Neurosteroid hormone vitamin D and its utility in clinical nutrition

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Purpose of review

Vitamin D is a seco-steroid hormone with multiple functions in the nervous system. We discuss clinical and experimental evidence of the role of vitamin D in normal and pathological brain functions, and analyze the relative importance of vitamin D-modulated brain mechanisms at different stages of life. We also outline perspectives for the use of vitamin D in clinical nutrition to prevent or treat various brain disorders.

Recent findings

Numerous brain dysfunctions are linked to vitamin D deficits and/or dysfunctions of its receptors. In both animals and humans, vitamin D serves as an important endogenous and/or exogenous regulator of neuroprotection, antiepileptic and anticalcification effects, neuro-immunomodulation, interplay with neurotransmitters and hormones, modulation of behaviors, brain ageing, and some other, less-explored, brain processes.

Summary

Vitamin D emerges as an important neurosteroid hormone in the brain, with a strong potential for age-specific applications in clinical nutrition.

Keywords

neurosteroid hormone, supplementation and therapy, vitamin D

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Abbreviations

1,25-D	1,25-dihydroxyvitamin D
CNS	central nervous system
MS	multiple sclerosis
VDR	vitamin D [nuclear] receptor

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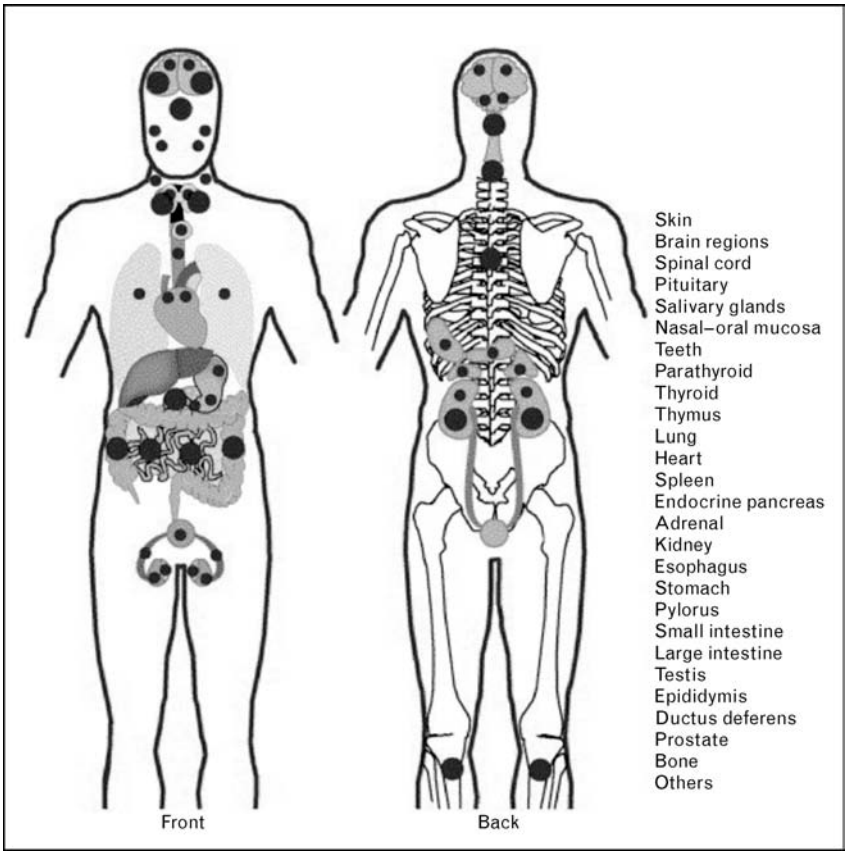
Introduction

