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Review

New hypotheses on sunlight and the geographic variability of multiple sclerosis prevalence

Bijal K. Mehta

Department of Neurology, Jacobs Neurological Institute, State University of New York-Buffalo, 100 High Street, Buffalo, NY 14203, USA

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ABSTRACT

Multiple sclerosis is an autoimmune demyelinating disorder of the central nervous system. Its etiology continues to be elucidated. The debate about the environmental impact on the disease etiology and progression has focused on sun light exposure in the recent past, but mainly as it applies to vitamin D and its derivatives.

This paper will discuss how sunlight stimulus may effect neuronal and microglial antigenic presentation based on sunlight-dependent neuronal activity, as well as how sunlight may alter the amount of vitamin A and melatonin levels during immune development in the central nervous system. Changes in the number of antigens presented to lymphocytes by antigen-presenting cells for self-selective removal during immune development could therefore alter the number of circulating self-recognizing B and T-lymphocytes. This situation would increase susceptibility to a significantly greater number of self-antigens, and lead to autoimmune disorders such as multiple sclerosis.

Contents

1. Introduction

Multiple sclerosis is a progressive demyelinating central nervous system disorder [1]. The etiology, or etiologies, of the various forms of MS remain elusive. The classical diagnosis of the disease is made both clinically and radiographically based on CNS lesions resulting in symptoms that are "separated by space and time," as outlined by the diagnostic McDonald Criteria [2]. Based on this spatial and temporal disassociation, MS is divided into 6 main groups: benign, relapsing–remitting, secondarily progressive, primary progressive, progressive relapsing, or malignant types of MS [3]. Whether each is a distinct form of the disease or they are manifestations of a single disease etiology, is still not clear and is under continued investigation. However, a suggested underlying commonality has been the concept of cell-mediated autoimmune demyelination, presumably precipitated by an unknown antigen or group of antigens, and perpetuated by the subsequent immune response [4].

E-mail address: bijal@yahoo.com.

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2. Autoimmunity of multiple sclerosis

The autoimmune response in MS is thought to involve T-cells, B cells, microglia, and cytokine-mediated effects, following antigen presentation by these antigen-presenting cells [1]. What these cells are reacting to remains under investigation. However, the concept of an antigenic "trigger" is still a predominant theory [5]. Although several possible antigens have been implicated in the literature, including myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein, expression and presentation of the antigens continue to be investigated with regard to the etiology of MS [6,7]. The idea that there may be many or multiple variant antigenic agents as well as variable expression of antigens could be a factor in the presentation and diagnosis of the various types of MS [7].

However, at the center of these proposed mechanisms is a disease with an unknown sentinel etiologic event. Whether the antigenic "trigger" is in fact a nascent protein or is altered in some way to make it a more foreign target is also a continued topic of the investigative debate, especially as it pertains to the environmental influence on the etiology of the disease [8]. One environmental factor supposed to have an influence on the etiology of MS is latitude, based upon a higher prevalence of MS equatorially versus at higher latitudes [9]. Prior theories have implicated sunlight exposure as a possible reason for these differences [10–13].

3. Previous theories of sunlight and multiple sclerosis

Prior research into the possible impact of sunlight exposure on multiple sclerosis has focused on sunlight's ultraviolet radiation, its ability to influence melatonin, and its association with vitamin D [10,20–22]. Previous hypotheses have implicated UV radiation in altering both antigens and antigen presentation by altering the genome or biochemistry involved in antigen presentation [10,14–19]. This environmental insult may lead to an alteration in the amino acid composition of antigens and receptors involved in antigen presentation, thus changing the epitope of self-antigens or altering the process of protein trafficking within and onto the cell surface [10]. An alteration in the epitopes may incite an immune response, as these antigens are no longer the original "self-antigens," but altered versions [10]. The immune system, being naive to these "new" antigens, would initiate the immune cascade to eliminate them [10]. However, this would result in autoimmunity against CNS epitopes only if the mutated antigens shared similar epitopes with proteins in the CNS. Alternatively, UV radiation may change immune cell populations, such as T-cells and natural killer cells, in addition to affecting the levels of certain cytokines and immune mediators [14–19]. MS mortality has been linked to decreased sun exposure [23].

