

Roberts, JE. Therapeutic Effects of Light in Humans. In: Photobiology for the 21st Century, edited by Thomas P. Coohill and Dennis P. Valenzano, Chapter 2, pp. 17-29
Valdenmar Publishing Company, Overland Park, Kansas, 2001

Therapeutic Effects of Light in Humans

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INTRODUCTION

The adverse effects of sunlight, from skin cancer to cataracts, are so well known that it is possible to forget that light has many beneficial effects. However, since man as well as all most animals and plants evolved under sunlight, it is not surprising that there are many positive effects of light on human health.

The potential therapeutic effect of light on any given human organ depends upon the wavelength transmitted to that organ. Ultraviolet radiation [UV-C (100-280nm), UV-B (280-320nm), and UV-A (320-400nm)] contains shorter wavelengths than visible light (400-700nm). The shorter the wavelength, the greater the energy but the less the penetration through biological tissues; conversely, the longer the wavelength, the less the energy but the deeper the penetration through the skin [Fig 1]. UV-C and UV-B are primarily absorbed by the epidermal layer. UV-A can pass through the dermal layer, while visible light has access to the circulating blood. The greater the energy, the greater the potential for harm: UV-C and UV-B cause sunburn and basal cell carcinoma; UV-A causes skin aging and is thought to induce dermal melanoma, while visible light is largely benign. On the other hand, the variety of potential therapeutic effects is greatest for visible light, moderate for UV-A, limited for UV-B, and practically nonexistent for UV-C.

VISIBLE LIGHT

Blue visible light (400-450 nm) has been used as a treatment for jaundice in babies for over 50 years and has been shown to modify human cells (Roberts 1981, Tyrell, 1980, 1986). Full spectrum visible light can improve a number of conditions and diseases (Roberts, 2000). These include circadian rhythm disorders such as seasonal depression

(SAD), jet lag, and shift work; modulation of the immune response (chronotherapy); and accelerated wound healing.

Neonatal Jaundice

One of the first reported uses of light for the treatment of a disease is the phototherapy of neonatal jaundice (Williams,1971). When babies are born, particularly prematurely, their livers often do not function sufficiently to remove or oxidize certain metabolites. One of these metabolites is bilirubin, which can accumulate in the liver, leading to jaundice and in the brain, leading to possible mental retardation. Blue light irradiation converts the normal toxic 4Z, 15Z form of bilirubin to its isomer the 4Z, 15E form, which probably is less toxic. Blue light also oxidizes the bilirubin to structural and configurational isomers that are excretable in bile and urine (McDonagh,1985). With proper protection of the newborn eye, light is a safe and effective treatment for hyperbilirubinemia.

Circadian Rhythm Disorders

Visible light not only drives the daily cycles of circadian rhythm (Aschoff, 1965), but can also, as a consequence of air travel, living indoors during changing seasons, and working during normal sleeping hours, alter them. The circadian response results from a complex series of neuroendocrine changes. When visible light impinges on the retina, it sends a signal to the suprachiasmatic nucleus (SCN) [Fig.2] in the hypothalamus (Takahashi, et al., 1984; Klein, 1991), leading to a cascade of hormonal changes in the pituitary, pineal, adrenal and thyroid glands. In some forms of blindness the circadian response may be blunted (Czeisler, et al., 1995; Lockley, et al., 2000). There may also be

secondary photoreceptors in the skin that control alternative circadian mechanisms (Campbell and Murphy, 1988; Murphy and Campbell, 2000).

Whatever the mechanism(s) of activation that are involved in circadian rhythm (Brainard et al., 2000; Oren et al., 2000; Johnson, 1995; Sadun, et al., 1984; Ding, et al., 1994; Deacon and Arendt, 1994; Lewy, 1980), the oscillation of hormones it induces has a profound effect on most physiological functions in the body (Roberts, 1995). When this process is disrupted through environmental light changes, it may lead to some of the more damaging emotional and physiological effects associated with seasonal depression (SAD), jet lag, and shift work. External control of the dark/light cycle and/or the administration of melatonin have led to effective treatments of these disorders.

