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Review

Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease

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ABSTRACT

Increasingly vitamin D deficiency is being associated with a number of psychiatric conditions. In particular for disorders with a developmental basis, such as autistic spectrum disorder and schizophrenia the neurobiological plausibility of this association is strengthened by the preclinical data indicating vitamin D deficiency in early life affects neuronal differentiation, axonal connectivity, dopamine ontogeny and brain structure and function. More recently epidemiological associations have been made between low vitamin D and psychiatric disorders not typically associated with abnormalities in brain development such as depression and Alzheimer's disease. Once again the preclinical findings revealing that vitamin D can regulate catecholamine levels and protect against specific Alzheimer-like pathology increase the plausibility of this link. In this review we have attempted to integrate this clinical epidemiology with potential vitamin D-mediated basic mechanisms. Throughout the review we have highlighted areas where we think future research should focus.

1. Introduction

Ten years ago it was suggested that vitamin D was the 'forgotten neurosteroid' (McGrath et al., 2001). Over the past 10–15 years, studies in which the diet or vitamin D signaling have been manipulated in experimental animals have provided convincing evidence that this vitamin, more accurately referred to as a hormone, is required for normal brain homeostasis and development. In order to better understand the exact mechanisms behind the diverse actions of vitamin D in brain, a large number of studies have been conducted in central nervous system (CNS) tissue or isolated cells.

The purpose of this review is fourfold; (a) to provide an up-to-date summary of the work implicating a role for vitamin D in both early and late events in brain cell growth and differentiation; (b) to explore potential mechanisms for some of these findings; (c) to summarise the increasing number of psychiatric conditions now being linked with deficiencies in this vitamin; and (d) to detail the most pressing questions remaining in order for us to more fully understand how the "sunshine hormone" exerts its diverse effects across the CNS.

2. Vitamin D metabolism

The Nobel Prize was awarded to Adolf Windausin 1928 for his role in the discovery of vitamin D. The synthesis of vitamin D begins with cleavage of the B ring of 7-dehydrocholesterol in the epidermis by ultraviolet UVB radiation (290–315 nM). After spontaneous isomerisation, this creates the secosteroid precursor molecule, cholecalciferol or vitamin D_3. A number of forms of vitamin D exist but D_3 is the form naturally present in animals and the form referred to in endocrinology studies. Vitamin D_3 is subjected to two further hydroxylations to form 25 hydroxy-vitamin D_3 ($25OHD_3$), which is a stable precursor form that is routinely measured to assess the status of vitamin D in humans. This hydroxylation occurs in the liver. A number of cytochrome P450 enzymes are responsible for this including *CYP*27A1, *CYP*2J2 and *CYP*3A4 but *CYP*2RA would appear to be principally responsible (Schuster, 1814). $25OHD_3$ is subsequently converted to the active hormone 1,25-dihydroxy vitamin D_3 ($1,25(OH)_2D_3$) by another cytochrome P450 enzyme, *CYP*27B1. This enzyme is strongly expressed in the distal tubules of the kidney, where its function is tightly governed by calcium, parathyroid hormone (PTH), and phosphate levels (Dusso et al., 2005). *CYP*27B1 is also expressed in other organs such

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as brain (Eyles et al., 2005), however in other sites its function is not regulated by calcium-related pathways. $1,25(OH)_2D_3$ is inactivated by a third cytochrome P450, *CYP*24A1, which is promptly upregulated in the presence of $1,25(OH)_2D_3$ – this enzyme is also present in brain (Dusso et al., 2005). The fact that the active hormone can be synthesized and eliminated in the brain suggests that vitamin D signaling may involved autocrine and paracrine pathways in this organ. These metabolic steps are outlined in Fig 1.

During the 1970s, a vitamin D-like species was found in chick brain after animals were dosed with vitamin D_3 with the unidentified compounds sharing chromatographic similarity with $25OHD_3$ and $1,25(OH)_2D_3$ (Taylor, 1977). Like other small ligands that bind to nuclear receptors (e.g. vitamin A), vitamin D metabolites have since been shown to cross the blood brain barrier (Gascon-Barre and Huet, 1983; Pardridge et al., 1985). Being a steroid, it was initially assumed the brain availability of $25OHD_3$ would be high. However, penetration of the blood brain barrier for these ligands is lower than that for other hormones involved in brain development such as the sex steroids (Pardridge et al., 1985).