Sunlight's association with MS has recently focused on vitamin D production, another UV mediated phenomenon. Previous research has proposed that the circulating levels of vitamin D and its derivatives alter MS pathophysiology in animal models [22]. Vitamin D derivatives have been shown to decrease the severity of the disease in Experimental Allergic Encephalomyelitis (EAE) animal models [24]. Vitamin D has also been shown to alter levels of cytokines that are involved in antigen presentation [25].

Human studies with vitamin D, its derivatives, and receptor agonists are ongoing. Preliminary results are showing findings similar, though not identical, to those seen in the EAE animal model [26]. Although EAE is an animal model for human MS, there are instances wherein studies on EAE mice do not translate to equal results in human studies [27,28]. Adequate vitamin D intake and subsequent normal levels may reduce the risk of developing MS [29,30]. Vitamin D levels early in life may even create a "protective" effect against developing MS, specifically in a susceptible pediatric population [31]. Variations in the vitamin D receptor may also affect multiple sclerosis pathogenesis, however, this data is mixed and may involve only certain polymorphisms of the vitamin D receptor [32–36]. Vitamin D levels at the time of diagnosis have coincided with disease severity and with changes in how intracellular contents are regulated via UV radiation-induced changes in both vitamin D processing and the altering of genes involved in antigen presentation [37]. T-cells specific to myelin basic protein are known to be inhibited by vitamin D [38]. An epidemiological study has linked disease severity as noted by Expanded Disability Status Score with vitamin D levels [39].

Recently, one study has shown that the expression of an MHC haplotype associated with MS, HLA-DRB1*1501 is regulated by vitamin D. They posulate that low vitamin D during immune development would result in less expression of this haplotype in the thymus and result in less "self-recognition" and subsequent removal of T-cells responsive to this haplotype. However, this postulate is counter to the notion that vitamin D is protective to MS patients, since treating these patients with vitamin D may result in more expression of this MS associated MHC and the T-cells would be responsive to these MHC surface molecules; resulting in lesion formation and possibly a clinical MS exacerbation [40].

Despite the fact that an adequate vitamin D level prevents disease onset in the EAE animal models and correlates with a lower risk of developing MS as well as possibly a lower relapse rate and lower disease progression in humans, the effect of vitamin D supplementation on disease severity and progression in MS in humans is not equally understood as with the EAE animal model, and remains under investigation [29,37,39,41–47]. Therefore, the vitamin D paradigm model is incomplete. Aspects of sunlight exposure may be overlooked. Three possible hypotheses as to how sunlight exposure may influence MS pathophysiology are discussed.

4. Action potential regulation of antigen presentation

Previous animal model studies show that the action potential activity itself can influence the level of antigen presentation by neurons, glia, and microglia [48–51]. Neurons that are able to fire action potentials have less MHC class I antigen presentation, except in a "hyperactive" pathologic state such as a seizure [49,50]. Microglia surrounded by actively firing neurons tend to have less antigen presentation [48]. Prior studies have not looked at the effects of visible light spectrum stimulation-induced action potentials along the optic pathways. These action potentials may influence antigen presentation on both neurons and microglia, especially during development of the nervous and immune systems [49,50]. Although the retina uses a center-surround, ON/OFF arrangement to detect light, it has been shown that optic nerve fibers have increased neuronal firing rates with greater levels of ambient brightness [52,53]. It has been suggested that the developments of the nervous and immune systems are co-dependent, particularly with MHC-based antigen recognition [50,54]. Therefore, decreased activity of action potentials by retinal and optic nerves may alter the antigens presented by the surround microglia during development of both the nervous and immune systems. Based on this variable expression, individuals whose neural development occurred in low sunlight exposure environments may have decreased neuronal firing and higher MHC class I expression by those neurons [49,50]. This situation may cause microglia to have higher expressions of type II MHC complexes in comparison to MHC class I, which tends to present antigens from within the cytosol [51,55]. MHC II molecules present material acquired from intracellular vesicles [51,55]. Microglia in the surrounding environment conceivably may be presenting "acquired" antigens of neuronal or glial origin via MHC class II molecules (and would be surrounded by MHC class I antigen presentation by neurons) since foreign antigens, such as from an infection, are less likely to be present. Self-antigens may be present in the surrounding milieu during the development of the nervous system, and more neurons may present self-antigens from the cytosol on MHC class I antigens (particularly the optic nerve and tracts,

