Light and Immunomodulation

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ABSTRACT: **The immune system is susceptible to a variety of stresses. Recent work in neuroimmunology has begun to define how mood alteration, stress, the seasons, and daily rhythms can have a profound effect on immune response through hormonal modifications. Central to these factors may be light through an eye-brain hormonal modulation. In adult primates, only visible light (400–700 nm) is received by the retina. This photic energy is then transduced and delivered to the visual cortex and, by an alternative pathway, to the suprachiasmatic nucleus (SCN), the hypothalamic region that directs circadian rhythm. Visible light exposure also modulates the pituitary and pineal glands, leading to neuroendocrine changes. Melatonin, norepinephrine, and acetylcholine decrease with light activation, whereas cortisol, serotonin, GABA, and dopamine levels increase. The synthesis of vasoactive intestinal polypeptide (VIP), gastrin releasing peptide (GRP), and neuropeptide Y (NPY) in rat SCN has been shown to be modified by light. These induced neuroendocrine changes can lead to alterations in mood and circadian rhythm as well as immune modulation. An alternative pathway for immune modulation by light is through the skin. Visible light (400–700 nm) can penetrate epidermal and dermal layers of the skin and may directly interact with circulating lymphocytes to modulate immune function. In contrast to visible light, *in vivo* exposure to UV-B (280–320 nm) and UV-A (320–400 nm) radiation can alter normal human immune function only by a skin-mediated response. It is therefore important, when reporting neuroendocrine immune findings, to control the intensity, timing and wavelength of ambient light.**

IMMUNOLOGY

The Immune Response

In very simple terms, the immune system involves a variety of white blood cells that work in concert to rid the body of the presence of a foreign pathogen (antigen). The primary cell types involved in an immune response are the macrophages, the T helper/inducer cells $CD4^+$ (T4), natural killer (NK) cells, B cells, and the T suppresser/cytotoxic cells $CD8^+$ (T8). The function of the macrophages is to first recognize and interact with antigen. The original antigen can also be recognized by other antigen-presenting cells such as dendritic cells or B lymphocytes. The T4 helper cells, NK cells, and B cells attack and destroy the antigen. The T8 suppresser cells turn off (anergize) the immune response.

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When the macrophage recognizes a pathogen as foreign (antigenicity), this antigen is ingested and fragmented into antigenic peptides. Pieces of these peptides are bound to major histocompatibility complex (MHC) molecules and are displayed on the surface of the macrophage. The binding of different macrophage-antigen-peptide MHC complexes to receptors on the T cells[1] now activates the resting helper T4 cells to release chemical signals known as lymphokines or cytokines (see FIGURE 1). These substances are biologically active factors (peptides) that regulate proliferation, differentiation, and maturation of various types of lymphoid and accessory cells.

Cytokine Control of the Immune Response

A diverse group of cytokines/lymphokines modulate the immune response. Among them are the interleukins 1 through 13 (IL-1–13), growth factors (GM-CSF), interferons (IFN-γ), and tumor necrosis factor (TNF). This has been reviewed elsewhere.[2] They function by stimulating or suppressing the activities of the specific immune cells as seen in FIGURE 1.

One of the original signals to activate the immune response is the release of IL-1 by macrophages. IL-1 activates T4 cells and stimulates the hypothalamus. The activated T4 cells release IL-2 and γ interferon (IFN-g), which induces proliferation of NK cells and macrophages, induces the B cells to produce antibodies, and anergizes

