Update on the Positive Effects of Light in Humans

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The adverse effects of sunlight, from melanoma to cataracts, are well known and frequently reported. (1) However, since humans evolved under sunlight, it is not surprising that there are many positive effects of light on human health. Light that reaches the human eye has two fundamental biological functions: regulation of the Visual Cycle and of Circadian Rhythm. We report here the most recent developments in both of these areas.

Regulation of the Visual Cycle:

Human day vision (photopic) is regulated by three cone photoreceptors, while vision in dim light or darkness (scotopic) is regulated by rod photoreceptors. This light input then triggers a response through the optic nerve to the visual cortex in the brain. This visual response is cyclical.

The photosensitive pigment for scotopic vision is rhodopsin, which is found in the rod photoreceptors of the retina and has a characteristic absorption maximum at 500 nanometers. Rhodopsin has been the model for studies of the G-protein coupled receptors, of which several hundred have been identified. (2, 3) This particular receptor has as its ligand, 11-cis retinal, which acts as an inverse agonist and holds the protein in an inactive conformation. The ligand is covalently linked to the protein *via* a Schiff base linkage, which is protonated for most pigments. The ligand confers photosensitivity to the protein, interacting in a manner still poorly understood with the protein through its Schiff base linkage to the polyene chain of the retinal. The action of light is to photoisomerize the 11-cis bond to the all-trans conformation. The movement of the ligand into this form forces conformational changes on the protein, allowing the binding of G-protein (transducin in the rod photoreceptors). The ligand in this state is acting as an agonist. The resulting steps in the signal cascade are to close the membrane channels, thus acting to send the neural impulse, deactivate the opsin, and remove the ligand from

the binding site and the photoreceptor so that it can be reisomerized to regenerate the photosensitive pigment.

As the ligand is key to the generation of the photosensitive pigments in both the rod and cone photoreceptors, there is considerable research on the "retinoid cycling" process. There is also mounting evidence that the absence or dysfunction of any of a number of binding proteins/enzymes involved in this process can cause clinical disorders, often resulting in blindness (4). One of best studied models of disruption of this process is the RPE65 knock out mouse (5). RPE65 is abundantly expressed in the retinal pigment epithelium and is known to be critical for the production of 11-cis retinal. In spite of extensive study, its exact role in the process of producing 11-cis retinal is not yet known. It is recognized that retinyl ester is the substrate for the isomerization process (6) and that the protein RPE65 can bind retinyl esters.(7, 8) Interestingly the RPE65 knockout animals have a trace of photosensitive pigment, which has been identified as containing the 9-cis retinal.(9) The source of this isomer is not yet known. There is extensive ongoing research on this and other animal models of the retinoid cycle.

The photopigment G protein-coupled receptors (opsin) responsible for photopic vision have characteristic absorption maxima at 414 (blue), 500 (green), and 560 (red) nanometers. (10) In several species (mouse, salamander and pig) a single cone can contain more than one opsin. (11) However, in primates, short wavelength sensitive cones (S cones) and medium- or long-wavelength-sensitive cones (L/M cones) are two separate populations. Each cone type has a different developmental time course, contributes to different intra-retinal circuits, and transmits different types of information to the brain (12).

The opsin proteins expressed for Short (S)-wavelength [blue]–sensitive cones and Medium [green] and Long [red]–wavelength sensitive cones have been sequenced for many species (for a recent review see (2)). Substitution of key amino acids in these sequences can drastically shift wavelength sensitivity. For instance, mice can see in the UV because their shortest wavelength sensitive cones have an absorption maximum of

358nm. A single amino acid substitution in this UV mouse opsin results in an 80 nm shift to the blue cone pigment having an absorbance maximum of 438 nm.(13) The molecular basis of the "spectral tuning" (14) of the wavelength of visual pigments as they interact with opsin is currently being defined for several species.

This current research distinguishing rod from cone function not only further defines night versus color vision but enhances our understanding of the evolution of vision.

