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Vitamin D and the brain: key questions for future research

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Abstract

Over the last decade a convergent body of evidence has emerged from epidemiology, animal experiments and clinical trials which links low vitamin D status with a range of adverse neuropsychiatric outcomes. This research demonstrates that the timing of exposure to low vitamin D influences the nature of brain phenotypes, as exposures during gestation versus adulthood result in different phenotypes. With respect to early life exposures, there is robust evidence from rodent experiments indicating that transient Developmental Vitamin D (DVD) deficiency is associated with changes in brain structure, neurochemistry, gene and protein expression and behavior. In particular, DVD deficiency is associated with alterations in the dopaminergic neurotransmitter systems. In contrast, recently published animal experiments indicate that Adult Vitamin D (AVD) deficiency is associated with more subtle neurochemical and behavioural phenotypes. This paper explores key issues that need to be addressed in future research. There is a need to define the timing and duration of the 'critical window' during which low vitamin D status is associated with differential and adverse brain outcomes. We discuss the role for 'two-hit hypotheses', which propose that adult vitamin D deficiency leaves the brain more vulnerable to secondary adverse exposures, and thus may exacerbate disease progression. Finally, we explore the evidence implicating a role for vitamin D in rapid, non-genomic mechanisms that may involve L-type calcium channels and brain function.

1. Introduction

Over the last decade there has been a marked increase in research exploring the role of vitamin D in the brain. This research was inspired by the pioneering work of Stumpf [1], Wion and Garcion [2, 3]. In a landmark study by Eyles and colleagues, the distribution of the vitamin D receptor (VDR) and the key rate limiting enzyme involved in the production of 1,25 dihydroxyvitamin D ($1,25(OH)_2D$), was mapped in the adult brain [4]. Of particular interest, the distribution of VDR in certain brain regions suggested that vitamin D may influence particular neurotransmitters and cortical function. For example, expression of the VDR was identified in the hippocampus and prefrontal cortex – brain regions required for learning and memory, and executive control, and implicated in a range of neuropsychiatric disorders. VDR expression appeared most prominent in the substantia nigra, a region rich in dopaminergic neurons. Subsequent research has provided robust evidence linking vitamin D related mechanisms and dopaminergic neurotransmission [5-8].

A growing body of epidemiological research has also linked vitamin D status and risk of brain disorders. The field has moved on from the early ecological studies (e.g those based on latitude gradients and seasonal variations), to stronger analytic methods that have directly measured vitamin D status. These studies have included (a) cross-sectional studies based on case-control samples, or (b) longitudinal cohort studies linking baseline vitamin D status and later incidence brain disorders. With respect to brain disorders, multiple sclerosis has long been linked to vitamin D [9-11]. Other brain disorders of interest to vitamin D related epidemiology research include (a) dementia and cognitive function [12-14], (b) Parkinson's disease [15], (c)

depression [16], (d) schizophrenia or psychosis [17-20] and (e) autism [21, 22]. The results of these studies are by no means consistent, but provide sufficient evidence to justify ongoing studies – the evidence of these studies is covered more extensively in reviews by Deluca and colleagues[23] and Groves and colleagues [24]. In the current article, we take a more forward-looking perspective and suggest key areas that are needed to inform future research.

2. Are there 'critical windows' when low vitamin D differentially impacts on brain function?

In keeping with the well known pro-differentiating and anti-proliferating properties of $1,25(OH)_2D$ [25], there is robust and consistent evidence from *in vitro* studies and animal experiments that low vitamin D alters brain development [26]. Based on a series of rodent experiments, it is now clear that the behavioural and neurochemical correlates of Adult Vitamin D (AVD) deficiency are distinct from those associated with Developmental Vitamin D (DVD) deficiency [27, 28]. Thus, timing is critical – exposure to low vitamin D during brain development will have different consequences on brain function compared to exposure to low vitamin D during adulthood. However, we do not understand the nature of the relationship between the timing and duration of exposure to low vitamin D versus the risk of different brain phenotypes.

Future animal studies need to be extended and refined in order to examine the impact of maternal vitamin D deficiency across all stages of pre- and early postnatal brain development. We have little information on the precise timing of the critical window in rodent studies and what implications these findings have for human brain