Seasonal depression. Seasonal depression is a depression occurring in the fall, with no apparent outside grief or stress, that is spontaneously reversed or triggers mania in the spring or summer (APA, 1994). The symptoms include sadness, decreased energy and libido, anxiety, increased need for sleep, and strong cravings for carbohydrates. The prevalence varies with latitude (i.e. 2% of the population of Florida vs. 10% in New Hampshire). Sub-seasonal depression patients with milder symptoms are even more prevalent. While 5% of the population of New York may have seasonal depression, it is estimated that over 15% have sub-seasonal depression.

Seasonal depression can be treated with light therapy consisting of the daily administration of visible light (between 2,500 and 10,000 lux) in the very early morning (APA, 1994; Wirz-Justice, 1994; Terman and Terman, 1992; Terman, et al., 1996; Swartz, et al., 1996; Lewy, 1987). A light box adjusted to eye level is often used to administer this light. Any ultraviolet light produced by fluorescent lamps must be filtered as it is both ineffective and potentially damaging to the lens and retina (Roberts, 1996). Treatment must be given without either prescription drug or herbal medications as it has been shown that several antidepressant treatments are phototoxic to the eye (Schey, et al., 2000; Roberts, 1992). The antidepressant response to visible light takes approximately 3-

4 days to take effect. Treatment should be continued throughout the winter months to avoid withdrawal symptoms.

Although the exact biochemical mechanism of induction of seasonal depression is not clear, the symptoms – increased carbohydrate appetite, weight gain and hypersomnia – fit a pattern of serotonin depletion. Furthermore, our recent studies have shown that both serotonin and dopamine are increased as a result of visible light (Roberts, 1992; Rao, 1990). These are the same neurotransmitters that are enhanced by more traditional antidepressant medication. It seems likely that disturbances in one or both of these neurotransmitters are involved in the pathophysiology of SAD.

Jet lag. Crossing several time zones significantly affects circadian rhythm. With this change comes a dramatic imbalance of not only neurotransmitters but other hormones (thyroid hormone, insulin), which can lead to drastic changes in mood and concentration. This syndrome is commonly called jet lag (Hirshfield, 1996). Typically problems occur when the circadian period is phase shifted (lengthened or shortened) as it is in a trip from west to east (i.e. New York to Paris) or east to west (i.e. Paris to New York).

The judicious use of light (therapy and/or sunlight) at the appropriate time can quickly rebalance circadian rhythm and speed recovery from jet lag, especially in conjunction with exogenous melatonin (Boulos et al., 1995; Wever, 1985; Dollins et al., 1994). Melatonin is the body's natural endogenous sleep aid, a tryptophan metabolite that is synthesized from serotonin by N-acetyl transferase (NAT) in the dark (Moore and Klein, 1974) [Fig 3]. In the presence of visible light received through the skin or eye, NAT is inhibited and the production of melatonin is shut down. Under normal circadian conditions, there is a small peak of melatonin production every afternoon at about 4 pm and a much larger peak that occurs later in the evening between approximately 10 pm and 3 am. Modifying this pathway by adding light and melatonin can have dramatic effects on the physiological responses of the body.

Internal melatonin can be enhanced by taking melatonin pills (0.5 mg is sufficient to fill all melatonin receptors associated with circadian imbalance) or by increasing its natural production by changes in the diet. Wurtman and his colleagues have demonstrated (Spedding et al., 1996) that consuming foods such as milk that contain protein high in tryptophan, especially together with sweets (increased insulin helps transport tryptophan across the blood-brain barrier), will increase melatonin and produce drowsiness. In contrast, high-protein food such as meat that is rich in tyrosine and low in carbohydrates can increase excitatory neurotransmitters and enhance wakefulness.

