



Light and ocular immunity

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Purpose of review

Current scientific evidence suggests that the systemic immune response is affected by exposure to light. During the past century man has been exposed for the first time in evolution to light at night, as well as increasing ultraviolet radiation through depletion of the ozone layer in our atmosphere. These ecological changes have enhanced the impact of light on our systemic immune response. We will review the effect of light on the systemic immune response with particular emphasis on ocular immunity.

Recent findings

Visible light is now recognized to be important in the maintenance of immune privilege within the eye; however, little is known about the mechanism through which this effect occurs. Recent studies suggest that the generation of regulatory T cells involved in immune privilege within the eye is dependent on retinoic acid formation by retinal pigment epithelial cells. Light is also important in modulation of multiple pathways including adjustment of circadian rhythm and production of vitamin D.

Summary

Light regulates our biologic systems in many different ways. Its effect on the systemic immune response suggests that it is important in maintaining health, as well as in the induction of disease. A better understanding of the interaction of light with our biologic systems may allow new preventive measures to avoid disease and novel forms of treatment.

Keywords

ACAID, circadian rhythm, immune privilege, light, vitamin D

INTRODUCTION

Light on earth emanates from the Sun, the center of our Solar System, which resides within the Milky Way galaxy. It is no surprise that 96% of all animal species have an organ (i.e. the eye) to detect light [1]. Vision is considered by most humans to be the single most important sense that we possess, and it is certainly one of the most important for survival. The preservation of vision is so important that the eye has developed novel immune mechanisms to protect it from inflammation that might be a response to potential infectious pathogens – a phenomenon known as immune privilege [2]. In 1873 Dooremall [3] recognized that the anterior chamber of the eye is endowed with special qualities that permit the survival of tumor grafts. The concept of anterior chamber immune privilege was explored by many different scientists over the ages, who confirmed this original observation and offered possible mechanisms, such as isolation (sequestration) from immune surveillance [4,5]. A 100 years after Dooremall's publication, Kaplan and Streilein [6] recognized that antigenic cells placed in the anterior chamber of the eye influence the systemic immune response by eliciting a dynamic down-

regulation of alloimmune responses, a phenomenon that was subsequently termed anterior chamber-associated immune deviation (ACAID) [6,7]. Subsequently, Ferguson *et al.* [8] demonstrated that ACAID was dependent on the presence of a specific wavelength of visible light.

Light is recognized as regulating our systemic immune response through at least two major mechanisms – the circadian rhythm and the production of vitamin D. In 1999, insight into the effect of light on circadian rhythm was provided by identification of a third class of photoreceptors in the eye – that is, the nonrod noncone photosensitive ganglion cells [9]. These cells provide primary input into the suprachiasmatic nucleus and regulate circadian rhythm.

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KEY POINTS

- Light changes the systemic immune response through alteration of the circadian rhythm and through vitamin D production.
- The activation of the vitamin D receptor on immune cells results in the regulation of immunoregulatory genes involved in several autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and multiple sclerosis.
- Ganglion cells affect the systemic immune response as a circadian photoreceptor gate.
- Visible light is essential to the generation of regulatory T cells and the existence of ACAID response within the eye.

The secretion of melatonin and cortisol from the supra-chiasmatic nucleus effects many immune-mediated responses. For example, the clinical symptoms of rheumatoid arthritis are thought to be related to the effects of melatonin on the release of interleukin (IL)-2, IL-6, and interferon (IFN)- γ by Th1 cells [10]. This explains why the clinical symptoms of rheumatoid arthritis, joint stiffness, and pain early in the morning follow a circadian pattern.

Although the sun remains our main source of light, for the first time in human evolution, electrical lighting in the late 19th Century exposed man to visible light from a different source (i.e. the light bulb) and at night. In addition, during the latter part of the 20th Century depletion of the ozone layer on the surface of the earth resulted in a marked increase in our exposure to ultraviolet (UV)-B irradiation [11[■]], the wavelength responsible for vitamin D production. It is likely that these ecological changes have also had a significant impact on our systemic immune response. In this review, we will discuss the physical properties of light, how it interacts with the immune system through alteration of the circadian rhythm and vitamin D production, as well as the effect of light specifically on the ocular immune response.