function [29]. After switching an adult rodent to a vitamin D deplete diet, it still takes 4 to 6 weeks to induce 25 hydroxyvitamin D (25OHD) deficiency. In contrast, after switching back to a standard rodent (vitamin D replete) diet, 25OHD concentrations can normalize over 7 to 10 days. By carefully increasing the duration of maternal vitamin D deficiency, it will be feasible to assess overlapping developmental periods and thereby help define the key vitamin D-sensitive developmental windows for the developing brain. The second key issue to consider relates to the fact that the gestational period in the rat and mouse is far shorter than in humans and the CNS in rodents is far less developed at birth. With respect to comparing developmental neurobiological stages between rat and humans, the most recent recommendation is that in the rat, the periods of (a) conception to embryonic day 18, and (b) embryonic day 18 to post-natal day 11, best reflect human brain growth during the first and second trimesters respectively [30]. By inference, rats after post-natal day 11 are entering the equivalent of the third trimester of human brain growth. This suggests that rodent offspring resulting from the standard DVD deficiency experimental model may only be vitamin D deficient for the equivalent of the first and most of the second trimester of human CNS development. By prolonging DVD-deficiency until weaning (post-natal day 21), this model covers the period of brain development equivalent to the third trimester of human development.

Animals that arise from dams that are vitamin D deplete until birth (DVD-deplete animals) have increased lateral ventricle volume at birth [31]. However if the reintroduction of vitamin D is delayed until weaning, a persistent increase in lateral ventricle volume can be shown in the adult offspring [32]. This finding is important as it suggests that although the absence of gestational vitamin D leads to abnormal

ventricle formation, there is a postnatal window when the reintroduction of vitamin D can partially ‘rescue’ this phenotype. Animal models that extend vitamin D deficiency beyond gestation and weaning induce rickets, which confounds the interpretation of many behavioural phenotypes [33].

In humans, it is also clear that a great deal of brain development happens in the first few years of life. Epidemiological and imaging studies indicate that peri-pubertal and adolescence stages are also implicated in disorders such as schizophrenia [34, 35]. It is feasible that different brain disorders are associated with different critical windows. Neonatal vitamin D status is linked to the risk of schizophrenia [36] but not multiple sclerosis [37]. Longitudinal birth cohort studies, with repeated measures of vitamin D status at multiple time points, may help define the timing and duration of the critical window [38, 39].

3. Adult vitamin D deficiency and brain function – does vitamin D deficiency leave the brain vulnerable to future insults?

As mentioned above, the impact of low vitamin D intake on adult brain function is very different to that in developmental models. The findings based on AVD rat and mouse models tend to be relatively subtle, and vary according to species and strain [27, 28], while some findings are more consistent than others. For example, mouse AVD deficiency studies have identified significantly reduced glutamic acid decarboxylase (GAD) 65/67 levels (key enzymes in gamma-aminobutyric acid

(GABA)-ergic interneurons) and decreased levels of glutamate and glutamine in brain tissue [27].

There is convergent evidence from animal experimental studies to suggest that vitamin D status may be important in how the brain recovers from a neurological insult. For example, *in vitro* studies indicate that optimal vitamin D status is 'neuroprotective' and pretreatment with $1,25(OH)_2D$ can ameliorate the impact of a range of experimental lesions [40-45]. In a key study by Brewer and colleague [46], it was found that $1,25(OH)_2D$ protected rat primary hippocampal cultures from excitotoxic insults (i.e. glycine and N-methyl-D-aspartate, NMDA). Patch clamp studies found that, under certain conditions, L type voltage dependent calcium currents were reduced following incubation with $1,25(OH)_2D$. Quantitative real-time PCR demonstrated that incubation with $1,25(OH)_2D$ reduced mRNA expression of genes encoding for subunits of these channels (e.g. CACNA1C and CACNA1D).

This neuroprotective capacity has lead researchers to develop 'two hit' animal models, based on the hypothesis that low vitamin D status exacerbates the impact of a lesion and/or reduces the ability of the organism to recover. Using an AVD deficiency model (as the first hit), and a model related to cerebrovascular accidents (as the second hit), Balden and colleagues [47] found that vitamin D deficiency was associated with significantly increased infarct volume and reduced behavioural recovery. For example, compared to animals with normal vitamin D concentration, AVD-deficient rats had a 20% increase of infarct volume in the striatum and a 40% increase in cortical volume 5 days after ischemia induced by middle cerebral artery

occlusion. These findings provide strong evidence that low vitamin D concentrations exacerbate recovery from brain lesions.

Convergent evidence in support of this hypothesis has been provided by a randomized clinical trial of vitamin D supplementation in Parkinson's disease [48]. In this study, those on placebo had a steady worsening on neurological outcomes. In contrast, those on vitamin D supplements had no change in Parkinson disease-related outcomes over the year. The results strongly suggest that low vitamin D status can influence disease progression. These findings have led us to speculate that adult vitamin D deficiency could exacerbate the progression of a wide range of other brain disorders such as multiple sclerosis, dementia and depression [49].

