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REVIEW

Impact of Dietary Antigens on Multiple Sclerosis

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Abstract

Background: *Current research provides evidence to support the theory that a diet restricting foods considered to have high antigenic potential might be beneficial in the treatment of multiple sclerosis (MS). Grains, legumes and dairy foods may have high antigenic potential and could be contributing environmental factors in genetically susceptible people.*

Design: *Literature review.*

Methods: *An Internet search of the National Library of Medicine and discussions with colleagues.*

Results: *One of the largest challenges that MS researchers face today is to find treatments that have positive clinical effects and yet are non-toxic. A host of epidemiological, animal and clinical data support the theory that the manipulation of dietary factors may possess potential for a positive effect upon the progression of MS. A variety of data indicate that food proteins and lectins from dairy, gluten, and legumes found in a Neolithic and in a modern diet, can be involved in the activation and expansion of autoreactive T cells by several mechanisms. These mechanisms vary from direct activation of T cells and immune components, to indirect activation by increasing intestinal permeability (leaky gut syndrome), peripheral antigenic stimulation, and the propensity for molecular mimicry. In particular, a milk protein (butyrophilin) has now been identified that may be triggering MS due to cross-reactivity, or molecular mimicry, with a myelin protein. Additionally, serum vitamin D levels, which were much higher on average in our Paleolithic ancestors, are observationally correlated to a reduction in MS lesion activity and may play an important role in the treatment of MS. The administration of vitamin D to animals has resulted in complete regression of the animal model of the disease. A protein in milk (bovine serum albumin) has molecular mimicry with the vitamin D-binding protein, and may interfere with vitamin D absorption.*

Conclusion: *It is theorized that incorporation of a diet that eliminates suspicious dietary elements may hold the potential to reduce the antigenic stimulus (both pathogenic and dietary) and possibly result in a diminution of disease symptoms in certain MS patients. Also, it is proposed that addition of vitamin D to the diet warrants further study to determine its efficacy in the treatment of MS.*

Keywords: dietary antigens, multiple sclerosis, vitamin D, lectins, leaky gut, molecular mimicry.

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INTRODUCTION

Nutrition

Numerous diets have been proposed to be of benefit for multiple sclerosis (MS) [1], but none of these has been rigorously tested under clinical conditions and, more importantly, none has been supported by an underlying immunological basis. However, there is substantial evidence that indicates a diet regime free of antigenic stimulus may be of benefit in modulating some autoimmune diseases, including MS, by its positive interaction with the immune system [2].

Viral Antigens and Molecular Mimicry

Pathogenic organisms, including bacteria and viruses, have long been suspected to be involved in the development of autoimmune disease (including MS). Over the past decade, evidence has increasingly suggested that these organisms may elicit certain types of autoimmune disease in genetically susceptible individuals via the process of molecular mimicry [3–6]. Wucherpfennig [5] demonstrated that certain viral peptides, including Epstein–Barr virus (EBV), contain an immunodominant sequence of amino acids that not only activates the immune system, but can result in a cross-reactive immune response to myelin basic protein (MBP), which contains similar amino acid sequences.

Dietary Antigens and Molecular Mimicry

There is also an emerging body of evidence to indicate that dietary antigens may also serve as an antigenic stimulus in the etiology of autoimmune disease, eliciting a similar cross-reactive immune response with human tissue [7–10]. In the case of MS, myelin oligodendrocyte glycoprotein (MOG) is a myelin autoantigen that is a major target for the autoimmune response in MS and in its animal model experimental autoimmune encephalomyelitis (EAU). Stefferl *et al*. [11] demonstrated that in EAU an encephalitogenic T-cell response to MOG could either be induced or alternatively suppressed by butyrophilin, a milk protein. The researchers also demonstrated that the pathology was mediated by a major histocompatibility complex (MHC) class II-restricted T-cell response that cross-reacts with the MOG peptide sequence 76–87 (IGEGKVALRIQN). Furthermore, there is compelling evidence from both human and animal trials to indicate that dietary glycoproteins (lectins) found in common food stuffs, such as grains and legumes, alter intestinal physiology and allow luminal pathogenic antigens access to peripheral tissues [12–14].