as these areas would be less actively firing in a low sunlight environment). A misinterpretation of a self-antigen as a foreign one is more likely to occur in this situation. With continued exposure to a low sunlight environment, these individuals may continue to have higher MHC class II antigen presentation from microglia and higher MHC class I presentation of "foreign antigens" from neurons to antigen-presenting cells when some of those "foreign" antigens may in fact be "self-antigens." Neurons and microglia present these antigens via MHC complexes to Th1 type CD4 T-lymphocytes, which possess an array of pro-inflammatory cytokines, so as to initiate a subsequent destructive immune cascade in addition to activating B cells [55]. Microglia can also induce Th17 cells via IL-6 to secrete IL-17 so as to disrupt the blood–brain barrier and likely to activate macrophages [56] (Fig. 1).

This situation may also then create a reserve of memory "self-antigen recognizing" T-cells and B cells, which may become active upon an encounter with those self-antigens later in life. This development may lead to an eventual presentation of a self-antigen via MHC molecules, either directly or through antigen-presenting cells, to T and B lymphocytes that had not been removed during the early immune development self-selection process. The lymphocytes may then be activated. This encounter must occur after a series of events that allow those cells either to enter the CNS across the blood–brain barrier or to become active upon contact with antigen-presenting cells outside the CNS, such as the Th17 cells. These events are not uncommon in the pathophysiology of MS. Immune cell migration into the CNS across the blood–brain barrier is indeed the target of a newer class of MS therapeutics, and Th17 cells have been implicated in membrane disruption via secretion of IL-17 and IL-22 [56–58].

5. The suprachiasmatic nucleus and pineal gland control of thymocytes via melatonin

Other indirect actions of sunlight have been postulated and investigated. Sunlight is noted to have possible direct and indirect effects via melatonin [14,20,59], though how melatonin from sunlight acts on the immuno-physiology is not completely understood. Although variable sunlight exposure may lead to differences in neuronal firing patterns over the pathways to and from the suprachiasmatic nucleus, and may therefore involve the above hypothesis, another scenario may also be in action. The suprachiasmatic nucleus receives input from the retina regarding the level of sunlight, and it sends output to the pineal gland, which regulates melatonin release. Melatonin is also produced by the skin and crosses the blood brain barrier. However, the retina can also produce melatonin and may have a direct paracrine action on retinal ganglion cells. The highest melatonin levels are achieved during darkness, although this appears to be a graded response based on the level of ambient brightness. With changes in sunlight exposure, melatonin levels may vary within the circulation [60]. Higher levels of sunlight correlate with lower circulating levels of melatonin [60].

Variations in melatonin can alter MHC expression in the brains of experimental animal models [61]. Melatonin is also a possible ligand to the retinoic acid-related orphan receptor alpha (ROR-alpha). It may be the paracrine action of local melatonin produced by the retina which acts on the retinal ganglion cells and any local Th17 cells that may be present. While the ROR-alpha receptor is found in multiple immune cell lines, the ROR-alpha is also found in Th17 cells and may be central to its survival and IL-17 secretion. With more sunlight exposure, more melatonin can be produced and released locally onto retinal ganglion cells and Th17 cells, and its circulating levels can be increased. This would result in higher levels of Th17 cells and higher circulating levels of IL-17. Clinically and symptomatically, this would lead to greater lesion loads and volumes, as Th17 cells are involved in lesion formation and immune cell recruitment to lesion areas [56,58]. This scenario is counter-intuitive unless we take into account the effects of neuronal activity, which would modulate antigen expression as well as vitamin D, which prevents T-cell induction into Th17 cells. With normal neuronal activity and adequate vitamin D levels, melatonin's actions would be mute. However, in low light environments, where neuronal firing would be less (and therefore antigen presentation being proportionately greater) and vitamin D levels chronically low, this would lead to a greater immune mediated response and resultant lesion formation associated with multiple sclerosis.