To counter the effects of jet lag, one can combine judicious exposure to light with careful timing of meals and melatonin pills to shift one's circadian rhythm. For example, as seen in Fig 4, on an eastbound trip (i.e. New York to Paris), you should spend at least one hour outdoors in the early morning upon arrival (between 10 am and 12 noon Paris time). The light exposure during that time will enhance your serotonin production, deplete melatonin, and shift your body's rhythm forward by 3 hours. To keep you alert in the early evening, eat a late afternoon/early evening meal high in protein and low in carbohydrates. Later in the evening (between 10 pm and 3 am), to raise melatonin levels and ensure a deep sleep, take melatonin [0.5 mg] along with a high carbohydrate, high tryptophan protein snack (e.g., milk and something sweet), turn out the light, and leave it off. During these hours, it is important to remain in the dark to allow melatonin levels to remain high. This regime will lead to a speedy recovery from jet lag, shortening the circadian rhythm's "day" by shifting the (New York) melatonin peak to match nighttime at the final eastern destination (Paris).

On the return flight (Fig. 5) from Paris to New York, spend time outdoors during the late afternoon, between 3 and 5 pm, to lengthen the day so that your internal clock will nearly match nighttime in New York. At bedtime (between 10 pm and 3 am New York time), the same regimen of melatonin [0.5 mg], a carbohydrate and milk snack, and darkness will also be beneficial (Brown, 1994).

Shift work. Working in the evening/late night or alternation of day and evening work schedules often results in sleeping difficulties, confusion and irritability, problems with metabolism, enhanced susceptibility to infectious disease and in some extreme cases suicidal ideation (Brewerton, 1995). This syndrome is due to the constant and persistent disruption of the patient's circadian response and the resultant fluctuation in neurotransmitters and other hormones. There has been some success in limiting these symptoms by using bright visible light exposure in the workplace followed by deliberate darkness (dark glasses, heavy window shades) in the daylight hours, together with the use of melatonin (0.5mg) as a sleep aid (Czeisler, 1990). Once the body has adapted to evening work and daytime sleep, symptoms are lessened. However, psychologically and physiologically devastating effects occur with alternating shift work patterns; these must be avoided if at all possible.

Visible Light Modulation of Immune Response

The immune system is susceptible to mood alteration, stress, the seasons, and daily rhythms through a neuroendocrine network. Central to these immune modulating factors is visible light working through an eye-brain hormonal modulation (Roberts, 1995; Roberts, 1992; Kasper, 1991; Rosenthal, et al., 1992).

When visible light activates the SCN, it triggers a response in both the pituitary and pineal glands, resulting in the final release of a number of neurotransmitters and neuropeptides (Tables I and II). The end result of light exposure is a decrease in melatonin, norepinephrine and acetylcholine levels with a concomitant increase in cortisol, serotonin, gaba and dopamine levels (Omura, et al., 1993; Brainard, et al., 1991; Scharrer, 1964). [Table I]. In addition, visible light has been shown to modify the synthesis of vasoactive intestinal polypeptide (VIP), gastrin releasing peptide (GRP) and neuropeptide Y (NPY) in the rat SCN (Table II) (Inouye, et al., 1992). All of these neuroendocrine changes can lead to immune modulation. When human volunteers were

irradiated with one half hour of visible light (10,000 lux) delivered to their eyes using a therapeutic SAD light box, the proliferation of their T, B and NK cells was enhanced. (Roberts, 1995; Roberts, 1992; Kasper, 1991; Rosenthal, et al., 1992.) This proliferation was associated with an increase in serotonin levels induced by visible light (Roberts, 1992).

An alternative pathway for immune modulation by light is through the skin. Visible light (400-700 nm) can penetrate epidermal and dermal layers to a depth of 2-3 mm and directly interact with circulating lymphocytes to modulate immune function. Half an hour after exposure of a small skin area (400 cm²) of healthy volunteers to visible light (12 j/cm²), there was enhanced phagocytic activity of monocytes and granulocytes, enhanced cytotoxic activity of natural killers, and induced secretion of tumor necrosis factor from mononuclear leucocytes (Obolenskaya and Samoilova, 2000).