Vitamin D (calciferol) is a fat-soluble seco-steroid synthesized in skin (as hormone) or ingested with food (as vitamin). Itself biologically inactive, vitamin D undergoes bioactivation by double hydroxylation in liver and kidney, leading to formation of 1,25-dihydroxyvitamin D (1,25-D, calcitriol, soltriol) – the main biologically active form of vitamin D. Its biological functions include the regulation of mineral homeostasis, tissue proliferation, differentiation and apoptosis, as well as the cardiovascular and immune systems [1•,2,3••,4•]. 1,25-D regulates the expression of numerous target genes through the nuclear vitamin D receptor (VDR), belonging to a common family of steroid receptors that also includes steroid, glucocorticoid and retinoic acid receptors. The mechanism of the genome effects of vitamin D is similar to that of all other steroid hormones. Upon binding 1,25-D, the VDR undergoes a conformational change and binds to vitamin D response DNA elements in the promoter regions of target genes, controlling their transcription. The rapid response to vitamin D uses a nongenomic signal transduction pathway and is believed to occur via putative membrane receptors for 1,25-D, whose functions and properties are not yet well understood [2,5,6••].

VDR autoradiography is an important tool to study vitamin D brain targets and its in-vivo histopharmacology with high resolution and sensitivity [7,8]. Since pioneering works [9,10] reported high-affinity vitamin D binding to the brain (Figs 1 and 2), the biological importance of this hormone in the central nervous system (CNS) is now recognized and these results are confirmed by immunological methods (e.g. [11,12]). Mounting evidence for the presence of vitamin D, its receptors (VDR), and enzymes of bioactivation/metabolism in brain neurons, glial cells, brain macrophages, spinal cord and the peripheral nervous system confirms its role as an autocrine or paracrine neuroactive steroid, thus fulfilling the criteria for a neurosteroid [9,12–14,15••,16,17].

Several recent reviews discussed the role of vitamin D in brain functioning and development [5,6••,14,18,19••]. This reflects a marked paradigmal shift in modern endocrinology, evolving from initial refusal to gradual acceptance of brain actions of vitamin D [9,10,14,20•] (Table 1). Clearly, it took both time and caution before vitamin D ceased being 'neglected' [17], and was finally accepted as a neuroactive/neurosteroid hormone [6••, 19••]. The aim of the present paper is to critically discuss recent developments in this field and outline future

Figure 1 Target tissues for vitamin D ('vitamin D receptor homunculus' [7,8], with permission), as identified through receptor microscopic autoradiography, include brain and spinal cord, pituitary, salivary glands, nasal and oral mucosa, teeth, parathyroid, thyroid, thymus, lung, heart, spleen, pancreas, adrenal, kidney, stomach, intestine, testis, prostate, bone and skin. Size of dots corresponds to intensity of vitamin D binding



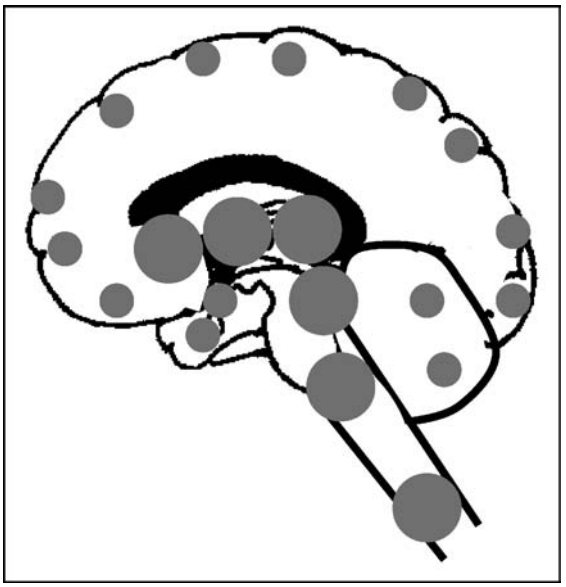
perspectives of research, focusing on vitamin D application for clinical nutrition.