6. Light-mediated vitamin A control of thymocytes

Vitamin A, or retinoic acid, has mounting evidence indicating its role in immune modulation of MS. Although vitamin A is a dietary supplement, studies have shown that the retina can influence its production and circulatory levels in animal models [62,63]. Variations in light exposure appear to modulate this function [62,63]. The role of light-mediated release of vitamin A has been previously hypothesized as playing a role in MS because of its role in leukotriene synthesis [64]. However, if light can alter vitamin A levels in the brain along the visual pathways, then the level of light-dependent vitamin A may play a role in the pathogenesis of multiple sclerosis through another possible pathway, since all-trans retinoic acids are inhibitory ligands to retinoid-related orphan receptor gamma (RORγ). RORγ is involved in Th17 cell survival and in modulation of this cell-specific immune response in the EAE animal models of MS [58]. Again, if this carries over to humans, sunlight exposure's effect on levels of vitamin A could therefore alter Th17 cell numbers and IL-17 levels in the brain and influence MS pathophysiology in humans.

The hypotheses presented, along with the compounded knowledge of vitamin D, present multiple sunlight-mediated effects that must act together in order to balance immune-destructive physiology within the brain. Should ambient light levels fall, stimulation of cells, vitamin A, and vitamin D levels drop. This situation may allow melatonin levels to rise and stay high. This would alter the number of T-cells types, including Th17 within the brain and thus alter MS pathophysiology.

7. Discussion

There are several known aspects of MS pathophysiology that correlate with these hypotheses. Firstly, the previously demonstrated variability of geographic distribution of MS may be due to differences in amounts sunlight exposure in early development, which lead to variations in CNS antigen presentation. Additionally, this hypothesis is congruent with prior studies showing that an individual who emigrates from northern latitudes to more southern areas (subsequent to onset of puberty) has a higher risk of MS, since his/her immune system's maturation of self-selective lymphocytes has already occurred. Individuals who move from higher latitudes, where sunlight exposure may not be as great, to areas closer to the equator will take with them their population-based risk of MS if they move after puberty [9]. This finding is consistent with our hypothesis; these individuals' immune systems have completed development without complete removal of self-selective lymphocytes and would already have circulating self-reactive lymphocytes upon moving to the lower latitude.

In contrast, individuals whose neural development occurred in high sunlight exposure environments would have increasing neuronal firing, more local release of vitamin A and lower melatonin. This situation would lead to less MHC class II self-antigen presentation by surrounding microglia [48]. Therefore, during development, lymphocytes in lymphoid organs would be less likely to identify self-antigens via MHC class II as "foreign." This may lead to a higher proportion of MHC class I antigen-presentation, and would provide the developing lymphoid organs and immune system with a proportionately higher