Regulation of **Circadian Rhythmn**:

Mammals, including humans, experience an increase and decrease in the production of most hormones and neurotransmitters over a 24 hour period. (15). The circadian (latin: circa dies- about a day) system refers to the coordination of these daily biological actions. The human circadian system is regulated by both environmental stimuli and endogenous clocks. (16) The most powerful external regulator of the circadian response in humans is visible light, which is transmitted through the eye (15) . When visible light impinges on the retina, it sends a signal to the suprachiasmatic nucleus (SCN) in the hypothalamus (17, 18), 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 (19) while in others it remains intact (20). This observation has led to the innovative concept that while the mammalian photoreceptors, rods and cones and their well-characterized photopigments are responsible for sight, there are other photoreceptor(s) and photopigments responsible for regulating the circadian response.

Within the last five years: 1) the human "circadian" photoreceptor has been located; (21) 2) the putative photopigment has been identified (22-25) and confirmed with knockout mice; and 3) the action spectrum responsible for circadian regulation (26) (at least for neural melatonin modulation) has been established.

The primary photoreceptor that regulates the neurohormonal fluctuations of the 24-h circadian clock has been located in the retinal ganglion cells (21). Knockout mice have shown that there is little contribution to circadian regulation by the rod and cone photoreceptors (27). The identity of the photopigment for this ganglion photoreceptor is most likely melanopsin (22-25), which is phylogenetically similar to invertebrate opsins. Visible light excitation of melanopsin within these ganglion cells provides a direct signal through the optic nerve to the SCN, which controls the resultant circadian hormonal cascade. One of the neurohormones regulated by this light induced circadian mechanism is melatonin. The action spectrum for melatonin regulation in humans has been found to be in the range of 446-477 nm, in the longer blue light region (26).

The oscillation of hormones under visible light regulation has a profound effect on most physiological functions in the body (15). 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. (28) Furthermore both **visible light and the absence of light at night (LAN)** can powerfully affect the human immune response (29). Francois Levi (30) has found that the immune response fluctuates in a rhythmic pattern during the day and evening. 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. Steroid hormone-dependent cancers (such as breast and prostate) may be particularly susceptible to chronotherapy (Baldwin and Barrett (31)). For instance, Levi(32), Lissoni (33), Maestroni (34), 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. On the other hand, inappropriate exposure to visible light at night leads to a greater risk for both breast and prostate cancer (35-37).

Based on animal studies, chronotherapy is proposed as a possible adjunct to treatment of disorders other than cancer for instance autoimmune disorders, heart disease and diabetes, which all have circadian components. (38)

It has become evident that cyclical visible light and darkness are very powerful tools in modifying human health. Control of circadian rhythm through these environmental stimuli opens up a whole new dimension to photobiology that goes far beyond merely modifying our mood and sense of well-being.

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1. Roberts, J. E. (2001) Hazards of Sunlight Exposure to the Eye. *In: Sun Protection in Man, edited by Paolo U. Giacomoni* **Chapter 8,**, 155-174 Elsevier, Amsterdam.
2. Ebrey, T. and Y. Koutalos (2001) Vertebrate photoreceptors. *Prog Retin Eye Res* **20**, 49-94.
3. Spudich, J. L., C. S. Yang, K. H. Jung and E. N. Spudich (2000) Retinylidene proteins: structures and functions from archaea to humans. *Annu Rev Cell Dev Biol* **16**, 365-392.

4. Rattner, A., H. Sun and J. Nathans (1999) Molecular genetics of human retinal disease. *Annu Rev Genet* **33**, 89-131.

5. Redmond, T. M., S. Yu, E. Lee, D. Bok, D. Hamasaki, N. Chen, P. Goletz, J. X. Ma, R. K. Crouch and K. Pfeifer (1998) Rpe65 is necessary for production of 11-cis-vitamin A in the retinal visual cycle. *Nat Genet* **20**, 344-351.

6. Moiseyev, G., R. K. Crouch, P. Goletz, J. Oatis, Jr., T. M. Redmond and J. X. Ma (2003) Retinyl esters are the substrate for isomerohydrolase. *Biochemistry* **42**, 2229-2238.

7. Jahng, W. J., C. David, N. Nesnas, K. Nakanishi and R. R. Rando (2003) A cleavable affinity biotinylating agent reveals a retinoid binding role for RPE65. *Biochemistry* **42**, 6159-6168.

8. Mata, N. L., W. N. Moghrabi, J. S. Lee, T. V. Bui, R. A. Radu, J. Horwitz and G. H. Travis (2004) Rpe65 is a retinyl ester binding protein that presents insoluble substrate to the isomerase in retinal pigment epithelial cells. *J Biol Chem* **279**, 635-643.