EPIDEMIOLOGICAL DATA

A notable aspect of MS is the distinct variations in disease prevalence throughout the world [15]. Genetic susceptibility to MS is well established [16–18]; however, it would appear that human leukocyte antigen (HLA) haplotype contributes only modestly to the overall susceptibility [19, 20], suggesting that the interaction of environmental factors plays a major role in the etiology of MS.

One obvious trend is the increase in MS prevalence in more temperate regions, the so-called north–south gradient [21]. There are also smaller scale trends that occur within the same general latitudinal zone. For example, in Canada, MS prevalence in the outports of Newfoundland ($\sim$25) is an order of magnitude less than in the rural areas of Alberta ($\sim$220), even though the genetics and latitude are essentially the same [22, 23]. These variations in MS prevalence in areas of genetic and geographical similarity are possibly explained by differences in dietary habits, with an increased consumption of dairy, gluten

and saturated fat correlating with areas of higher MS prevalence [24–27]. Fish consumption, on the other hand, is associated with an increased intake of vitamin D. Additionally, fish oil has demonstrated an effect of decreasing the quantity and intensity of the expression of class II MHC molecules on monocytes [28]. The Newfoundland/Alberta difference in prevalence demonstrates the contrast of this dietary variance: the fishing and vegetable patch food sources of the Newfoundland outports as opposed to the cattle ranches and wheat farms of Alberta. Additionally, in Norway, MS prevalence is higher inland and lower on the coast, where fish sources provide omega 3 fatty acids and vitamin D [29]. Thus, the epidemiological data is compatible with the hypothesis that Neolithic, agricultural foods may play a role in MS etiology, whereas a diet free of antigenic stimulus and replete in vitamin D may offer protective effects.

MS PATHOGENESIS

It has been postulated that MS is an autoimmune disease caused by activated T helper cells that are reactive with one or more proteins in myelin in the central nervous system (CNS). Such potentially autoantigenic proteins include MBP, protolipid protein, MOG, myelin associated glycoprotein, heat shock proteins and alpha-beta crystallin [30]. Furthermore, it is most often interpreted that the autoreactive T cells are activated in the periphery by foreign antigens [30, 31]. The two favored mechanisms for such peripheral activation of myelin-sensitive T cells are by superantigens and by molecular mimicry [31]. Little evidence has been offered for the role of superantigens; however, numerous studies have provided supporting evidence that molecular mimicry is an effective mechanism for precipitating an autoimmune response [3–6]. For example, the Rand *et al.* study [32] identified a specific IgG antibody that occurred in the cerebrospinal fluid of MS patients and which was cross-reactive for both a common infectious agent (EBV) and a CNS autoantigen (alpha-beta crystallin). It still remains to be determined exactly which foreign proteins may be mimicking CNS proteins and how and when such foreign proteins engage the immune system such that mimicking reactions may occur.

Current data indicate that numerous common viruses and bacteria have the potential to mimic the immunodominant epitope of MBP, which many favor as the most likely target of autoaggressive T cells [5, 6]. In the case of butyrophilin, the milk protein, Stefferl *et al.* [11] believe that their study results identify a mechanism by which the consumption of milk products may modulate the pathogenic autoimmune response to MOG. Similar studies have not been performed for the other common myelin proteins in the CNS and thus many more potential mimics may exist.

