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11

Vitamin D and the brain

Lauren R. Harms, B.Sc. Hons., Ms., Thomas H.J. Burne, Ph.D., Dr., Darryl W. Eyles, Associate Professor, Dr., John J. McGrath, MD, Ph.D., FRANZCP, Prof. *

Queensland Brain Institute, University of Queensland, St. Lucia, QLD 4072, Australia

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Vitamin D is a member of the superfamily of nuclear steroid transcription regulators and as such, exerts transcriptional control over a large number of genes. Several other steroids, such as thyroid hormones, vitamin A, androgens and the glucocorticoids, are known as 'neurosteroids' and their role in brain development and function is well defined. It has only been in the last decade or so that vitamin D has been thought to function as a neurosteroid. In this review we have collated a diverse array of data describing the presence of vitamin D metabolites and the receptor in the brain, the evidence that vitamin D may be an important modulator of brain development, and the potential role of vitamin D in neurological and neuropsychiatric disorders.

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Introduction

Research in the last 10 years has yielded a large amount of knowledge regarding vitamin D and its previously unknown role in brain development and function. For example, the distribution of the vitamin D receptor (VDR) and the enzyme associated with the synthesis of the active form of the hormone 1α-hydroxylase (CYP27B1) has been mapped in human brain.[1] Moreover, vitamin D may also be an important modulator of brain development. Indeed developmental vitamin D (DVD) deficiency has been proposed as a risk factor for several psychiatric disorders of developmental origin, such as schizophrenia and autism[2,3] and the biological plausibility of these hypotheses has been supported by several studies using animal models.[4–7] Finally, several animal and clinical studies indicate that vitamin

* Corresponding author. Tel.: +61 7 3246 6372; Fax: +61 7 3346 6301.
E-mail addresses: l.harms@uq.edu.au (L.R. Harms), t.burne@uq.edu.au (T.H.J. Burne), eyles@uq.edu.au (D.W. Eyles), john_mcgrath@qcmhr.uq.edu.au (J.J. McGrath).

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D may be somewhat 'neuroprotective' for conditions such as epilepsy, multiple sclerosis, Parkinson's disease and chronic stress.

Vitamin D and the vitamin D receptor in the brain

The major metabolites of vitamin D include 25OHD3, 1,25OH2D3 and 24,25OH2D3, and these are present in human cerebrospinal fluid (CSF).[8] In a similar fashion to other neurosteroids, vitamin D metabolites have been found to cross the blood brain barrier.[9] Blood brain barrier permeability may not be necessary, however, because the P450 enzymes involved with the conversion of 25OHD3 to 1,25OH2D3 and 1,25OH2D3 to 24,25OH2D3 (CYP27B1 and CYP24A1, respectively) are present in the brain. CYP27B1 has been identified in fetal human brain, cultured glial cells and throughout the adult human brain.[1,10–12] In the adult brain, CYP27B1 was present in both neurons and glia and was most strongly expressed in the substantia nigra and the supraoptic and paraventricular nuclei of the hypothalamus.[1] This indicates that the brain has the potential to synthesize the active metabolite 1,25OH2D3. Conversely, CYP24A1 deactivates 1,25OH2D3, converting it to the inactive 24,25OH2D3. In rat primary glial cell cultures, the expression of CYP24A1 mRNA was increased in a dose-dependent manner upon addition of 1,25OH2D3,[13] indicating that levels of active 1,25OH2D3 can be regulated locally in the brain.

The VDR protein is expressed throughout human and rat brains in the pontine–midbrain area, cerebellum, thalamus, hypothalamus, basal ganglia, hippocampus, olfactory system and the temporal, orbital and cingulate cortices.[1,14] VDR mRNA in the mouse brain had a similar expression pattern, as shown in the Allen Mouse Brain Atlas (an open-source internet-based synthesis of in situ gene expression data[15]). The VDR was found to be present in most neurons and some glia in the adult rat and human brains[1,14] and followed similar patterns of expression in both species. For example, in both human and rat brains, the VDR was strongly expressed in pyramidal cells of the CA1 and CA2 regions of the hippocampus, with less intense staining in the CA3 region.[1,16] With regard to glia, the VDR was present in oligodendrocytes in rats[17] and in glial fibrillary acidic protein (GFAP)-stained cells in primary rat hippocampal cultures, which was confirmed in secondary oligodendrocyte cultures and glial cell lines.[18]