The early work of Stumpf and colleagues provided consistent evidence that vitamin D species could be found in the brain. Using radiolabeled $1,25(OH)_2D_3$ and autoradiographic detection methods, these workers showed that not only could the active hormone partition into the brain from the periphery but there also appeared to be some regionally discrete localization possibly indicating some receptor mediated binding (Bidmon et al., 1991; Musiol et al., 1992; Stumpf and O'Brien, 1987b; Stumpf et al., 1982; Walters et al., 1992). The three aforementioned major metabolites of vitamin D, $25OHD_3$, $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$, have also been reported in human cerebrospinal fluid prompting the question that they may be formed locally (Balabanova et al., 1984).

2.1. Evidence for Vitamin D metabolism and catabolism in brain

To the best of our knowledge neither vitamin D_3 nor the enzymes responsible for its initial hydroxylation have been reported in brain. However, as previously mentioned, both *CYP*27B1 and *CYP*24A1 have. *CYP*27B1 is prominent in kidney but its immunohistochemical presence in the cerebellar Purkinje cells as well as within neuronal cells of the cerebral cortex have also been described (Zehnder et al., 2001). *CYP*27B1 has also been detected in foetal human brain (Fu et al., 1997), as well as within glial cells in culture, which were functionally active being able to catalyse the conversion of $25OHD_3$ to $1,25(OH)_2D_3$ (Neveu et al., 1994c). The distribution of *CYP*27B1 across human brain regions was described in detail in 2005 (Eyles et al., 2005). Strongest immunohistochemical responses were observed in the supraoptic and paraventricular nuclei within the hypothalamus and the substantia nigra. Confocal microscopy was used in this study to confirm the cytosolic location of this enzyme and co-staining with neuron and glial specific markers confirmed this enzyme was present in both cell types.

*CYP*24A1 mRNA has not yet been reported in normal brain tissue. However, it has been identified in both C6 glioma and rat primary glial cells in culture. The expression of *CYP*24A1 mRNA was not detected *de novo* in either cell system but *CYP*24A1 mRNA was induced in a dose-dependent manner upon the addition of $1,25(OH)_2D_3$ to the culture medium (Naveilhan et al., 1993). Therefore, in summary the potential for both the formation of the active hormone and its elimination exist in brain. These findings raise important questions regarding the distribution of this vitamin in the brain see Box 1.

Box 1. Questions regarding the distribution of vitamin D species in the brain.

- Although vitamin D ligands would appear to be present in brain the evidence still remains at best, indirect. Therefore, if vitamin D signaling is to be directly relevant for this organ it is a matter of priority to directly establish which metabolites are present, their individual concentrations and distributions within mammalian brain. Once established a host of secondary questions emerge.
- The concentrations of the three afore-mentioned vitamin D species in human CSF are lower than those found in corresponding sera but nevertheless are tightly correlated (Balabanova et al., 1984). But it is unknown how vitamin D enters the brain. Current dogma suggests that the free fraction of $25OHD_3$ and $1,25OHD_3$ enter cells via energy-independent passive mechanisms (the molecules are small and lipophilic). However, it remains to be determined if energy-dependent mechanisms also transport protein bound vitamin D through the blood-brain barrier and into target cells in the brain. Megalin and cubulin are multipurpose transport proteins that play an important protein-bound vitamin D transport in the distal renal tubules (Kozyraki and Gofflot, 2007). These systems also are critical for early brain development (Wicher and Aldskogius, 2008).
- Are vitamin D concentrations higher or lower than in classic target tissues for this steroid such as gut or kidney? Are vitamin D levels higher or lower in the developing brain. Do vitamin D concentrations fluctuate across developmental stages?
- Is the brain ''protected'' compared with other organs from vitamin D deficiency? There is already some evidence to support such a suggestion. It is well-known that the VDR is auto-regulated by its ligand $1.25(OH)_2D_3$ and in situations of deficiency its expression is down-regulated. However VDR protein in developing brains is not affected by severe vitamin D deficiency (Eyles et al., 2003). Additionally dietary vitamin D deficiency induces a significant increase in expression of the vitamin D regulated intracellular calcium binding protein Calbindin in renal tissue but again the brain is not affected (Clemens et al., 1988b; Huang and Christakos, 1988). Again the situation in the developing brain is unknown?
- Are vitamin D related pathways more prominent concentrated in any particular brain region given the variable distribution for its receptor in this organ (Eyles et al., 2005)?
- Is vitamin D present in neurons and glia? If so what is its intracellular distribution, especially in situations of diminished availability?
- To a large extent these questions have remained unaddressed due to the available technology. Traditional bioassays are subject to certain tissue extraction incompatibilities, require far more sample and are relatively insensitive. With the emergence of the new generation of highly selective mass spectrometry assays this may now allow us to address these quantitative questions.

3. The vitamin D receptor (VDR) in developing and mature brain

3.1. Vitamin D is a neuroactive steroid

Vitamin D is part of a large family of ligands that signal via nuclear receptors – this includes testosterone, estrogen, corticoste-