Vitamin D and the nervous system

We have recently summarized [6••] brain functions of vitamin D, outlining potentially important targets for the creation of novel effective neurotropic drugs for human disorders (see also Table 1 for details). In addition to altering brain morphology, neurochemistry and physiology, there are numerous data that link vitamin D and VDR to the regulation of behavior. VDRs are found in key brain areas including the cortex, cerebellum and limbic system, all known to regulate behavior [9,12] (Figs 1 and 2). In humans, vitamin D deficiency has long been known to be accompanied by irritability, anxiety, depression, psychoses and defects in mental development [6••,53••,54,61,65]. The psychotropic mood-elevating effects of vitamin D have also been well documented in the literature [18,54,57] (but see [66]). As Stumpf and Privette [18,67] suggested that vitamin D plays a unique role of regulator of seasonal rhythms, the role of this hormone in seasonal depression [54] is in line with this notion. Importantly, human VDR genes are highly polymorphic and their variations occur frequently in the population. Leading to various vitamin D-related dysfunctions, these mutations are sometimes accompanied by severe psychiatric phenotypes [60•,61,68•, 69•], further confirming the important role of vitamin D for brain functioning and development.

Among many disorders (Table 1), multiple sclerosis (MS) has specific relevance to vitamin D and its supplementation [4•,69•,70–73]. MS is an autoimmune disorder whose risk is linked to insufficient solar radiation and hypovitaminosis D, and reduced markedly by vitamin D supplementation [70,73]. Munger *et al.* [72] reported a 40% reduction in the risk of MS among women who use a vitamin D-rich diet. Another recent study used a 1,25-D-rich diet for 48 months [74••], confirming that vitamin D represents a safe, well-tolerated therapy in MS patients. These data suggest that dietary vitamin D supplementation may prevent the risk of MS, while early vitamin D therapy is effective in treatment of progressing disorder.

Figure 2 Central nervous system targets for vitamin D, derived from animal autoradiographs [9,10,18] and recent human data [15••], include neocortex, striatum, bed nucleus of stria terminalis, hypothalamus, hypophysis, thalamus, amygdala, hippocampus, piriform cortex, cerebellum, raphe, substantia gelatinosa and spinal cord. Size of dots corresponds to relative intensity of vitamin D binding



Animal models of vitamin D-related dysfunctions

As mounting evidence indicates the importance of early nutrition in later health in animals and humans [75•,76•], new animal models of vitamin D deficiency [21••,26] are emerging as a useful tool to examine the role of vitamin D and behavioral effects of its deficits. In rats, maternal vitamin D deficit markedly altered brain morphology, neurochemistry and production of key proteins [21••,26]. Kesby *et al.* [77•] have recently shown that developmental vitamin D deficiency altered behaviors of adult rats, leading to increased baseline and psychostimulant-evoked locomotion. Combined prenatal and chronic postnatal vitamin D deficiency has been reported to impair prepulse inhibition and produce hyperlocomotion in rats [23••,78,79]. Transient prenatal vitamin D deficiency has been shown to result in alterations in memory and learning in rats [80•,81••]. Collectively, this suggests that vitamin D could be an important endogenous and exogenous factor controlling brain functions and behaviors, and its deficiency leads to marked behavioral and physiological anomalies (see also [6••,82•] for reviews of some earlier data).

Mice with genetically impaired VDR (knockout mice) represent another interesting model of vitamin D dysfunctions, focusing on the biological functions of vitamin D and VDR in the brain [55,82•,83,84•]. Marked behavioral differences were found in these mice, including high anxiety and aberrant grooming [55,82•]. VDR knockout mice also displayed specific motor impairments, indicating serious motor (and, possibly, vestibular) defects [82•,85•]. Interestingly, VDR knockout male and female mice built less-complex and incomplete nests, and also showed a dramatic impairment of the VDR knockout maternal behavior [84•], implying possible involvement of prolactin and oxytocin-related mechanisms (see, e.g., [86] for prolactin deficits in these mice).