If low vitamin D status delays recovery and/or worsens clinical symptoms, then it is understandable how low vitamin D may be identified as a candidate risk factor in case-control studies (i.e. affected individuals are drawn from prevalent cases, often those in contact with clinical services). In summary, low vitamin D status during adulthood may be associated with worse health outcomes and disease burden, but via more complex mechanisms involving comorbidity with other disorders.

4. What is the role of rapid non-genomic vitamin D-related mechanisms in the brain?

Early work based on the DVD deficiency model suggested that vitamin D deficiency altered brain development via mechanisms such as altered neuronal proliferation, differentiation and apoptosis. Steroid hormones in general, including vitamin D, are known to influence the cell cycle and differentiation via nuclear receptors and

genomic response elements [50] and there is evidence indicating that these mechanisms operate in the developing brain [31, 51, 52]. However it is less clear what roles non-genomic (or rapid) mechanisms may play in mediating the association between vitamin D and brain function. To date, most of the *in vitro* studies exploring the rapid non-genomic properties of $1,25(OH)_2D$ have been carried out on non-neuronal tissue [53-56].

Brewer and colleagues have already provided evidence linking $1,25(OH)_2D$ and L-type calcium channel (LTCC) [46]. There is now a solid body of evidence linking LTCC activity with $1,25(OH)_2D$ in non-neuronal cell types (e.g. skeletal muscle, osteoblast) [57, 58]. Patch-clamping studies and calcium imaging in transfected cells confirm that $1,25(OH)_2D$ alters LTCC-mediated events [59, 60]. The influence of $1,25(OH)_2D$ on adult neurogenesis in the hippocampal dentate gyrus is also contingent on LTCCs. Based on BrdU/NeuN studies in transgenic animals lacking the enzyme required to produce $1,25(OH)_2D$, the absence of $1,25(OH)_2D$ was associated with a two fold increase in neurogenesis (in keeping with the well-known pro-differentiating and anti-proliferative properties of $1,25(OH)_2D$). Additionally, the absence of $1,25(OH)_2D$ can lead to the increased expression of LTCCs, which can subsequently be blocked by the LTCCs antagonist nifedipine [61]. Furthermore, several studies have provided support for the links between $1,25(OH)_2D$, LTCC and neuronal function, as well as the association between $1,25(OH)_2D$ concentration and the expression of CACNA1C transcripts [62-66].

In summary, there is now strong evidence indicating that $1,25(OH)_2D$ impacts on LTCC function, and that these processes are highly relevant to neuronal function.

Indeed, the modulation of calcium entry into neural cells by the 1,25$(OH)_2$D could influence a wide range of neuronal functions, such as maturation of the nervous system during development, and/or neuroprotection during adulthood [67, 68].

In 2013 a major collaborative study from the Psychiatric Genomics Consortium was published in the Lancet [69]. The study combined approximately 30,000 cases of autism, attention deficit disorder, bipolar disorder, major depressive disorder and schizophrenia and 28,000 controls. Across all disorders, SNPs in two LTCC genes were identified that met genome-wide significance (in CACNA1C and CACNB2). Pathway analysis supported a role for genes involved in calcium channel signalling genes for all five disorders. These findings provide further evidence of the importance of these pathways in neuropsychiatric disorders [70, 71] and possibly in Alzheimer's disease [72].

5. Future directions

We have learnt a great deal about vitamin D and the brain in the last 10 years. In particular, rodent experiments have provided a solid experimental framework to examine the neurobiological correlates of vitamin D status. Key discoveries include the robust links between DVD deficiency and altered brain development in the rodent. It remains to be seen if low vitamin D during development is associated with clinical disorders, but there is emerging evidence linking low neonatal 25OHD concentrations and an increased risk of schizophrenia [20].

In the adult brain, there is emerging literature suggesting that low vitamin D status may exacerbate brain lesions (i.e. a two-hit hypothesis). Key gaps in the literature

related to the timing and duration of the critical window throughout life when low vitamin D may have a differential impact on disease outcomes. Furthermore, the links between vitamin D and LTCC provide tantalizing clues to guide future research. Curiously, estrogen directly potentiates LTCC via non-genomic (and estrogen receptor independent) mechanisms [73]. This raises the potential that a wider class of steroid and seco-steroids may also operate via these mechanisms. These are tractable research questions as modern electrophysiology and calcium imaging techniques will be able to further explore and dissect these research questions. Of course, clues from basic neuroscience need to cross-talk with epidemiology (i.e. translational epidemiology) [74]. If convergent evidence does link low vitamin D status with particular brain disorders, then clinical trials are needed to confirm the association, and inform future health practices. Even if low vitamin D is ultimately shown to cause only a small fraction of the burden of neuropsychiatric disorders, because vitamin D supplementation is safe, cheap and publically acceptable, these finding could have important implications for public health.

Conflicts of Interest: None

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