Circadian Immune Response. Both light and the absence of light can powerfully affect the immune response. Francois Levi (1991) has found that the immune response fluctuates in a rhythmic pattern during the day and evening. B (antibody producing) cells are most active in the morning so that hay fever or asthma may be more severe on awakening. On the other hand, T cells and NK (natural killer) cells that attack tumors are more active in the evening. These immune cells have receptors for neurohormones and transmitters, and this rhythmic immune cell activity appears to be under an as yet undetermined neuroendocrine control.

Because of this circadian fluctuation of immune responses, it is possible to adjust the time of day a particular disease is treated to optimize the immune response. This is known as chronotherapy. For instance, Lissoni et al. (1992), Maestroni (1996), Levi (2000) have found that treating cancer in the evening, when the NK cells are activated, is much more effective than administering the treatment at random times of day. They report that chronotherapy is particularly effective for cancer treatments that involve immune system boosters such as IL-2 (immunotherapy). Baldwin and Barrett (1998)

suggest that steroid hormone-dependent cancers (such as breast and prostate) may be particularly susceptible to chronotherapy.

Chronotherapy is now being considered as an adjunct to treatment of disorders other than cancer (Conti and Maestroni, 1998) for instance autoimmune disorders, heart disease and diabetes, which have circadian components. It has become evident that the understanding and control of circadian rhythm is a very powerful tool in modifying human health.

Wound healing. Visible light in the form of low level laser irradiation appears to accelerate wound healing. Chronic leg ulcers (Schindl, 1999; El-Batanouny, 1999a) and Achilles tendon injuries (El-Batanouny, 1999b) have healed more quickly after irradiation from a He:Ne laser ($\lambda=632.8$, 4 J/cm²). It appears that the light stimulates cell proliferation of human keratinocytes and/or fibroblasts through the induction of growth factors, particularly bFGF (Yu, 1994; Zubanova and Samoilva, 2000).

ULTRAVIOLET RADIATION

While visible light (above 400 nm) induces changes in the human immune response through both eye-brain and dermal mechanisms, the adult human lens filters all UV radiation and prevents it from entering the brain through the retina (Barker, et al., 1991). Thus, in contrast to visible light, in vivo exposure to UV-B (280-320 nm) and UV-A (320-400 nm) radiation can only alter normal human immune function by a skin mediated response. Hence each UV subgroup (B, A) induces an immunosuppressive response but by unique mechanisms, involving the regulation of differing interleukins and growth factors. As UV-C has no substantive beneficial effects on human health it will not be discussed in this chapter.

UV-A

Although the human biological response to UV-A has been found to be damaging to many systems (Urbach, 1992), UV-A light is particularly effective as a treatment for atopic dermatitis (Krutmann and Morita, 1999; Morita, 2000; Abeck, et al., 2000) and autoimmune diseases such as systemic lupus erythematosus (McGrath, 1999). In these cases the immunosuppressive effect of UV-A is exploited to treat an excessive immune response.

Historically, sunlight in conjunction with externally applied extracts of psoralen has been a treatment of choice for vitiligo, as documented by ancient Egyptian and Indian medicine (Blum, 1949). More recently, UV-A irradiation in conjunction with the internal use of psoralen was found to be an effective clinical treatment of psoriasis (Parrish, 1974; Rodighiero and Dallacqua, 1986). Since then Psoralen + UVA (PUVA) photochemotherapy has been used as a treatment of choice for more than 24 heterogeneous groups of diseases (Momtaz and Fitzpatrick, 1998; Lerner, et al., 1999). The newest additions to this list include scleroderma and lupus erythematosus (Asawanonda, et al., 1999).