There is evidence that the VDR is also expressed in the brains of several species during development. The VDR was expressed in the embryonic rat brain from gestational days 12–21 and was most highly expressed in the proliferating zones of the developing rat brain,[19,20] and was identified from E11.5 in the developing mouse brain.[21] In the developing rat brain, the VDR appeared to be preferentially localized in differentiating fields.[20] Furthermore, VDR expression was shown to increase with gestational age in the embryonic rat, and was coincident with increased apoptotic and decreased mitotic activity in these brains.[22] Therefore, the presence of vitamin D metabolites, activating enzymes and the VDR in the brain indicates that, like other neurosteroids, the vitamin D system may play a role in maintaining normal brain function. Furthermore the presence of the VDR in high levels in the developing brain may indicate that vitamin D is involved in neurodevelopment.

Developmental vitamin D deficiency as a risk factor for neuropsychiatric disorders

Based on several epidemiological findings, it has been hypothesized that low prenatal vitamin D may be a risk-modifying factor for schizophrenia.[3] The most consistent finding in schizophrenia epidemiology is the season of birth effect – those born in Winter/Spring are more likely to develop the disorder than those born in Summer/Autumn.[23–26] This is more pronounced as distance from the equator increases.[27] Secondly, increased rates of schizophrenia are found in those born in urban areas, regardless of location throughout life.[28] Lastly, second-generation migrants with dark skin in cold climates have been found to have an increased risk of developing schizophrenia.[29] The causative factors behind these findings could be due to stress or maternal infection. However, one parsimonious factor that could underlie many of these effects is vitamin D deficiency during development. Vitamin D deficiency is more common in winter, particularly at higher latitudes due to lower sunlight intensity and duration and more skin coverage.[30–33] Vitamin D deficiency is more prevalent in urban as opposed to rural populations, most likely due to lifestyle differences.[34] Dark-skinned individuals have a higher concentration of melanin, which absorbs UVB radiation, thus inhibiting its synthesis of vitamin D.[34] This, combined with a move to a high latitude

country such as the UK could produce an increased risk of vitamin D deficiency. Therefore, developmental vitamin D (DVD) deficiency could explain a number of prominent risk factors for schizophrenia.

Several other studies have provided more direct evidence for an association between low developmental vitamin D and the risk for schizophrenia. A small pilot study investigating 25OHD3 levels in expecting mothers in their third trimester found a trend-level association with schizophrenia in a dark-skinned population.[35] Another study found an association between maternal vitamin D supplementation in the first year after birth and a decreased incidence of schizophrenia in male offspring.[36]

A more recent study used dried blood spots taken from a large cohort of Danish babies several decades ago. Cases (people who went on to develop schizophrenia) were matched to controls that were born on the same day and levels of 25OHD3 were measured from these banked blood spots. When compared to the forth quintile of vitamin D levels, it was found that the lower three quintiles of vitamin D levels were associated with an almost twofold increase in the risk of schizophrenia.[37] Surprisingly, infants with vitamin D levels in the highest quintile also had a small increase in schizophrenia risk, but this was not as large as the increased risk associated with deficiency. This was the first large case–control study to find a direct association between DVD deficiency and risk for schizophrenia and awaits replication.

There is some evidence emerging that DVD deficiency may also be associated with an increased risk for autism,[2,38] although there is not as much evidence for this link as there is for the link between DVD deficiency and schizophrenia. One major line of evidence for such an association is that autism occurs more frequently in African-American children as opposed to their Caucasian counterparts.[39] DVD deficiency may be a factor here because high levels of the skin pigment melanin is a risk factor for vitamin D deficiency, and indeed it has been found that only 4% of dark-skinned women, but 37% of fair-skinned women had sufficient vitamin D levels during pregnancy.[40] A recent study measured serum 25OHD3 in Swedish mothers with or without children with autism, and sampled from a migrant Somali group, as well as a native Caucasian group. No association between maternal 25OHD3 and autism in children was found.[41] However, in that study 25OHD3 levels were measured in mothers several years past their children's weaning age and was considerably underpowered,[42] therefore, no definitive conclusions could be drawn. The association between DVD deficiency and neuropsychiatric disorders warranted neurobiological studies of vitamin D's role in brain development. Models of DVD deficiency have been developed in rats and mice to establish the biological plausibility of the link between DVD deficiency and schizophrenia and to investigate the possible neurobiological mechanisms behind such an association.