DIETARY ACTIVATION OF T CELLS

If the hypothesis that agricultural food proteins are involved in MS pathogenesis is to be demonstrated, it must be shown that such proteins can play one or more roles in promoting and/or participating in immunological reactions, such as molecular mimicry. A variety of data indicate that the food proteins from dairy, gluten, yeast and legumes can indeed be involved in the activation and expansion of autoreactive T cells in at least four ways:

1. Agricultural dietary staples, such as cereal grains and legumes, contain glycoproteins called lectins [e.g. wheat germ agglutinin (WGA), phytohemagglutinin (PHA)]. These lectins can promote an overgrowth of gut bacteria such as *Escherichia coli* and *Klebsiella*, which are potential mimics that can initiate an autoimmune reaction against human tissue [12]. Such an overgrowth of gut bacteria increases the number of potential mimics and the probability of autoimmune involvement.
2. The lectins themselves can also result in substantially increased intestinal permeability

[13, 14]. Such an increase in intestinal permeability, known to be exhibited by MS patients [33], results in the translocation of pathogenic viruses and bacteria to the periphery [34], where they can participate in molecular mimicry and other immune responses. Such mimicry reactions may involve three-way cross-reactions between viral antigens, myelin antigens and HLA antigens, similar to that hypothesized for rheumatoid arthritis [35, 36].

3. Additionally, dietary lectins from grains and legumes that escape into the periphery have the ability to interact with components of the immune system in a manner that can promote autoimmune reactions. Both WGA and PHA have been shown to rapidly cross the gastrointestinal barrier in a number of animal experiments [37, 38]. PHA has been demonstrated to promote the expansion of activated T-cell lines [39], to elevate intracellular adhesion molecule (ICAM) expression [40, 41] and to stimulate the production of pro-inflammatory cytokines such as interleukin-1 and tumor necrosis factor alpha [42–44]. All of these actions would promote previously initiated autoimmune reactions.
4. Finally, dietary antigens have the potential to participate in the molecular mimicry of tissue autoantigens and infectious agents. Currently, aside from the work carried out by Stefferl *et al.* [11] associating a milk protein with a myelin autoantigen, there has been no investigation of the molecular similarities between peptides derived from dairy, gluten and legumes with myelin protein epitopes. However, similarities between these food peptides and other autoantigens involved in rheumatoid arthritis, uveitis and type 1 diabetes [7–9] as well as infectious agents (EBV) [7] have been established. Additionally, it has also been established that the bovine serum albumin (BSA) protein in milk evokes molecular mimicry with vitamin D binding protein and complement protein C1q (C1q combines with antigen–antibody complexes and causes the lysis of cells and the destruction of bacteria/foreign antigens), potentially having an adverse effect on immune regulation [45].

VITAMIN D

Vitamin D as an Immune Regulator

Vitamin D has been proposed as a possible environmental regulator of the immune system that could potentially inhibit MS [46]. As early as 1974, Goldberg noted the high prevalence of MS in areas that received a low amount of sunlight. This theory incorporates the idea of sunlight catalyzing the production of active vitamin D3 [unless otherwise specified, vitamin D will herein refer to the biologically active form of vitamin D, 1alpha,25-dihydroxyvitamin D3 (1,25(OH)2D3)], and although the evidence is circumstantial, it is compelling, and could explain the influence of latitude on the prevalence of MS. Vitamin D production from the sun would diminish as the distance from the equator increases. This would explain why in Switzerland the MS prevalence is higher at sea level and lower in the elevation of the mountains, where sun exposure is greater [46].

It has been pointed out that the milk protein BSA affects the immune system by mimicking complement C1q; BSA also mimics vitamin D-binding protein, possibly having implications for reducing serum levels of the vitamin, which in turn would also affect the immune status [45]. Our Paleolithic ancestors had higher vitamin D levels, probably due to increased sun exposure, and also possibly at least in part due to avoidance of milk, which contains the BSA that mimics vitamin D-binding protein, and also possibly due in part to the avoidance of phytate-containing grains, which bind nutrients including vitamin D [47]. Vieth [48] estimated that our ancestors had large intakes of vitamin D, with a naked human in Africa getting at least 10,000 IU a day. Nieves *et al.* [49] studied 80 MS patients and reported that they exhibited low mean levels of 25(OH)D (calcidiol), with a quarter of the subjects presenting with frank vitamin D deficiency ($<25\,\mathrm{nmol\,l^{-1}}$). It is hypothesized that

MS patients spend less time outdoors and receive less sun exposure; it is a known fact that corticosteroids, which are used as a treatment for MS, deplete vitamin D.