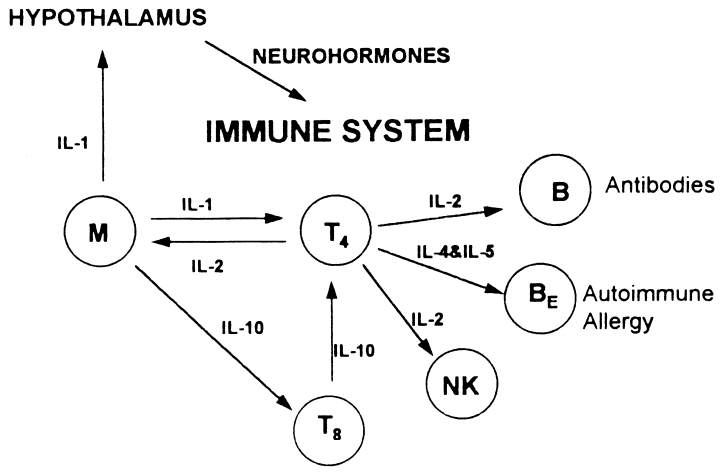

FIGURE 1. The cytokine/lymphokine control of the immune response. Macrophages (M) release IL-1, which activates T4 cells and stimulates the hypothalamus to release neurohormones. Activated T4 cells release IL-2 and other factors that stimulate the proliferation and differentiation of M and natural killer (NK) cells. IL-2 also directs the B cells to make specific antibodies against the antigen present. There can be a single switch with IL-4 and IL-5, which now direct the B cells to make immunoglobin E and other factors that lead to an allergic or autoimmune response. IL-10 released from the M and T8 cells shuts down (anergizes) the immune response.

the T8 cells. When a bacterial or viral infection is arrested, the immune response is shut down through the macrophage release of cytokine IL-10, which stimulates the suppresser T8 cells and suppresses the functioning of the T helper cells, B cells, and NK cells.

Although B cells can be stimulated by IL-2 and IFN-γ to make specific antibodies against antigens, the presence of IL-4 and IL-5 (synergy) induces B cells to synthesize immunoglobin E (IgE) instead of antibodies. IgE is involved in allergic and autoimmune responses. The IL-4 stimulation of synthesis of IgE can be blocked (antagonism) by the presence of IFN-γ.

Among its many properties,[3] IL-6 is important in T cell and NK proliferation and stimulates B cell immunoglobin production.

PHOTOIMMUNOLOGY

All wavelengths of light have the potential to modify the immune response. This includes the change of seasons (cirannual) and daily (circadian) light.[4] The timing, intensity, and *wavelength* of light contribute to immune modulation. Ionizing and nonionizing ultraviolet (UV) radiation (below 400 nm) have been found to suppress immune function.[5,6] This is a skin-mediated response. Visible radiation may affect the immune system through both skin-mediated and eye-brain–mediated mechanisms (see FIGURE 2). Wavelengths above 400 nm can penetrate epidermal and dermal layers of the skin and directly interact with circulating lymphocytes which modulate immune function. There is also a possible indirect mechanism, which would involve light above 400 nm transmitted through the retina to the brain. There, specific areas such as the pituitary, hypothalamus, and the pineal glands are stimulated to produce neurochemicals[7] that could direct changes in immune function.[8–11] Either or both pathways may be involved.

Skin-Mediated Response

The wavelengths of light transmitted through different layers of skin do not vary dramatically from lower mammals to primates. The longer the wavelength of light, the deeper the penetration in skin. The shortest wavelengths of UV light elicit the strongest immune response,[12–15] whereas the skin-mediated visible light response is weak but detectable.[16]

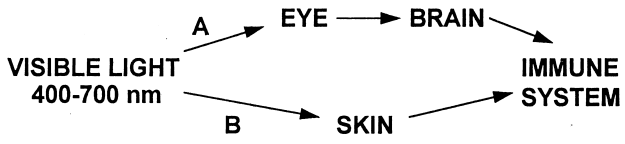

FIGURE 2. Visible light can affect the immune response through an eye-brain– or skin–mediated response.