Brain development in DVD-deficient rats

The majority of the work examining the impact of DVD deficiency on brain development has occurred using Sprague–Dawley rats, using a protocol defined in Burne et al.[4] Female rats were fed a diet containing either 0 (vitamin D deficient) or 1000 IU/kg (control) vitamin D from 4 weeks of age. They were mated with vitamin D normal males after 6 weeks on the diet. Upon birth of the pups, all maternal rats were placed on the control diet containing vitamin D. Therefore, DVD-deficient rats were only deficient from conception until shortly after birth. At birth and as adults (10 weeks of age), DVD-deficient rats had normal $Ca2+$ and body weight, indicating that the 3-week period of vitamin D deficiency is not severe enough to affect $Ca2+$/bone homeostasis.[43] This is ideal because the effects of the absence of vitamin D can be investigated independent of any secondary effects of hypocalcaemia such as musculoskeletal dysfunction.

Several studies have investigated the effect of DVD deficiency on several aspects of brain development in embryonic and neonatal rats (Table 1). DVD-deficient rats had decreased neurotrophic factor levels, increased mitosis and decreased apoptosis in their brains during embryonic development and as neonates.[5,44] These findings, based on the absence of vitamin D during brain development are consistent with in vitro work done in cancer cell lines that document the largely pro-neurotrophic factor, anti-mitotic, pro-apoptotic and pro-differentiation properties resulting from the addition of vitamin D.[45–52] Another study found that neural progenitor cells from the subventricular zone of the DVD-deficient rats at E18 had enhanced proliferative capacity using the neurosphere assay.[53] Consistent with changes in proliferation and apoptosis, DVD-deficient rats had altered brain morphology as neonates.[5] The brains of the DVD-deficient neonates were larger in volume and were longer, but not wider than controls.

Table 1
Phenotype of DVD-deficient rats with regard to developmental neurobiological measures.

Developmental Neurobiology – Measure	Phenotype of DVD-deficient rat	References
Brain morphology	↑ in volume of lateral ventricles ↓ in cortex thickness	5
Mitosis	↑ in percent mitotic cells in dentate gyrus, hypothalamus and basal ganglia/amygdala at P0 ↑ in percent mitotic cells in dentate gyrus at E19 ↑ in percent mitotic cells in dentate gyrus at E21 ↑ in percent mitotic cells in basal ganglia at P7 (while still on vitamin D deficient diet)	5,44
Apoptosis	↓ in percent apoptotic cells in cingulate cortex, dentate gyrus and basal ganglia at E21 ↓ in percent apoptotic cells in cingulate cortex, dentate gyrus, basal ganglia and hypothalamus at E23	5,44
Neurogenesis	↑ Number of neurospheres from cultured SVZ at P0	19
Neurotrophic factors	↓ NGF and GDNF protein in whole brain at P0	5
Gene expression	↓ nurr1 mRNA in midbrain at E12 and E15 ↓ p75NTR mRNA in whole brain at P0 ↓ COMT mRNA in cerebrum at P0	5,120,121
Apoptosis-specific microarray	64% of pro-apoptotic genes ↓ and 15% ↑ at E19 74% of pro-apoptotic genes ↓ E23 9% of pro-apoptotic genes ↓ and 68% ↑ at P7	44
Cell cycle-specific microarray	21% pro-mitotic genes ↑ and 38% ↓ at E19 48% pro-mitotic genes ↑ and 14% ↓ at E23 12% pro-mitotic genes ↑ and 64% ↓ at P7	44
Dopamine turnover	↓ Conversion of DOPAC-HVA	121

↑ Increase in DVD-deficient rats compared to controls.
↓ Decrease in DVD-deficient rats compared to controls.
E#, embryonic day (days post-conception); P#, postnatal day; NGF, nerve growth factor; GDNF, glial cell line-derived neurotrophic factor; SVZ, subventricular zone; COMT, Catechol-O-methyl-transferase; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid.