Ironically, because of reports of development of squamous cell carcinomas, genotoxicity (Peritz and Gasparro, 1999), phototoxic side effects to the skin and the eye (Barker et al. 1986), and modulation of the immune response (Tokura Y. 2000) resulting from internal PUVA, there has been a movement back to the external use of psoralen in the form of bath and/or topical PUVA-therapy (Calzavara-Pinton PG et al. 1997; Der-Petrossian et al. 2000, Honigsmann, 2000). These external treatments have been found to be successful while avoiding the side effects associated with internal PUVA therapy. In addition, to improve efficacy while reducing the risk of PUVA therapy, studies are under way to test the use of low dosage (Tanew, et al., 1999; Ortel, 2000 paper 742), more specific wavelengths of radiation (Peritz and Gasparro, 1999), systemic antioxidants

(Potapenka and Kyagova, 1998; Gonzalez, 2000), and new chromophores as substitutes for psoralen (Hearst, 2000; Talib, et al., 1999; Truitt et al., 1999).

UV-B

The most demonstrably positive effect of UV-B in humans is the ability of the skin to photoproduce the usable form of Vitamin D, namely Vitamin D-3 (Vit D-3). Vit D-3 is synthesized when 7-dehydrocholesterol is photoconverted by UV-B radiation (0.5 J/cm^2) (Holick, et al., 1980; Obi-Tabot, et al., 2000) to previtamin D-3, which is then thermally isomerized to Vit D-3. Vitamin D-3 plays a role in calcium and bone metabolism, and its deficiency leads to the disease rickets, a mineralization defect of the skeleton (Holick, 1981). Recent studies have also linked Vitamin D deficiency to an increased risk of mortality from breast, colon and prostate cancers. These particular cancers have receptors for and the capacity to activate 1-alpha-2,5-dihydroxyvitamin D-3 to a potent agent which can in turn inhibit the proliferation and invasiveness of these cancer cells. Derivatives of the natural product are being considered as new therapeutic agents against cancer (Chen, et al., 2000).

CONCLUSION

Daylight, in particular visible light, is important to our overall health and well being. Visible light not only relieves depression and circadian imbalances but may have a positive effect on our immune responses. Although improper exposure to ultraviolet radiation can be damaging, the judicious use of ultraviolet of light can be useful in treating diseases such as atopic dermatitis, lupus erythematosus and rickets. Sunlight and dark nights have been with us since the beginning of life on this planet, and as we have seen here, we have just begun to understand what powerful effects both have on human health.

Acknowledgment

I would like to thank Dr. Ann Motten, NIEHS for helping in the preparation of this manuscript.

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Fig. 1. The transmission of different wavelengths of radiation through the skin.

Fig. 2. The transmission of light through the eye to the brain.

Fig. 3. Serotonin is increased with visible light and melatonin is decreased with visible light. Serotonin is synthesized from tryptophan and is converted to melatonin by acetylating and methylating enzymes.

Fig. 4. Resetting the biological clock going West to East.

Fig. 5. Resetting the biological clock going East to West.

TABLE I

NEUROTRANSMITTERS MODIFIED BY VISIBLE LIGHT

INCREASED

CORTISOL
SEROTONIN
DOPAMINE
GABA

DECREASED

MELATONIN
NOREPINEPHRINE
ACETYLCHOLINE

TABLE II

NEUROPEPTIDES CHANGES MODIFIED BY LIGHT

<p>UVA</p> <p><u>Unregulated</u> α-MELANOCYTE STIMULATING HORMONE (MSH) ADRENOCORTICOTROPIC -ACTH</p> <p>VISIBLE LIGHT</p> <p><u>Unregulated</u> GASTRIN RELEASING PEPTIDE-GRP CORTICOTROPIN-RELEASING HORMONE-CRH NEUROPEPTIDE Y FOLLICLE STIMULATING HORMONE-FSH</p> <p><u>Downregulated</u> VASOACTIVE INTESTINAL PEPTIDE</p>
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