Ultraviolet Radiation (200–400 nm)

Ultraviolet radiation (UR) may be divided into three components: UV-C (200–290 nm), UV-B (290–315 nmn), and UV-A (315–400 nm). *In vivo* exposure to UV radiation alters normal immune function by a skin-mediated response. Each UV subgroup (A, B, C) induces an immunosuppressive response, but by differing mechanisms. In general the effects that have been observed in humans are: inhibition of allergic contact dermatitis, inhibition of delayed hypersensitivity to an injected antigen, prolongation of skin-graft survival, and induction of a tumor-susceptible state.[5,6] This induced cutaneous anergy apparently proceeds via suppressor cells and serum factors. UV radiation can alter the normal antigen presenting function of nsepidermal Langerhans cells (LC), blocking their ability to activate T4 helper cells while allowing the activation of T8 suppressor cells. UV radiation can also upregulate and, in some cases, induce the secretion by keratinocytes of immunosuppressive factors.[14] Hersey[17] found that UV radiation reduces the number of T helper lymphocytes (l3%), increases the number of T suppressor lymphocytes (29%), and reduces the ratio of T helper/T suppressor lymphocytes (32%). T cell proliferation requires IFN-γ and IL-2, and these are downregulated after UV irradiation.[1,18]

Visible Light (400–700 nm)

As has been reported to date, visible light has little direct skin-mediated suppression of the immune response. Even in the presence of phototoxic agents such as eosin and rose bengal, visible light does not produce suppression of contact hypersensitivity with T8 suppressor cells.[16] Light directly applied to the skin has been shown to alter circadian rhythm[19] and may alter the immune response through a hormone- and/or cytokine-mediated response.[4]

PHOTONEUROIMMUNOLOGY

Eye-brain mechanisms are both species specific and age dependent and are determined by the wavelengths of light transmitted through the eye and reaching the retina that can then be transmitted to the brain.

Species Specificity

The wavelengths of light that might induce an eye-brain–mediated immune response depend upon the transmission properties of the eye of the particular species (see FIGURE 3). In lower animals, UV-B, UV-A, and visible light may be transmitted to the retina because these wavelengths are not filtered by their cornea or lens. Therefore, both UV and visible light might induce an eye-brain–mediated response. In adult primates, including humans, the cornea cuts out all light below 295 nm, while the lens filters out light between 295 and 400nm, so that only visible light (400–700 nm) reaches the primate retina. This photic energy is transduced in the retina and sent to the visual cortex for vision and through alternative pathways to the hypothalamic, pineal, and limbic structures.[20, 21]

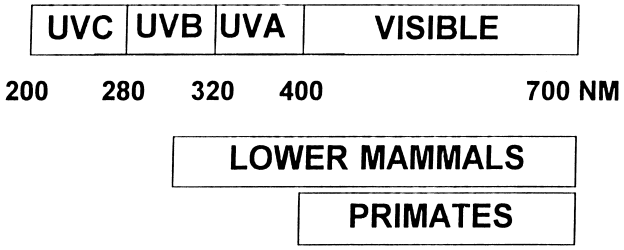

FIGURE 3. The light transmitted to the retina and transduced to the brain differs with species. In lower animals UV-B, UV-A, and visible light are transmitted to the retina. In adult primates the lens filters UV-B and UV-A, so only visible light reaches the retina.

Age

Age is also a factor involved in the transmission of specific wavelengths of light to the brain of primates, because the filtering characteristics of the lens change throughout life.[22]

The young human lens transmits light in the range of 320 nm to the retina (see FIGURE 4). The physiological function of this UV light in the development of the brain has yet to be determined. This UV light is completely filtered by the human lens by puberty. The elderly lens prevents much of the blue light (400–450 nm) from reaching the retina. This presumably protects the elderly from light-induced retinal damage[23] at a time when their quenchers (glutathione) and antioxidant enzyme systems have decreased production and/or effectiveness. Aphakia (removal of the lens) and certain forms of blindness may also change the wavelength characteristics of light impinging on the retina and transmitted to the brain.[24]