These mice were predictably insensitive to known therapeutic effects of 1,25-D in experimental allergic encephalomyelitis, an animal model of MS [45], confirming the importance of vitamin D and VDR in neuro-immunomodulation. Recently, some other brain anomalies, including higher sensitivity to seizures and thalamic calcification, have been reported in these mice [52•], emphasizing the growing interest in the use of the VDR genetic ablation as an animal model of human vitamin D-related brain disorders. In general, animal data parallel clinical findings in showing how inherited or acquired vitamin D dysfunctions may lead to brain and behavioral anomalies.

New directions of research

Mounting clinical and experimental data evidence a particularly important role of vitamin D in the ageing brain, as due to both low dietary intake and sun exposure, the elderly have insufficient vitamin D levels [87], accompanied by well-documented behavioral and cognitive decline. Using animal models, Moore *et al.* [46•] reported that vitamin D protects against age-related inflammatory changes in the rat hippocampus. In line with this, Brewer *et al.* [88•] noted that chronic vitamin D treatment in rats effectively reduces hippocampal neurophysiological biomarkers of ageing. Given the important role of the hippocampus in cognitive processes during ageing, such effects of vitamin D on the hippocampus may explain why vitamin D status influences age-related cognitive dysfunctions. Interestingly, Razzaque *et al.* [89,90] have recently shown that fibroblast growth factor 23 knockout mice are characterized by premature ageing accompanied by pronounced hypervitaminosis D and aberrant mineral homeostasis.

Similar results have been reported for klotho, a new hormonal regulator of ageing, strongly linked to the vitamin D system [90–93]. The klotho gene is expressed in kidney and choroid plexus in the brain [94,95], and its ablation in mice leads to premature ageing [92,93]. While vitamin D administration upregulates this gene, mice lacking klotho display elevated serum calcium, phosphorus and 1,25-D [91–94]. Reduced vitamin D levels (by dietary restriction or genetic ablation of 1α-hydroxylase) alleviate many of these phenotypes, indicating that klotho regulates vitamin D levels and that both hormones

Table 1 Summary of potential roles of the vitamin D neuroendocrine system (see also Fig. 3)