PROPERTIES OF LIGHT

The only electromagnetic waves that we can see are visible light waves with red having the longest wavelength and violet the shortest. The human eye responds to wavelengths from 390 to 750 nm. The peak sensitivity of ganglion cell photoreceptors which regulate the circadian rhythm and the pupillary response is between 460 and 484 nm [12]. UV light is electromagnetic radiation in the range

10–400 nm. Sunlight has UV-A (400–315 nm), UV-B (315–280 nm), and UV-C (280–100 nm) bands. A small fraction of UV-B reaches the earth and is responsible for the formation of vitamin D with the wavelengths between 295 and 297 nm being most important.

LIGHT AND THE SYSTEMIC IMMUNE RESPONSE

Although light exerts many physiologic and behavioral changes [13[■]], the two effects we will discuss are vitamin D production and regulation of circadian rhythm (Fig. 1).

VITAMIN D AND IMMUNITY

Vitamin D is recognized as having an increasing importance in the systemic immune response. Vitamin D receptors have been identified on immune cells and have been linked to the development and progression of autoimmune diseases such as systemic lupus erythematosus [14[■]–16[■]], rheumatoid arthritis [17[■],18], diabetes mellitus [19,20], and multiple sclerosis [21[■]].

Sunlight and its UV-B radiation is an important determinant of circulating 25-hydroxyvitamin D₃ [25(OH)D₃], the active form of vitamin D. Although this vitamin is well known for its role in bone mineral metabolism, its immunomodulatory properties have only been recognized recently [20,22,23,24[■]]. The vitamin D receptor is a steroid hormone nuclear receptor also known as Nr111. Engagement of this receptor leads to a significant

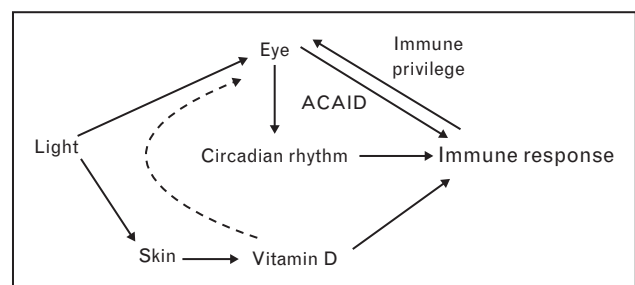


FIGURE 1. A schematic drawing on how light affects the immune system. Light influences our immune system mainly through two organs – the skin and the eyes. UV-B light is the main source of vitamin D production from the skin. Activated vitamin D₃ with its receptor on immune cells has multiple immunomodulatory effects. Low levels of vitamin D may be associated with the early development of age-related macular degeneration (dashed line). Light entering our eye influences our immune system through changes in our circadian rhythm and the induction of systemic and anterior chamber-associated immune deviation (ACAID).

increase in expression of more than 200 genes, including many immunoregulatory genes [25]. Genome-wide association studies identified vitamin D receptor binding sites in proximity to several autoimmune and cancer-associated genes, such as PTPN2 and CD226 – the former is associated with rheumatoid arthritis, the latter with tumor immune surveillance. Blocking CD226 reduces natural killer (NK) cell and cytotoxic T cell-mediated lysis of many tumor cell lines and is associated with colorectal cancer [26[¶]].

Vitamin D receptors are also present on a variety of immune cells including monocytes, macrophages, neutrophils, CD4⁺ and CD8⁺ T cells, and dendritic cells [27–29]. The vitamin D receptor is up-regulated during the adaptive immune response and the vitamin controls activation of T-cell antigen receptor signaling [24[¶]]. However, it also reduces the expression of co-stimulatory molecules CD80, CD86, and major histocompatibility complex class II antigens on monocytes and macrophages [30,31], and monocyte proinflammatory cytokines, including tumor necrosis factor (TNF)- α , IL-1 β , IL-6, IL-8, and IL-12, are reduced [32]. Vitamin D receptor knockout mice lack two populations of regulatory T cells – NK T cells and CD4/CD8⁺⁺ intraepithelial lymphocytes – and are prone to immune-mediated diseases in the gut [33^{¶¶}]. On the contrary, vitamin D enhances innate immunity through regulating expression of the endogenous antimicrobial peptide cathelicidin in immune cells [34,35]. Thus, vitamin D₃ is now being investigated as a potential therapeutic agent for various infections such as tuberculosis, influenza, HIV, and fungal infections [36].