Moreover, these pups had a thinner cortex and larger lateral ventricles, even when corrected for brain volume. DVD-deficient rats also had a numeric increase in ventricular volume as adults, but this only reached statistical significance if rats were deficient in vitamin D until weaning, not birth.[54] Enlarged ventricles and decreased cortical grey matter thickness are the two most commonly found neuroanatomical abnormalities in schizophrenia.[55] Although enlarged ventricles are not seen in all patients, they are highly predictive of symptom severity and psychotic risk.[56]

Behaviour in DVD-deficient rats

Tables 2 and 3 summarize the adult neurobiological and behavioural phenotypes of DVD-deficient rats. DVD-deficient rats were found to have altered behaviour. They exhibited spontaneous hyperlocomotion in a novel environment,[4,6,57,58] which was ameliorated by restraint stress or vehicle injection immediately prior to testing.[6,57] Hyperlocomotion in response to novelty can be influenced by subcortical DA[59] and, therefore, may reflect an alteration in DA signalling in DVD-deficient rats. Moreover, other models of schizophrenia exhibit increased spontaneous locomotor activity,[60,61] indicating that hyperlocomotion may be a rodent behaviour analogous to symptoms of schizophrenia.

Psychotomimetic agents were used to further probe the locomotor phenotype of DVD-deficient rats. First, the glutamate N-methyl-d-aspartic acid receptor (NMDAR) antagonist, MK-801 was used. Other classes of NMDAR antagonists such as ketamine and phencyclidine (PCP) are psychotomimetics that mimic the range of positive, negative and cognitive symptoms of schizophrenia in healthy people and exacerbate symptoms in patients with schizophrenia.[62,63] NMDAR antagonists such as MK-801 induce

Table 2
Neurobiological phenotype of DVD-deficient adult rats.

Adult neurobiology – measure	Phenotype of DVD-deficient rat	References
Brain morphology	↑ in volume of lateral ventricles in P70 rats depleted of vitamin D to P21	54
Neurotrophic factors	↓ in NGF protein in one whole cerebral hemisphere at P70	54
Gene expression	↓ Expression of GABA-Aα4, MAP2 and NF-l in one whole cerebral hemisphere at P70	54
Microarray	Dysregulation of pathways such as: Oxidative phosphorylation, redox balance, cytoskeleton maintenance, Ca2+ homeostasis, chaperoning, post-translational modifications, synaptic plasticity and neurotransmission In one whole cerebral hemisphere at P70	122
DAT binding and density	↑ DAT binding in the CPu at P70 ↑ DAT density in the CPu at P70	7
Proteomics	Dysregulation of 36 brain proteins in pathways such as: Oxidative phosphorylation, redox balance, cytoskeleton maintenance, Ca2+ homeostasis, chaperoning, synaptic plasticity and neurotransmission In hippocampus and prefrontal cortex at P70	123
Cell proliferation	↓ BrdU positive (proliferating) cells in dentate gyrus at P84 (normalized by haloperidol)	124

↑ Increase in DVD-deficient rats compared to controls.
↓ Decrease in DVD-deficient rats compared to controls.
NGF, nerve growth factor; P#, postnatal day; CPu, caudate–putamen; BrdU, bromodeoxyuridine (5-bromo-2-deoxyuridine)

several behavioural alterations in rodents, including hyperlocomotion.[64,65] Models that are more sensitive to the locomotor-enhancing effects of MK-801 and similar agents are believed to have altered neurobiology analogous to that of patients with schizophrenia. It was found that DVD-deficient male rats were more sensitive to the locomotor-enhancing effects of MK-801 (dizocilpine), and were restored to control levels of locomotion by the antipsychotic haloperidol.[6] The attenuation of MK-801-induced locomotor activity by haloperidol, which primarily acts by blocking D2Rs, indicates that the DA system in DVD-deficient rats may be altered in DVD-deficient rats.

Second, the psychotomimetic amphetamine was used in DVD-deficient rats. Amphetamine increases extracellular DA levels by inhibiting DA reuptake through the dopamine transporter (DAT) and by reversing transport so more DA is released into the synaptic cleft.[66–69] In a similar fashion to

Table 3
Behavioural phenotype of DVD-deficient adult rats.