Potential roles	Mechanisms of action and potential therapeutic applications	Key references
Developmental	Due to antiproliferative activity, vitamin D regulates brain development, differentiation and apoptosis, whereas its deficiency leads to marked brain anomalies. Developmental role of vitamin D is particularly important during early life. Therapeutic applications may include preventive vitamin D supplementation, minimizing the risk factors of developmental brain disorders.	[21••,22,23••,24–27]
Anticancer	Antiproliferation pro-differentiation and pro-apoptotic action of vitamin D corresponds to its general antitumor activity in different tissues, including brain, where vitamin D seems to contribute to anticancer protection throughout the life. This also underlies the utility of vitamin D and its analogs (as well as their supplementation) in therapy of brain tumors.	[28•,29,30]
Antiepileptic	A growing body of literature suggests the link between vitamin D-related disorders and epilepsy. In humans, seizures accompanied by hypocalcemia and lowered vitamin D levels are often seen in patients with hereditary or nutritional rickets, while chronic vitamin D supplementation reduces these symptoms. These observations have led to a wide practice of using vitamin D in epilepsy, as both the main and supplementary therapy. Direct fast antiepileptic effects of 1,25-dihydroxyvitamin D have been reported in animals, collectively implying its role in the regulation of epileptogenesis during lifetime, and potential utility as antiepileptic therapy or supplementation.	[31–36]
Neuroprotective	Vitamin D/vitamin D receptor-mediated neuroprotection includes the reduction of calcium toxicity, modulation of glutathione metabolism, direct antioxidant-like effects, reduction of nitric oxide synthesis, the induction of neurotrophins and neuritogenesis, modulation of cytokine release, anti-ischemic action (accompanied by altered expression of heat-shock proteins and heme oxygenases) as well as protection of neurons against mediator- or hormone-induced cell death. Baseline vitamin D supplementation may be suggested as an effective neuroprotective therapy. Neuroprotective role of vitamin D increases with age, and vitamin D supplementation may be particularly useful in the elderly, including therapy of neurocognitive disorders such as parkinsonism and Alzheimer's. Novel neuroprotectors may be expected based on vitamin D and its analogs, acting via one or several above mechanisms.	[5,20•,37–40,41•, 42,43•,44•]
Neuro-immunomodulating	Numerous vitamin D receptor-mediated immunosuppressant effects have been reported in the literature, including systemic and local increases in the expression of cytokines, altered macrophage, dendritic and T cell functions, their sensitization to apoptotic signals, as well as actions on the central nervous system component of pathogenesis. Vitamin D supplementation may be important during early life, prevention risks of autoimmune disorders such as multiple sclerosis. During later life, modulation of the immune system by vitamin D supplementation may also be important in relation to neuroprotection. Vitamin D and its analogs may represent a base for creation of novel anti-inflammatory immunomodulating drugs.	[4•,14,45,46•]
Anticalcification	In humans, hypovitaminosis D associated with hypocalcemia and hyperparathyroidism has long been known to be accompanied by soft tissue mineralization, including intracranial calcification (affecting basal ganglia, cerebral cortex and cerebellum) that is relieved by vitamin D therapy. Calcium deposits were seen in basal ganglia in patients with normal calcium/phosphorus levels, but reduced plasma vitamin D levels, further strengthening the link between the abnormal vitamin D/vitamin D receptor system and intracranial calcification. Pathogenesis has strong age-dependent character, as brain mineralization is most commonly found in patients above 50 years old. Vitamin D supplementation may be recommended to treat/prevent brain calcification due to hypovitaminosis D (especially in the elderly), although caution and vitamin D monitoring are necessary, as hypervitaminosis D/hypercalcemia may also provoke brain calcinosis.	[47–51,52•]
Psychotropic (antidepressant, anxiolytic?)	Psychotropic (antidepressant-like) effects of vitamin D and/or sun therapy have long been reported in the literature. Mechanisms of antidepressant-like action of vitamin D are yet unknown and require further studies. Potential mechanisms of anxiolytic-like action of vitamin D are also unknown, and evidence is based on vitamin D receptor mutant mouse data (see text for details). Psychotropic effects of vitamin D may be increasingly important with age, due to higher risks of anxiety and depression in older age.	[18,53••,54–57]

(*continued overleaf*)

Table 1 (*continued*)

Potential roles	Mechanisms of action and potential therapeutic applications	Key references
Other effects	Although role of early vitamin D deficits has been hypothesized to increase risk of schizophrenia, this hypothesis still needs further studies in both clinical and experimental models (see also developmental effects of vitamin D above). Convincing antipsychotic effects of vitamin D or its analogs have not yet been reported in clinical literature, although some recent experimental data seem to support this notion. Several experimental data suggest that neonatal vitamin D treatment affects sexual behavior, most likely due to early programming of other steroid receptors by vitamin D. Vitamin D (1,25-dihydroxyvitamin D) also regulates brain metabolism, normalizing cerebral cortex metabolism and glucose transport disturbed by rickets in rats. These data suggest that vitamin D supplementation may be used to correct brain metabolism, and novel drugs improving brain metabolism may be based on vitamin D and its analogs.	[26,58,59•] but see [60•,61–64]

interact in the regulation of ageing. Klotho insufficiency causes atrophy and dysfunction of the spinal neurons [96], as well as reduction of hippocampal synapses [94]. Mice lacking klotho display cognitive deficits [97], accompanied by increased oxidative stress and apoptosis in hippocampus, reversed by antioxidant therapy. Recently, cognitive impairments were associated with human klotho genetic polymorphism [98,99]. Together, these data confirm that interplay between klotho and vitamin D may be crucial for the regulation of brain functions and ageing. These and other [46•,88•,89–90] results add further complexity to multiple functions of vitamin D, including its potential role as an endogenous regulator of CNS ageing.

