selective reuptake inhibitor, is known to improve depressive symptoms; however, a recent study showed that combining vitamin D treatment with fluoxetine improved depressive symptoms significantly more than fluoxetine alone did (103). Another recent clinical trial (138) was undertaken in adults who were vitamin D deficient and suffering from depression. Participants were given either a single dose of 150,000 IU or 300,000 IU vitamin D or no treatment and were tested again for depression three months later. The single dose of 300,000 IU vitamin D not only proved safe but also was effective at significantly improving depression. This study shows that correcting vitamin D deficiency can improve the depression state (138).

However, in subjects who were not vitamin D deficient, high-dose vitamin D treatment did not have the same benefits (92), nor did all studies find improvement of depression with vitamin D treatment (105). Randomized controlled studies based on general population samples also have not found an association between vitamin D supplementation and scores on measures of depression (167).

Schizophrenia

Schizophrenia is a group of disorders with symptoms including hallucinations, delusions, thought disorder, blunted affect, social withdrawal, and cognitive impairments (64, 149). It is most likely a neurodevelopmental disorder and is characterized by alterations in brain morphology and abnormal laminar organization as well as altered expression of proteins related to the early migration of neurons and glia, cell proliferation, formation of neural circuitry, and apoptosis (56). Risk factors for the development of schizophrenia include both genetic factors and environmental influences.

Some environmental risk factors include pregnancy and birth complications, maternal infection, immigration, adverse life events, and substance abuse (125).

Developmental vitamin D deficiency was first suggested as a risk factor for schizophrenia in 1978 because people with schizophrenia tend to be born in winter (135). Additional epidemiological findings, including increased schizophrenia in dark-skinned migrants to cold climates and in the urban versus rural setting and an increased risk of schizophrenia with prenatal famine, led McGrath (126) to propose that vitamin D deficiency during development could adversely affect the developing brain and lead to an increased risk of adult-onset schizophrenia (126).

Recently, a case-controlled study analyzed neonatal vitamin D status and risk of schizophrenia. It was found that low neonatal vitamin D is significantly associated with an increased risk of schizophrenia (128). A recent genome-wide analysis comparing genes involved in schizophrenia and genes related to vitamin D found a significant overlap of 70 genes (4).

Autism

Autism is a neurodevelopmental disorder characterized by impaired social interaction, communication, and stereotypical behavior. Although it is well known that autism has a strong genetic component, research has also shown that environmental factors are likely to contribute to the development of autism (1). Epidemiological data have shown a number of factors that are associated with autism, including prenatal exposure to mutagens and advanced paternal age. A number of the other exposures can be linked to vitamin D deficiency. These include regions at higher latitudes (especially for dark-skinned individuals), urban residence, and regions with high precipitation rates (104).

Studies have shown that autistic children have lower serum 25(OH)D levels compared to healthy controls (129, 136). For example, a cross-sectional study in Egypt showed that children with autism have significantly lower serum 25(OH)D, $1,25(OH)_2D$, and calcium levels compared to controls (129). Other studies have found no significant association between serum 25(OH)D and autism (61). Recently, autism prevalence was shown to be inversely correlated with solar UVB doses in an ecological study, which suggests that vitamin D deficiency during fetal brain development or early life could be relevant to the development of autism (73).

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease. It is characterized by slow, selective dopaminergic neuronal loss. Symptoms include dyskinesia, rigidity, and tremor as well as postural instability and gait disorders (17).

Epidemiological evidence from cross-sectional studies provides some support for a link between vitamin D deficiency and PD incidence (50, 168). Furthermore, the first longitudinal study investigating the association between vitamin D status and subsequent occurrence of PD showed that low serum vitamin D levels predicted an elevated risk of PD (106). Subsequent studies have shown that vitamin D deficiency is also associated with more advanced severity of disease (45).

A recently published study related to PD has lent support for the neuroprotective properties of vitamin D. Using a placebo-controlled, randomized trial, Suzuki and colleagues (177) examined the impact of vitamin D supplementation (1,200 IU per day, for one year) on various PD-related outcomes. Those on placebo had a steady worsening of PD outcomes. In contrast, those on vitamin D supplements had no change in PD outcomes over the year. The results strongly suggest that low vitamin D status exacerbates progression of PD (40).