Adult behaviour – measure	Phenotype of DVD-deficient rat	References
Locomotion	↑ spontaneous locomotion in a novel environment, normalized under conditions of habituation or stress at P70	6,57,75,125
Exploration	↓ in levels of exploration on the 5-day hole board test at P70	4,75
Learning and memory	↓ Latent inhibition ↓ Habituation in 5-day hole board test Behavioural pharmacology	75
Amphetamine	↑ Sensitivity to the locomotor-enhancing effects of 2.5 mg/kg amph in females at P70	7
MK-801	↑ Sensitivity to the locomotor-enhancing effects of 0.2 mg/kg MK-801 in males at P70	6,43
Anti-pyschotics	0.1 mg/kg haloperidol normalized locomotor sensitivity to MK-801 in DVD-deficient males at P70 0.075 mg/kg haloperidol normalized habituation impairments of 5-day hole board test in DVD-deficient rats at P70	6,124,126

↑ Increase in DVD-deficient rats compared to controls.
↓ Decrease in DVD-deficient rats compared to controls.
P#, postnatal day; Amph, amphetamine.

MK-801, animal models that exhibit enhanced sensitivity to amphetamine are believed to have alterations in the DA system that could be analogous to those in patients with schizophrenia. Female, but not male, DVD-deficient rats were more sensitive to the locomotor-enhancing effects of a high dose of d-amphetamine,[7] which was associated with increased levels of DAT binding in the caudate–putamen (CPu) and increased DAT density.[7] This indicates that DVD deficiency may have altered the developmental trajectory of the DA system, changing the density and binding dynamics of DAT.

With regard to learning and memory, DVD-deficient rats performed similarly to controls in an active avoidance paradigm, in which a light and a sound predicted a foot shock the rat needed to escape from one identical chamber to another to avoid the shock. However, DVD-deficient rats had impaired latent inhibition (LI) on this task. LI is a learning phenomenon in which prior inconsequential exposure to the conditioned stimulus (light and tone) alone retards subsequent learning of an association with the unconditioned stimulus (shock). Under the right conditions, LI can occur in numerous learning paradigms and in many species and can be used as a test of attentional processing. Patients with schizophrenia have impaired LI, i.e., they learn the CS-US pairing after being preexposed to the CS just as well as if they were not preexposed.[70,71] It is believed that this reflects the inability to ignore irrelevant stimuli in patients. Several animal models of schizophrenia also exhibit LI impairments.[72–74] In this study, control rats that were preexposed to the light and tone had impaired learning of the association with the shock and made fewer avoidance responses. DVD-deficient rats that were preexposed made the same number of avoidance responses as non-preexposed rats, indicating a LI impairment.[75]

DVD deficiency has also been shown to alter behaviour in two strains of mice (129/SvJ and C57BL/6J).[76] One strain (129/SvJ) exhibited spontaneous hyperlocomotion in the open field arena, a finding consistent with that from DVD-deficient rats. Both strains demonstrated increased frequency of head dips in a hole board arena, indicative of increased exploratory behaviour.[76] To investigate cognition, control and DVD-deficient C57BL/6J mice were trained on the olfactory tubing maze.[77] A learning deficit was seen on the final day of training, with DVD-deficient mice showing a reduction in the number of correct responses when compared to controls. This was associated with a reduction in the size of the lateral ventricles of DVD-deficient mice.[77] The model of DVD deficiency in mice presents some features that overlap with the model in rats (spontaneous hyperlocomotion), but also some unique phenotypes that do not occur in DVD-deficient rats (enhanced exploration and reduced ventricular volume).

The behavioural studies in DVD-deficient rats and mice have shown that there are long-lasting effects of DVD deficiency on brain function, such that selective behaviours (locomotion, exploration, LI) were altered. Taken together with the evidence of altered neurodevelopment in DVD-deficient rats, these findings establish biological plausibility for the role of DVD deficiency as an environmental risk factor for schizophrenia.

