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REVIEW

A review of the anterior visual pathway model and the study of vitamin D in demyelinating disease

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Abstract
In recent years, theories about the anti-inflammatory properties of vitamin D in demyelinating disease have been well substantiated by human studies examining relapse reduction, MRI lesion activity and risk of MS conversion. However, the evidence that vitamin D may protect against neurodegeneration has not been established as of yet, and comes with the challenges of a manageable target over a manageable time period. Such challenges might be overcome by the anterior visual pathway (AVP) model of the central nervous system, which allows the non-invasive study (e.g. imaging, electrophysiology and clinical) of form and function within a much shorter time frame than pure clinical activity. This review outlines the state of current knowledge about vitamin D in demyelinating disease, and highlights the potential utility of using the AVP to study its neuroprotective effects.

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1. Introduction

Vitamin D insufficiency is now an accepted risk factor for the development of multiple sclerosis (MS). Evidence that latitude and sun exposure are correlated to the geography and prevalence of MS has been accumulating for decades, with more recent evidence that vitamin D plays a direct role in this relationship (Ulett, 1948; Acheson et al., 1960; van der Mei et al., 2001, 2003; Islam et al., 2007; Munger et al. 2006; Soilu-Hanninen et al., 2005; Schwalfenberg et al., 2010). As one would suspect, vitamin D deficiency is a common finding in patients with MS. In fact, both vitamin D deficiency and MS have extremely high prevalence rates in North America, particularly in the northern-most regions (Schwalfenberg et al., 2010; Hanley and Davison, 2005). In recent years, there has been an attempt to intervene in those patients who are vitamin D deficient in an effort to positively impact demyelinating disease outcomes. There are even large-scale efforts underway to improve vitamin D status at a population level in the hopes of reducing the development of the disease at all. Immunological studies have given us a window into the possible mechanisms of this agent, once thought solely to impact calcium homeostasis. The evidence that vitamin D is an effector in the inflammatory cascade is quite robust, but is this enough to truly avoid MS development, and in those with the disease, to avoid the disability that often comes after a relapsing course?

While the reduction and attenuation of relapses has some impact on disability, it is the progressive insidious changes over time, due to axonal and neuronal death, that lead to the potentially life-altering disability MS patients fear and often must face. Studying the impact of putative agents on disability, typically defined by surrogate markers such as changes in the expanded disability status scale (EDSS) score and MRI T1 "black holes" and atrophy, is a challenge. Clinical and MRI metrics of progression require many years to assess, and trials typically do not continue for the time it takes to assess these outcomes properly. Extension trials are a way to try and obtain more long-term results, but patient withdrawal becomes a major source of bias. What would be most useful would be an early measure of neurodegeneration that one could target, and as we learn more about MS pathology and imaging, early degeneration is in fact happening.

The intention of this review paper is not to provide an exhaustive description of all evidence for the role of vitamin D in the risk of demyelinating disease, but rather, to show how the anterior visual pathway can assist in taking us from proof of the anti-inflammatory properties of vitamin D to evidence of impact on neuroprotection and neurodegeneration. That being said, a little background of the role of vitamin D in demyelinating disease is in order.

2. A review of vitamin D in multiple sclerosis

Several recent studies have found clinical evidence to further support the epidemiological, genetic and immunological relationships between vitamin D and MS. In a study of children with a first demyelinating event or confirmed MS, serum 25(OH)D was the primary predictor of subsequent relapse rate after controlling for season and other potential covariates, with every 10 ng/mL increase associated with a 24% decrease in relapse rate (Mowry et al., 2010). Soilu-Hanninen et al. (2008) studied the relationship between markers of vitamin D status and relapse events in MS patients, finding that 25(OH)D serum levels were lower and intact PTH levels were higher during MS relapses versus remission. Vitamin D insufficiency was most common in progressive versus relapsing MS patients, and associated with a greater risk of relapse and higher EDSS in a cross-sectional study, although potential confounders may have contributed to these results (Woolmore et al., 2007). Studies in individuals with demyelinating disease have inversely correlated serum 25(OH)D values with relapse rates (Soilu-Hanninen et al., 2008, 2005; Smolders et al., 2008). In adults, each 10 nmol/L increase in 25(OH)D correlated with a hazard ratio of 0.88 for subsequent relapse (Simpson et al., 2010), and each 25 nmol/L increase in 25(OH)D with a 34% decrease in relapse rate in children (Mowry et al., 2010). Our own research in treatment with high-dose vitamin D suggested high-dose vitamin D (an escalating dosing scale up to 40,000 IU/day and a mean of roughly 14,000/day) use was associated with a reduced relapse rate and T-cell proliferation versus those on a mean dose of vitamin D in keeping with current recommendations in the general public in Canada (Burton et al., 2010; Health Canada). Woolmore et al. (2007) used validated questionnaires to study skin type and UVR in 448 Caucasians with MS, looking at the relationship between skin/UVR variables and MS disability measures. In female patients, sun sensitivity skin types (i.e. people with greater skin melanin content are less "sun sensitive") were associated with reduced risk of higher EDSS scores while UVR exposure was not. Further support for the role of vitamin D in MS activity is the association between vitamin D status, season, and the number of gadolinium (Gd) enhancing lesions on MRI in MS patients, a commonly employed surrogate marker of disease activity and treatment response. In a study of 469 patients,