To investigate a correlation between lesion activity and fluctuations in vitamin D intake, Embry *et al.* [50] compared published monthly 25(OH)D levels in 415 people, aged 50–80 years from southern Germany, with the data from Auer *et al.* [51]. Auer's study demonstrated a strong, near sinusoidal variation in the number of active lesions in 53 MS patients. After taking into consideration a 2 month lag period, which was a reasonable time period to allow for the efficacy of a therapeutic effect of vitamin D, there was a close correspondence, with high levels of 25(OH)D correlating with low levels of lesion activity, and vice versa [50].

Vitamin D as a Disease Modulator

Strong evidence in the animal model demonstrates that: (1) vitamin D can completely prevent the development of EAU; (2) vitamin D can prevent the progression of EAE when administered at the appearance of the first disability symptoms; (3) the withdrawal of vitamin D supplementation results in the resumption of the progression of EAE; and (4) a deficiency of vitamin D leads to an increased susceptibility to EAE [52, 53]. Vitamin D has also successfully protected against the animal models of other diseases, including rheumatoid arthritis [54], lupus [55], and type 1 diabetes [56]. Some researchers have offered the stimulation of inflammatory cell apoptosis as a mechanism whereby vitamin D reverses EAE [57].

Mechanisms of Immune Regulation by Vitamin D

There are many aspects of vitamin D that are thought to positively affect immune status. Although it is known that the primary function of vitamin D is the regulation of calcium and phosphorus metabolism, many other characteristics for the vitamin have come to light in recent years, including the inhibition of cancer cell proliferation [58]. Of these characteristics, one of the most important functions is inducing nerve growth factor [59]. Other important functions relating to autoimmune disease are the inhibition of memory T cells [60], the inhibition of nitric oxide (a factor in demyelination) [61], the down-regulation of antigen expression by antigen-presenting cells such as macrophages [62], and the inhibition of T-cell proliferation [63]. Mechanistically, the data point to a role for vitamin D in the development of self-tolerance. 'The vitamin D hormone (1,25-dihydroxy vitamin D(3)) regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. The net result is a decrease in the Th1-driven autoimmune response and decreased severity of symptoms' [64]. Van Halteren *et al.* [65] reported that dendritic cells preconditioned with vitamin D may interfere with ongoing autoimmunity *in vivo* without affecting T cells with other specificities.

The Role of Fat in Immune Regulation

The evidence suggests that food-derived peptides, in addition to the viral/bacterial peptides, also have the potential to influence autoimmune reactions, and possibly even mimic myelin protein epitopes. The other aspect of diet that can affect immune reactions is the type and amount of fat [66–68]. Notably, omega 3 essential fatty acids (EFAs), which are an important component of nutritional balance [69], have been demonstrated to down-regulate immune responses [68, 70]. As mentioned previously, Hughes *et al.* [28] demonstrated that fish oil, which is high in omega 3 EFAs, has the ability to specifically down-regulate the quantity and intensity of MHC class II molecule expression.

Thus, dietary proteins from agricultural foods, such as dairy, yeast, gluten and legumes,

can theoretically play a significant role in the currently held model of MS pathogenesis. Furthermore, the replacement of omega 3 EFAs by agricultural-derived saturated fats and omega 6 EFAs may play a subsidiary role. As discussed by Cordain [47], it would appear that proteins from various foods (e.g. gluten, dairy) result in autoimmune reactions mainly by increasing intestinal permeability and by mimicking infectious and self-antigens. Such food-driven autoimmune reactions, although of relatively low magnitude in comparison with infection-driven autoimmune reactions, occur almost on a daily basis and thus have a significant cumulative effect. A diet that eliminates suspected dietary antigens and lectins and focuses on nutrient density-rich foods, such as fresh fruits, vegetables, lean meats and fish (which also provide vitamin D), may provide a safe, effective answer for an MS treatment protocol. Clinical trials, however, need to be conducted to prove the theory that a diet low in antigenic stimuli provides protection against the neurological disease of MS.

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