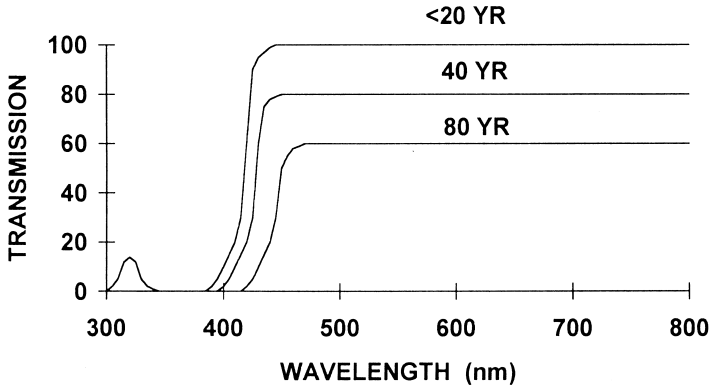

FIGURE 4. Changes in the transmission characteristics of the human lens with age. The young human lens transmits UV-B (320 nm), the adult human lens transmits only visible light (above 400 nm), and the elderly humans filters much of the blue light (400–450).

Retinal Light Transmitted to the Brain

Neural Chemical Control

Photons reaching the photoreceptor layer of the retina are transduced. This process is mediated by the release of retinal serotonin and dopamine and the suppression of melatonin.[25] *N*-acetyltransferase, which converts serotonin to melatonin, is specifically blocked by light. This enhances the production of serotonin and decreases the production of melatonin. Dopamine production is enhanced by light-induced activation of the enzymes tyrosine hydroxylase and phenylalanine decarboxylase.

Retina-Hypothalamus

Although most of the light energy received by the retina is relayed to the visual cortex for vision, an alternative pathway (see FIGURE 5) from the retina relays a small part to the suprachiasmatic nucleus (SCN), which is part of the hypothalamic region in the brain.[21,26] The SCN is thought to direct circadian rhythm and therefore controls a variety of events in the body such as temperature, reproductive cycles, appetite, and mood.[27] The pituitary and pineal gland are also involved in visible light–induced neuroendocrine changes. The neuroendocrine hormones that are particularly sensitive to modification of circadian rhythm are growth hormone, thyroid-stimulating hormone, thyroid hormones, prolactin, plasma cortisol, and melatonin.[4,7] Circadian rhythm is phase shifted by visible light.

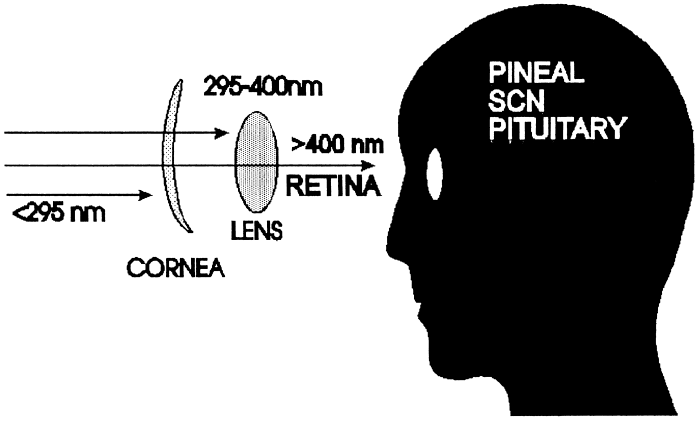

FIGURE 5. In primates UV light is filtered by the lens and cornea, and only visible light is transmitted to the retina. This light is transduced and sent to the visual cortex and, through an alternative pathway, to the SCN in the hypothalamus. There are further neural pathways that directly connect the hypothalamus with the pineal and pituitary glands. Irradiation of the eye leads to induction of the production of neurotransmitters and neuropeptide hormones from the SCN, pituitary, and pineal gland.

TABLE 1. Neurotransmitters/hormones with immunomodulatory properties[a]