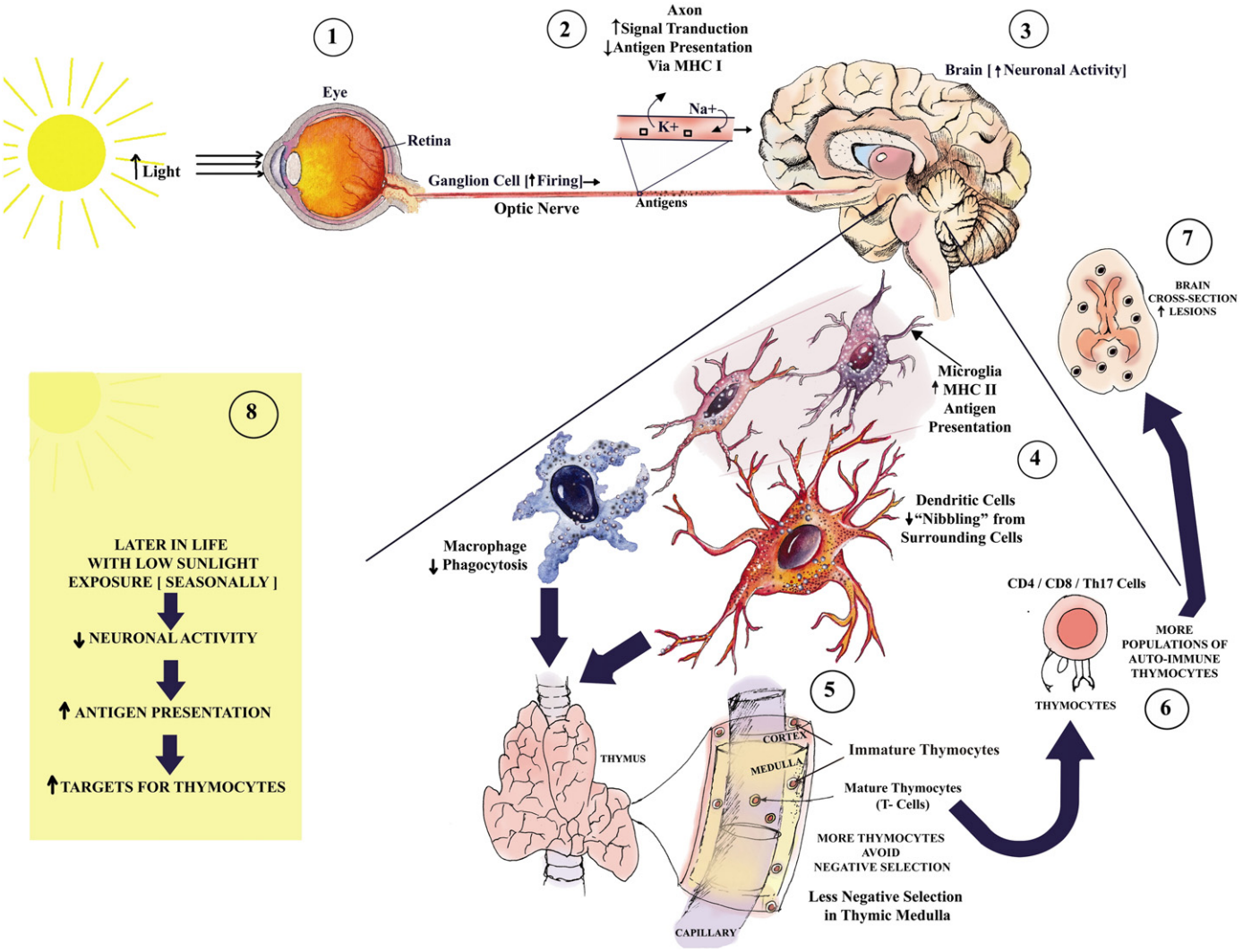

Fig. 1. Light-stimuli-mediated hypothesis. (1+2) Increased sunlight stimuli results in increased neuronal firing over the ganglion cells of the optic nerve. This increased signal [3] propagates in the brain this increased neuronal activity results in [4] less antigen presentation by neurons (MHC class I) but increased presentation by microglia (MHC class II). As a result, [5] less self-antigen recognition occurs at the thymus and other lymphoid organs during development. This allows for [6] more self-antigen recognizing thymocytes to enter into circulation since they are not negatively selected. These thymocytes can then act [7] as the mediators for autoimmunity in the CNS. Later in life [8], as sunlight levels fluctuate, changes in the amount of self-antigen presentation can occur, thereby allowing for more targets for these self-antigen directed thymocytes.

amount of self-antigens to select against self-reactive lymphocytes [49]. There would also be less Th1 and Th17 cell activation via MHC class II antigen-presentation later in life, due to the lower likelihood of having a reserve of self-reactive lymphocytes.