Stroke

Studies in humans have revealed that low levels of serum vitamin D are independently predictive for the occurrence of strokes (122, 152), and a large population-based prospective study showed stepwise increases in the risk of ischemic stroke with decreasing serum 25(OH)D (21). A further study in China not only showed that patients with acute ischemic stroke had significantly lower vitamin D levels compared to controls, but also that vitamin D levels were a prognostic marker of short-term functional outcome and death in stroke patients (185).

Epilepsy

Epilepsy is a brain disorder characterized by recurrent and unpredictable interruptions in normal brain function (epileptic seizures) (62). Epidemiological studies indicate that epilepsy is another brain disorder that shows seasonal variation of birth, with an excess of those with epilepsy born in winter compared to summer (155–157). Additionally, epileptic seizures themselves show seasonal variation, with a reduction in seizures during summer (38). A very early small controlled pilot study showed a reduction in the number of seizures following treatment with vitamin D compared to placebo (37). Nearly 40 years later this study was followed up with another pilot study showing a median reduction in seizures of 40% following vitamin D supplementation (86).

Multiple Sclerosis

Multiple sclerosis (MS) is a slow progressive disorder of the central nervous system that is characterized by demyelination of the brain and spinal cord. Although its etiology is unclear, it seems to be multidimensional, with environmental factors, genetic factors, and dysregulation of the immune response all playing a part (189). Environmental risk factors include infection, cigarette smoking, and low vitamin D (148, 160). A significant positive association exists between MS prevalence and latitude globally, which supports the role of UV radiation and vitamin D in its development (173). Additionally, studies show that vitamin D intake is inversely associated with the risk of MS (139, 140), and serum 25(OH)D levels are significantly lower in patients with MS compared to healthy subjects (124). Furthermore, vitamin D concentrations correlate with the severity of MS (172). Genetic studies have shown links between MS susceptibility and both CYP27B1 and CYP24A1, vitamin D metabolism enzymes (162, 169). However, not all studies show a significant effect of vitamin D on MS, and more work is required (154).

FUTURE DIRECTIONS

Accumulating evidence supports the need for optimal vitamin D levels both during development and throughout adulthood for proper brain function. However, it is still unknown what the optimal vitamin D level is for the brain or how the timing or length of vitamin D deficiency can alter the risk of disease. Recommendations for optimal vitamin D concentrations are usually based on bone outcomes (e.g., parathyroid concentrations) (85). More research is required to determine if vitamin D treatment of brain diseases is an effective tool or if prevention of vitamin D deficiency is the only method to lower risk.

The results from recent animal and human studies suggest that vitamin D deficiency during adulthood may exacerbate underlying brain disorders and/or worsen recovery from brain stressors. Therefore, research is required to determine the molecular mechanism behind this possible vulnerability. For example, the direct regulation of calcium by vitamin D within the brain

may be a key molecular mechanism to protect against the neurotoxicity that can occur in disease and aging, or it may be vitamin D's immunomodulatory and neurotrophic effects providing neuroprotection to maintain a healthy brain. Therefore, both animal experiments and in vitro research are required to explicate these mechanisms within the brain, such as electrophysiology of calcium transport. Research in animals that combines vitamin D deficiency with relevant animal models of neuropsychiatric and neurodegenerative disorders is also required.

Additionally, with the extensive links between vitamin D deficiency and a wide range of neuropsychiatric, neurodegenerative, and other brain disorders now evident, there is a need for large, well-controlled clinical trials.

CONCLUSION

This review has shown that vitamin D is a neurosteroid that exerts a multitude of effects that are important in both the correct development of the brain and the proper functioning of the adult brain. In addition, mounting evidence suggests that maintaining optimal vitamin D levels may lower the risk of developing a wide range of brain disorders. With vitamin D deficiency widespread throughout the world, it is no wonder that research is focusing on elucidating the mechanisms of vitamin D's actions within the brain. In light of the advantage that vitamin D supplementation is readily available and affordable, this review highlights the need for further research.

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