Vitamin D in health and disease

Excitotoxicity and epilepsy

There is some evidence that vitamin D has a protective effect on neurons in vivo. For example, systemic administration of vitamin D (in the form of calcitriol) has been shown to increase levels of antioxidants, such as glutathione in the brain.[78,79] Furthermore, 1,25OH2D3 blocked the neuronal uptake of reactive oxygen species such as hydrogen peroxide and protected against excitotoxicity from glutamate.[80] This may be mediated, at least in part, by the effects of vitamin D on calcium channels. 1,25OH2D3 has been shown to down-regulate the expression of mRNA for the α1C and α1D pore-forming subunits of L-type voltage-gated calcium channel (L-VGCCs).[81] Furthermore, increased expression of L-VGCCs was found in mice lacking the gene for CYP271B, which is required for the synthesis of 1,25OH2D3. These findings may indicate that the neuroprotective effects of vitamin D may be due to its inhibitory effect on Ca2+ influx. Intracellular Ca2+ binding proteins such as calbindin and parvalbumin also limit excitotoxicity by chelating intracellular Ca2+. Indeed 1,25OH2D3 has been shown to up-regulate the expression of the Ca2+-binding proteins calbindin and parvalbumin in motorneurons.[82] Moreover, chronic treatment with high levels of calcitriol has been shown to increase parvalbumin expression in the caudate–putamen of rats.[83] Such protection against excitotoxicity may indicate that vitamin D may also be protective against seizures. This has been confirmed in animal models, in which 1,25OH2D3 has been shown to increase the

electroconvulsive threshold for seizures, decrease the severity of seizures and enhance the action of the anticonvulsive agents valproate and phentoin.[84–86] While severe vitamin D deficiency (as indicated by 25OHD3 levels) in neonates has been associated with seizures, this is mediated via profound disruption of calcium levels.[87] However, despite strong experimental evidence in animal models, the link between hypovitaminosis D in either paediatric or adult populations and increased seizure risk has not been well established. This picture is complicated somewhat by an apparent inverse relationship between anti-epileptic drugs and 25OHD3 levels.[88]

Vitamin D and multiple sclerosis

Vitamin D deficiency has been associated with an increased risk of developing Multiple Sclerosis (MS), a disease of progressive demyelination in the nervous system most likely caused by an autoimmune response.[89] MS is more common at higher latitudes,[90] and vitamin D supplementation has been shown to decrease the risk of developing MS.[91,92] The role of vitamin D in disease prevention is unclear, but it may be due to the immunomodulatory effects of vitamin D. 1,25OH2D3 has a general immunosuppressive effect, and can, therefore, protect the brain from inflammatory damage. For instance, 1,25OH2D3 suppressed macrophage activity after lipopolysaccharide (LPS), a bacterial endotoxin that promotes an immune response.[93] Experimental Autoimmune Encephalitis (EAE) is used to model MS in rodents. 1,25OH2D3 was found to protect against inflammatory damage myelin induced by EAE in rats[94] and dietary vitamin D deficiency was associated with increased EAE symptom severity in adult animals.[95] However, dietary vitamin D deficiency that was limited to development was unexpectedly protective against EAE in adult mice, an effect that may have been due to increased levels of VDR in these animals.[96]

Neuroprotection of the dopamine system

Additional research has supported vitamin D's role as a neuroprotective agent with specific effects on the dopamine (DA) brain systems. Administration of 1,25OH2D3 was shown to protect against damage from 6-hydroxydopamine (6OHDA), a neurotoxin that specifically lesions DA and noradrenergic cells.[97,98] Moreover, 1,25OH2D3 offered protection against neurotoxic doses of methamphetamine by preserving DA and serotonin (5-HT) levels.[99] 1,25OH2D3 has also been shown to increase DA synthesis by promoting the synthesis of its rate-limiting enzyme, tyrosine hydroxylase (TH[100]). Finally, administration of cholecalciferol, the inactive precursor to 1,25OH2D3, to neonatal rats was shown to increase DA in brain stem, as well as the brain stem of their offspring, suggesting a possible epigenetic imprinting effect.[101,102] Such neuroprotection of DA neurons may be relevant for Parkinson's disease, a motor disorder caused by the loss of DAergic neurons in the substantia nigra. Indeed several investigations have linked vitamin D insufficiency with increased risk of Parkinson's disease.[103,104] Moreover, in a large patient cohort (50–79 years, $n = 3000$), higher levels of 25OHD3 were associated with a reduced risk of developing Parkinson's disease in later life.[105] Abnormalities in the vitamin D receptor have also been linked with risk of developing Parkinson's disease.[106]

Vitamin D and stress

There is also some evidence that vitamin D may attenuate the effects of glucocorticoids. Glucocorticoids are secreted by the adrenal glands in response to stress, and chronically elevated glucocorticoid levels in response to prolonged stress had been shown to induce neuronal atrophy and eventual cell death.[107] 1,25OH2D3 was found to completely antagonize the inhibitory effects of dexamethasone (a synthetic glucocorticoid) on cell differentiation and impeded glucocorticoid receptor function in a hippocampal progenitor cell line.[108] Vitamin D's effects on growth factors and neuroprotective actions could possibly hint at a role for vitamin D in the treatment of psychiatric disorders.