Therefore, it is possible that sunlight exposure early in life affects the amount or frequency of antigens presented by the CNS, and influences antigen presentation in early development of both the immune and neurologic systems. Additionally, later in life, circulating lymphocytes may become reactive to self-antigens that are expressed due to variation in sunlight exposure.

Optic neuritis, a common MS disease manifestation, also correlates with our hypothesis. It has been suggested that since the optic nerve is the only CNS component exposed directly to sunlight, it may hold the answer as to the geographic variation of MS prevalence [20]. Presentation of an optic nerve antigen (or an antigen that shares an epitope with that of the optic nerve) upon arrival to the newer sun exposure environment may lead to autoimmune responses via Th1 and Th17 cell activation and may manifest as optic neuritis; an inflammatory event that is not unique to MS but is correlated with its occurrence [65].

These hypotheses may be applicable to other neuroimmunological diseases. For example, neuromyelitis optica (NMO) shares similarities with MS but is an independent entity. This disease involves lesions predominantly in the spinal cord and optic nerves [66]. The autoimmune antibody appears to be directed against aquaporin-4 [66]. This may also be an example of a specific self-antigen to which lymphocytes that are not selectively removed during immuno-development may react because of variation in sunlight stimuli-mediated action potentials, subsequent differences in antigen presentation, and higher proportion of Th1 and Th17 cells surrounding the optic nerve ganglion cells. Therefore, additional research is needed to elucidate the hypotheses presented.

8. Proposed further research

Although vitamin D levels likely play a role in antigen presentation in the MS patient, one might also determine whether neuronal activity, vitamin A and melatonin from sunlight exposure play independent roles. Assays utilizing the EAE model could be used to investigate the hypotheses.

One study has already shown changes to the thymus in EAE rats reared in continual darkness versus continual light [67]. One could rear pregnant rats in total darkness so that the reared newborns are also not exposed to sunlight but supplemented with vitamin D, and

then compare this population with reared rats or mice that are exposed to normal diurnal sunlight. A comparison of the two populations for disease presentation and lesion load could then be undertaken.

Additionally, EAE rats could be administer antibodies against melatonin while being reared in low light and low vitamin D diets and compared with EAE rats with normal light environments and sufficient vitamin D diets.

Another experiment could be performed using EAE animals with low vitamin A diets and low light exposure while measuring levels of Th17 cells and IL-17 production. This group could then be compared to EAE animals with normal and even high vitamin A diets.

With any of the above proposed experiments, a "crossover design" could also be implemented to determine if early versus late light exposure to sunlight alters the course of the disease. This could correlate with the prior findings of people who migrate from higher to lower latitudes, or vice versa, and later changes to their MS incidence and prevalence [9].

Auto-reactive Th17 cells with receptors for vitamin A and melatonin-mediated receptors that are not directed by vitamin D may already exist in MS patients, in congruence with this hypothesis, and resultantly the anti-inflammatory effects of vitamin D metabolites may be less effective in humans with MS compared to the EAE mice model [58].

9. Conclusion

Sunlight and vitamin D as treatment modalities or disease modulators have been suggested [20] and attempted previously. Small studies on vitamin D treatment for MS have been attempted, with promising results, but require confirmation via larger studies/trials [68]. Prior animal studies have used extracorporeal sunlight exposure to show changes in disease manifestation, based on light photons changing the metabolites of vitamin D [69]. However, sunlight and vitamin D's role as a disease-modifying modality in MS patients remains to be determined.

Although vitamin D has been shown to be influential in the natural history of MS, it may not be the only sunlight-mediated effect on multiple sclerosis. The role of vitamin A and melatonin require further investigation as they may play a role in both the pathophysiology of the disease as well as potential treatment avenues.

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