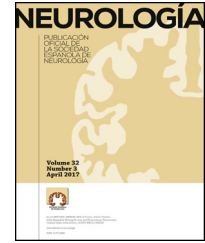




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REVIEW ARTICLE

Vitamin D and remyelination in multiple sclerosis[☆]

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Abstract

Introduction: Several studies have found an association between multiple sclerosis and vitamin D (VD) deficiency, which suggests that VD may play a role in the immune response. However, few studies have addressed its role in remyelination.

Development: The VD receptor and the enzymes transforming VD into metabolites which activate the VD receptor are expressed in central nervous system (CNS) cells, which suggests a potential effect of VD on the CNS. Both in vitro and animal model studies have shown that VD may play a role in myelination by acting on factors that influence the microenvironment which promotes both proliferation and differentiation of neural stem cells into oligodendrocyte progenitor cells and oligodendrocytes. It remains unknown whether the mechanisms of internalisation of VD in the CNS are synergistic with or antagonistic to the mechanisms that facilitate the entry of VD metabolites into immune cells.

Conclusions: VD seems to play a role in the CNS and our hypothesis is that VD is involved in remyelination. Understanding the basic mechanisms of VD in myelination is necessary to manage multiple sclerosis patients with VD deficiency.

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PALABRAS CLAVE

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Vitamina D;
Receptor de Vitamina D;
Oligodendrocito;
Células precursoras de oligodendrocitos;
Esclerosis múltiple

Vitamina D y remielinización en la esclerosis múltiple**Resumen**

Introducción: Diferentes estudios han asociado la deficiencia en VD a la esclerosis múltiple lo que ha llevado a plantear su potencial papel en la respuesta inmune. Existe menos información sobre su papel en la remielinización.

Desarrollo: En las células del SNC existe el receptor VD así como las enzimas que transforman los metabolitos de la VD para poder activar este receptor, lo que plantea un potencial efecto de la VD. Tanto estudios in vitro como modelos animales han mostrado que la VD puede tener un papel sobre la mielinización actuando en factores que influyen en el microambiente que favorece la mielinización como en la proliferación y diferenciación tanto de las células madre neuronales en células precursoras de oligodendrocitos como en éstas en oligodendrocitos. No se conoce si los mecanismos de internalización de la VD en el SNC son sinérgicos o antagónicos a los que permiten la entrada de los metabolitos de la VD en las células inmunes.

Conclusiones: La VD debe tener un papel en el SNC y se puede hipotetizar si actúa en la remielinización. El conocimiento de los mecanismos básicos de los efectos de la VD en la mielinización parece necesario para poder aconsejar a los pacientes con esclerosis múltiple ante deficiencias de VD en la clínica.

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Introduction

Vitamin D (VD) is a group of hormones including vitamin D₂, or ergocalciferol, and vitamin D₃, or cholecalciferol. VD is acquired mainly from the diet and through exposure to sunlight. Several analytical epidemiological studies have suggested an association between VD deficiency and multiple sclerosis (MS).^{1–6} The biological basis of this association is unknown. Hypotheses include causal mechanisms, the interaction between genetic and environmental factors, or simply the combination of multiple environmental factors. Research on the topic has focused on the role of VD and its metabolites in experimental allergic encephalomyelitis (EAE) in in vitro and animal studies.^{7,8} Most researchers have analysed the association between VD and the risk of inflammation, while others have evaluated the role of VD in myelination and remyelination.⁹ The present review addresses the latter topic.

Vitamin D deficiency

VD levels are usually determined by measuring plasma 25-hydroxyvitamin D (25[OH]D) concentration, due to the long half-life of this metabolite (15–35 days). However, the suitability of using total 25(OH)D levels to determine VD sufficiency has been questioned in recent years: detractors propose determining levels of the active forms or the free fraction, given that protein-bound metabolites may be inactive and may therefore not constitute adequate markers.¹⁰ Circulating VD may be either free or bound to albumin or to vitamin D-binding protein (DBP). The free fraction of VD constitutes a very small proportion of circulating metabolites (below 1%) and may have a different biological function from that of the protein-bound fraction.^{11,12}

The concepts of VD sufficiency or deficiency are therefore difficult to define. Furthermore, the plasma concentration of circulating 25(OH)D varies depending on the patient's health status and certain genetic factors.¹³ The issue is further complicated by the fact that the free fraction of circulating VD is usually calculated through mathematical estimation rather than by direct measurement¹⁴; these 2 methods deliver considerably different results. The terminology used in the literature is also potentially confusing. The term "bioavailable" 25(OH)D is used for circulating 25(OH)D which is not bound to DBP, that is the free and albumin-bound fractions; this represents approximately 10% of total circulating 25(OH)D; this should not be mistaken for free 25(OH)D. These methodological aspects make it difficult to determine the role of VD deficiency as a risk factor for MS in general, and even more difficult in individual patients.

Plasma transport of vitamin D and transformation into active metabolites

As mentioned previously, VD is transported to cells and tissues via transport proteins (DBP and albumin). DBP is produced in the liver. In addition to transporting VD, this protein promotes the conversion of the prohormone 25(OH)D, an inactive circulating metabolite, into the active metabolite, 1,25-dihydroxyvitamin D (1,25[OH]₂D). This requires the action of 25-hydroxyvitamin D-1 α -hydroxylase, also known as cytochrome p450 27B1 (CYP27B1) or simply 1- α -hydroxylase, which is encoded by the *CYP27B1* gene. This enzyme is expressed in renal tubule cells and other types of cells, such as immune and central nervous system (CNS) cells. It catalyses the conversion of 25(OH)D to 1,25(OH)₂D. This metabolite acts on the VD receptor (VDR), the nuclear receptor for 1,25(OH)₂D. As mentioned previously, 99% of

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