Neuropsychiatric disorders

The link between the developmental absence of vitamin D with neuropsychiatric disorders such as schizophrenia and autism has been discussed above. The evidence for a beneficial effect of vitamin D

for treatment of some psychiatric or neurological disorders in unclear. Hypovitaminosis D has been associated with depression, cognitive decline in the elderly, Parkinson's disease and Alzheimer's disease.[103,109–111] In a large prospective study of cognitive decline, aging and 25OHD3, cognitive decline and the rate of decline were increased in subjects severely deficient in 25OHD3 (<25 nM).[110] However, it is unclear if associations between hypovitaminosis D and psychiatric disorders are causative or circumstantial, but there is some evidence for symptom improvements with vitamin D supplementation.[109] If vitamin D does have an effect on psychiatric or neurological disorders, it is likely a modest one and treatment with vitamin D would most likely be in parallel to other treatments.

Future directions and conclusions

The rapid accumulation of experimental evidence over the past 10 years indicating vitamin D could play a role in brain development and function is compelling.[112] Models of DVD deficiency in rodents may provide important discoveries in aiding our understanding of the neurobiology of psychiatric diseases. Considering the epidemiological evidence linking vitamin D with a variety of adverse neurological, psychiatric and cognitive outcomes, [113,114] further well-designed observational studies, and, more importantly, randomized clinical trials of vitamin D supplementation are warranted in those with neurological and neuropsychiatric disorders. Vitamin D supplementation is an attractive candidate for supplementary treatment because it is a simple, safe and inexpensive intervention to alleviate disease burden for many different adverse health outcomes.

There remain many unanswered questions regarding the dynamics of vitamin D status and it's effects on brain structure and function. For example, what constitutes a minimum level of supplementation of vitamin D, and what level of serum 25OHD3 that would predispose an individual to various diseases remains a topic of intense debate.[115] Although vitamin D deficiency can be modelled in animals via dietary restriction, there is insufficient research on chronic vitamin D insufficiency, which is far more likely to be observed clinically. Whether there is a threshold of 25OHD3 levels in which the risk of adverse brain-related outcomes increases or such risk increases steadily with decreasing concentrations of 25OHD3 remains an important experimental variable to be addressed. Additionally there is little knowledge about whether an earlier deficiency/insufficiency can predispose an individual to later brain insults such as infection, autoimmunity or oxidative damage.

The large amount of data accumulated over these past 10 years have led to the tentative inclusion of vitamin D into the broader family of neuroactive steroids.[116] This group includes agents such as the sex steroids and glucocorticoids whose actions in shaping brain development and function have been well described. It would appear, therefore, that vitamin D is no-longer "The Neglected Neurosteroid".[117]

Practice points

- Test for vitamin D deficiency in patients with neurological and psychiatric disorders and supplement if necessary.
- Supplement with vitamin D during pregnancy if required.

Research agenda

- The epidemiological link between developmental vitamin D deficiency and psychiatric or neurological disorders needs to be further investigated.
- There is a need for investigating the effect of vitamin D supplementation on neurological, neurocognitive and psychiatric outcomes using clinical trials, not just observational studies.
- Further studies need to elucidate the minimum level of supplementation needed for adequate brain function as well as adequate bone and calcium homeostasis.
- Future studies using animal models should focus on chronic vitamin D insufficiency and the effects of brain function and behaviour to more accurately model what is seen in human populations.

Given the alarming prevalence of hypovitaminosis D in both pregnant women[118,119] and in the general public, ensuring the diverse functional capacities of this neuroactive steroid in the developing and adult brain are preserved through either environmental or dietary interventions would appear to be a vital public health priority.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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