CIRCADIAN CYCLE AND IMMUNITY

The circadian rhythm affects the systemic immune response through the effect of light on the pineal gland, which secretes melatonin in a nocturnal pattern [37]; in contrast, light enhances the secretion of cortisol which reaches a peak in the morning. As a consequence the circulatory proinflammatory cytokines IFN- γ , TNF- α , IL-1, and IL-12 are most evident during the night and early morning [37]. The circadian rhythm also has a direct effect on immune cells with T-lymphocyte proliferation being maximal in the morning, and B cells reaching peak circulating numbers and antibody production in the evening [38]. Disruption of the circadian rhythm with dim light at night continues the increase in antibody production, bactericidal capacity, and corticosterone levels observed in the daytime in rats [39].

Regulation of the circadian rhythm is dependent on multiple genes. Mice with a loss of function

in the clock gene Period 2 (Per2) show irregular production of IL-10 and IFN- γ in response to lipopolysaccharide [40,41[¶]]. Mutation in another clock gene, Bmal1, reduces the life span of Bmal1 knockout mice with early development of signs of senescence including cataracts, as well as loss of bone and muscle mass [42].

The systemic immune response in humans is also affected by an alteration in the circadian rhythm. Night-shift workers exposed to light have increased C-reactive protein and circulating leukocyte counts [43]. An altered light cycle is a risk factor for the development of type 2 diabetes mellitus [20,44], hypertension [45,46], mood and sleep disorders [47–49], metabolic [50[¶]] and sexual hormonal imbalance [51], and disrupted neuroendocrine rhythmicity [52,53]. Epidemiological studies have confirmed that night-shift employees are at an increased risk of breast, prostate, lung, colon, and endometrial cancer, as well as non-Hodgkin's lymphoma [54,55[¶],56]. These observations confirm that disruption of the circadian rhythm is an important factor in maintaining health and presumably acts, at least in part, through aberrant regulation of the systemic immune response.

OCULAR IMMUNITY

Immune privilege resides within the anterior chamber of the eye and has been investigated experimentally through the phenomenon termed ACAID. The name was coined after it was recognized that placement of alloantigens into the anterior chamber inhibited systemic delayed-type hypersensitivity but not antibody production or cytotoxic T-lymphocyte responses [57]. ACAID is known to be generated through antigen-specific afferent suppressor CD4⁺ T-regulatory cells and efferent suppressor CD8⁺ T cells [2]. The intact ocular microenvironment has a wide range of immunomodulating molecules including tumor growth factor- β (TGF- β) [58], Fas ligand [59], α -melanocyte-stimulating hormone [60], immunoreactive vasoactive intestinal peptide [61], thrombospondin [62], and complement activation products [63] to suppress inflammation while protecting vision. Despite the evolution of protective immune mechanisms to maintain vision while simultaneously protecting the eye from infection, intraocular inflammation (i.e. uveitis) is a common ocular disease and accounts for 10–15% of visual disability in the USA.

LIGHT AND EYE

Ferguson *et al.* [8,57] demonstrated that visible light has a direct effect on the intraocular generation of

regulatory T cells. Light deprivation of a specific wavelength (500–510 nm) prevented the formation of regulatory T cells and abolished ACAID following inoculation of antigen into the anterior chamber [8,57]. Zhou *et al.* [64²²] performed an interesting experiment in which they showed that the generation of regulatory T cells by TGF- β *in vivo* is dependent on the presence of retinoic acid, an oxidized form of vitamin A – the latter is a major component of the visual pathway in photoreceptors [65,66].