In addition to other mechanisms that underlie neurotropic activity of 1,25-D [5,6••,14] (Table 1), this steroid modulates brain neuromediators, including metabolism of central acetylcholine, dopamine and serotonin [5,14,21••,100]. In line with this, Stumpf *et al.* [101] reported serotonin-elevating effects of a vitamin D-rich diet in rat hypothalamus. Our recent studies using chemically induced seizures [36,102] suggested a link between vitamin D/VDR and central γ-aminobutyric acid. Clearly, further studies are needed to clarify the exact role of vitamin D (and its deficiency) on key brain mediators, as well as its interplay with other steroid-like [62] and nonsteroid hormones [6••] in both central and peripheral tissues.

Notably, using different types of vitamin D depletion in rats, Burne *et al.* [78] have demonstrated that behavioral effects (impaired prepulse inhibition) of vitamin deficiency were only seen in combined prenatal plus chronic postnatal, but not in the early life groups. These findings outline a new direction of research in this field, as they not only demonstrate the importance of vitamin D status for brain functions throughout lifetime, but also contribute to our understanding of potential environmental postnatal (vs. purely genetic or prenatal) vitamin D-related influences on brain disorders.

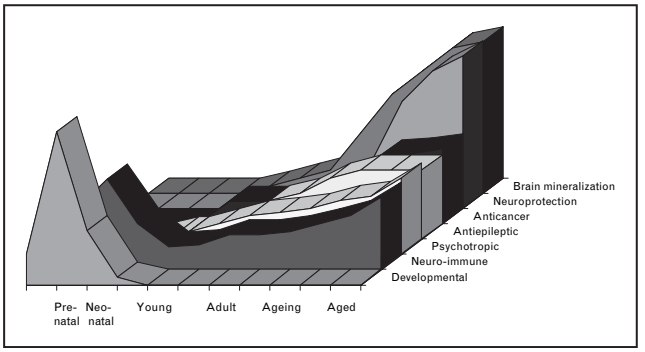
In addition to future experimental studies using mutant and transgenic animals with aberrant vitamin D system, further clinical studies are needed to examine the link between genetic anomalies in the vitamin D/VDR system and various psychiatric disorders. For example, it is necessary to examine whether vitamin D deficiency may lead to MS and other disorders only in susceptible individuals [58,73]. Likewise, it is necessary to assess whether vitamin D supplementation would differentially affect genetically susceptible individuals [71]. Finally, more clinical and preclinical research is needed to study the role of other genes beyond VDR, as well as the role of gene–gene and gene–environment interactions in vitamin D-related mechanisms of ageing [88•,89,90], MS and other CNS disorders [58,73,74••].

Conclusion

Overall, the data summarized here support the crucial role of vitamin D in the brain, including brain ageing. With global vitamin D deficiency on the rise [3••,103], these data further stress the importance of vitamin D pre-, neo- and postnatal supplementation for normal brain functioning. As recent findings show that early-life vitamin D deficits lead to altered brain development, vitamin D supplementation is crucial at this stage. In contrast, neuroprotective/anti-MS effects of vitamin D are becoming increasingly important with age, indicating the utility of vitamin D supplementation in the elderly. Therefore, application of vitamin D for clinical nutrition should consider multiple mechanisms of vitamin D actions and their importance at different periods of life (Table 1, Fig. 3).

Notably, the major problem with vitamin D therapy at any stage is its widely recognized toxic (hypercalcemic) and cardiovascular effects. This fact divides scientists into those who express reservation and caution (e.g. [104]) or who strongly support vitamin D therapy [3••,4•,57,59•,73,105]. Thus, a better knowledge of vitamin D mechanisms and their different age-dependent roles in the brain (Table 1, Fig. 3) may help resolve these discrepancies, maximizing patients' benefits from vitamin D supplementation. From this point of view, high dietary doses of vitamin D merit further testing in various animal models [39,78]. Finally, a rational strategy

Figure 3 Relative importance of vitamin D-related mechanisms for brain functioning at different stages of life (see Table 1 for details)



is to facilitate the search for novel selective drugs based on vitamin D low-calcemic analogs (e.g. [44•]) that retain other beneficial neuroactive properties of this hormone.

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- •• of outstanding interest

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