Hormone/Neurotransmitter	Effect
Immune enhancers	
Prolactin	Activates macrophages Proliferates NK cells Produces IL-2
Growth hormone	Activates antibody synthesis Activates macrophages Produces IL-2
Somatostatin	Proliferates T, NK, and B cells and macrophages
Vasointestinal protein	Proliferates T and NK cells and macrophages
Substance P	Proliferates T and NK cells and macrophages
α-Melanin stimulating hormone	Proliferates NK cells Downregulates IL-1 and TNF-α Upregulates IL-10
Thyroxine	Activates T cells
β-Endorphin	Activates T cells and macrophages Suppresses B cells
Acetylcholine	Stimulates T and NK cells Increases IFN-γ
Melatonin	Activates T, NK, and B cells Upregulates IL-2
Serotonin	Proliferates T cells
Dopamine	Stimulates T and NK cells through stimulation of acetylcholine
Estrogen	Promotes IFN-γ Activates autoimmune response
Immune suppressors	
ACTH/CRH/cortisol	Impairs T and NK cell and macrophages Blocks antibody production Inhibits IL-4, Ig-E
Serotonin	Deactivates immune response through ACTH/CRH/cortisol modulation
Epinephrine/norepinephrine	Blocks IL-1, IL-2
Testosterone	impairs immune function through enhanced cortisol production

[a]See Refs. 34–36.

VISIBLE LIGHT EFFECTS IN HUMANS

All of the neurohormones shown in TABLES 1–3 that are modulated by light have been shown to affect immune response. Therefore, there may be one or more fundamental photoneuroendocrine–mediated mechanisms that control part of the immune system. This has been demonstrated in a few human studies.

We[28] and others[29,30] have found a small but significant enhancement in the number of peripheral lymphocytes induced by visible light through the eye. The proliferation of T4 and T8 cells in response to visible light was also reflected in seasonal changes.

In those studies, most subjects' response to visible light was a small but significant increase in the number of T lymphocytes. This result contrasts with what has been seen for UV irradiation in humans. Ultraviolet light (200–400 nm) reduces the number of T4 lymphocytes (l3%), increases the number of T8 lymphocytes (29%), and reduces the ratio of T4/T8 lymphocytes (32%).[17] T cell proliferation requires IFN-γ and IL-2, and these are downregulated after UV irradiation.[18]

TABLE 2. Neurotransmitters modified by visible light[a]

Modification	Neurotransmitter
Increased by light	Serotonin
	Dopamine
	GABA
Decreased by light	Melatonin
	Norepinephrine
	Acetylcholine

[a]See Ref. 37.

TABLE 3. Effects of light on neuropeptides

Wavelength of light	Effect	Neuropeptide
UVA	Induces	α-Melanocyte-stimulating hormone (MSH)
		Adrenocorticotropic hormone (ACTH)
Visible light	Upregulates	Gastrin-releasing peptide (GRP)
		Corticotropin-releasing hormone (CRH)
		Neuropeptide Y
		Follicle-stimulating hormone (FSH)
	Downregulates	Vasoactive intestinal peptide (VIP)

CIRCADIAN IMMUNE RESPONSE

Circadian (daily) rhythm has a profound effect on immune responsiveness in humans. This has been reviewed by Levi[31] and Maestroni.[32] Briefly, the immune response to antigen presentation differs both quantitatively and qualitatively, depending upon the time of exposure. Also, the proliferation and circulation of T, B, or NK lymphocytes in the peripheral blood differs throughout the day. T lymphocyte response to antigen and proliferation of those cells is most efficient in the morning. On the other hand B cells have maximum antigen response, proliferation, and circulation in the evening. The enhanced expression of IL-2 receptors and proliferation of NK cells appear in the early afternoon. The mRNA synthesis for T cells peaks at l A.M., for B cells at 10 A.M., and for NK cells at 7 A.M.

Cirannual (seasonal) rhythms in immune response have been documented in many species.[33] T cell immunity was found to be depressed in most species in the winter even when natural light sources (photoperiod) are kept constant. On the other hand we have found a direct correlation between changes in immune response during visible light treatment and the seasons in humans.[4]

CONCLUSION

In conclusion, light modulates the immune system through both eye-brain and skin responses. The longer the wavelength, the greater the penetration of light through ocular and dermal tissues. The potential to suppress or activate the immune response depends on the wavelength. Light also induces specific changes in the production of neuroendocrine hormones, which in turn can indirectly modulate the immune response. Since light affects neuroendocrine processes, the wavelength, intensity, and timing of ambient light must be taken into consideration in designing and interpreting immunological experiments.

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