Retinal pigment epithelial cells phagocytose approximately 10% of the outer segments of photoreceptor cells each day and are involved in the regulation of the innate and the adaptive immune response through several mechanisms including the generation of TGF- β , cytotoxic T-lymphocyte antigen-2a, retinoic acid, and so on [67,68]. Kawazoe *et al.* [69²³] recently showed that primary cultures of retinal pigment epithelial cells constitutively express retinoic acid-associated molecules involved in the generation of regulatory T cells. Since retinoic acid is proposed to play a dual role both in vision and in the generation of immune privilege, it would be interesting to determine if the effect of visible light on the latter is through the conversion of retinal from the *cis* to *trans* confirmation.

Two common eye diseases which are clearly associated with exposure to light are pterygium and age-related macular degeneration (AMD).

Pterygium

Pterygium is the invasive growth of fibrovascular tissue from the conjunctiva onto the superficial cornea. The development of both primary and recurrent pterygium has been linked to UV exposure. The predominance of pterygia on the exposed nasal and temporal cornea and the high prevalence in fishermen and sailors, who are exposed to UV radiation reflected from the sea, support the causative role of light exposure. Two important proinflammatory cytokines, IL-6 and IL-9, have been shown to be released by the epithelial cells in pterygia after UV-B irradiation [70]. The release of these proinflammatory cytokines into the tears is thought to result in chronic inflammation, fibrovascular in-growth, and pterygium formation. Blocking both retinoic acid and IFN- α reduces the production of these potent proinflammatory cytokines and may have therapeutic application [71]. Previously, topical IFN- α [72,73] and retinoic acid [74] have been successfully used to treat primary, as well as recurrent, corneal/conjunctival neoplasia without side-effects. Moreover, topical IFN- α has shown to be effective in the treatment of recurrent pterygium [75]. Considering the many similarities between

pterygia and corneal neoplasia [76²⁴], such as their association with UV light and recurrent invasion of the ocular surface, clinical trials using topical interferon and/or retinoic acid should be considered for the treatment of pterygia.

Age-related macular degeneration

The most frequent cause of visual loss over age 55 in developed countries is AMD [77]. There are two forms of AMD – the nonexudative (dry/atrophic) form and the more severe exudative (wet/neovascular) form. The role of UV light in AMD is not firmly established. Several studies report AMD to have a positive association with UV exposure [78,79], but other studies suggest no association [80,81] or even a negative association [82²⁵].

The role of the immune response in AMD is also controversial. The extracellular deposits that form below retinal pigment epithelium (RPE) cells, termed drusen, are one of the hallmarks of AMD. Among the molecular constituents of drusen complement proteins, for example activation products and negative regulators of complement [83–85], and oxidative fragments such as carboxyethylpyrrole protein (CEP) adducts [84]. Activation of the complement system may have a role in the development of AMD, but the mechanism of this disease still remains to be determined [86²⁶]. A number of serum IgG antibodies to retinal tissue antigens – such as antigial fibrillary acid protein, CEP, α -crystalline, and α -enolase [87], have been identified in the serum of AMD patients. Recently, Hollyfield *et al.* [88] demonstrated that immunizing mice against CEP generates AMD-like lesions in mice and the light-damaged rat retina also contains increased amounts of CEP adducts [89]. However, the significance of these observations to the clinical disease is unknown.

Parekh *et al.* [90] demonstrated an inverse relationship between serum vitamin D levels and the progression of AMD. This work involved a cohort study on 481 sibling pairs. Although serum levels of vitamin D was not statistically higher in unaffected individuals compared to their affected siblings, a genetic variation in the major vitamin D catabolic gene, CYP24A1, was shown to be highly associated with all forms of AMD, especially neovascular AMD [82²⁷]. How vitamin D may play a role in the development of AMD is unknown at the present time.

CONCLUSION

Light is not only important for vision but also for regulation of the systemic immune response. It affects immunity through multiple pathways including the circadian rhythm and production of

vitamin D. Our future understanding of the effect of light on immunity in humans may be very important in both the prevention and treatment of immune-mediated diseases, including uveitis.

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Conflicts of interest

There are no conflicts of interest.

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