9. Fan, J., B. Rohrer, G. Moiseyev, J. X. Ma and R. K. Crouch (2003) Isorhodopsin rather than rhodopsin mediates rod function in RPE65 knock-out mice. *Proc Natl Acad Sci U S A* **100**, 13662-13667.

10. Pugh, E. N. (2001) Rods are rods and cones cones, and (never) the twain shall meet. *Neuron* **32**, 375-376.

11. Ma, J., S. Znoiko, K. L. Othersen, J. C. Ryan, J. Das, T. Isayama, M. Kono, D. D. Oprian, D. W. Corson, M. C. Cornwall, D. A. Cameron, F. I.

Harosi, C. L. Makino and R. K. Crouch (2001) A visual pigment expressed in both rod and cone photoreceptors. *Neuron* **32**, 451-461.

12. Calkins, D. J. (2001) Seeing with S cones. *Prog Retin Eye Res* **20**, 255-287.
13. Hunt, D. M., J. A. Cowing, S. E. Wilkie, J. W. Parry, S. Poopalasundaram and J. K. Bowmaker (2004) Divergent mechanisms for the tuning of shortwave sensitive visual pigments in vertebrates. *Photochem Photobiol Sci* **3**, 713-720.
14. Fasick, J. I., M. L. Applebury and D. D. Oprian (2002) Spectral tuning in the mammalian short-wavelength sensitive cone pigments. *Biochemistry* **41**, 6860-6865.
15. Roberts, J. E. (2000) Light and immunomodulation. *Ann N Y Acad Sci* **917**, 435-445.
16. Berger, J. (2004) Regulation of circadian rhythms. *J. Appl. Biomedicine.* **2**, 131-140.
17. Takahashi, J. S., P. J. DeCoursey, L. Bauman and M. Menaker (1984) Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. *Nature* **308**, 186-188.
18. Klein, D. C., R. Y. Moore and S. M. Reppert (1991) Suprachiasmatic Nucleus. The Mind's Clock. *Oxford University Press, NY*
19. Lockley, S. W., D. J. Skene and J. Arendt (2000) Light and circadian rhythms in the blind. *Abstr. 13th International Congress on Photobiol.* 700.

20. Czeisler, C. A., T. L. Shanahan, E. B. Klerman, H. Martens, D. J. Brotman, J. S. Emens, T. Klein and J. F. Rizzo, 3rd (1995) Suppression of melatonin secretion in some blind patients by exposure to bright light. *N Engl J Med* **332**, 6-11.

21. Berson, D. M., F. A. Dunn and M. Takao (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* **295**, 1070-1073.

22. Hannibal, J., P. Hindersson, J. Ostergaard, B. Georg, S. Heegaard, P. J. Larsen and J. Fahrenkrug (2004) Melanopsin is expressed in PACAP-containing retinal ganglion cells of the human retinohypothalamic tract. *Invest Ophthalmol Vis Sci* **45**, 4202-4209.

23. Foster, R. G. (2004) Seeing the light...in a new way. *J Neuroendocrinol* **16**, 179-180.

24. Panda, S., T. K. Sato, A. M. Castrucci, M. D. Rollag, W. J. DeGrip, J. B. Hogenesch, I. Provencio and S. A. Kay (2002) Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. *Science* **298**, 2213-2216.

25. Rollag, M. D., D. M. Berson and I. Provencio (2003) Melanopsin, ganglion-cell photoreceptors, and mammalian photoentrainment. *J Biol Rhythms* **18**, 227-234.

26. Brainard, G. C., J. P. Hanifin, J. M. Greeson, B. Byrne, G. Glickman, E. Gerner and M. D. Rollag (2001) Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* **21**, 6405-6412.

27. Ablonczy, Z., R. M. Darrow, D. R. Knapp, D. T. Organisciak and R. K. Crouch (2004) Rhodopsin Phosphorylation in Rats Exposed to Intense Light. *Photochem Photobiol*

28. Veitch, J. A., G. van den Beld, G. Brainard and J. E. Roberts (2004) Ocular Lighting Eggects on Human Physiology and Behavior. *CIE* **158**, 1-50.

29. Roberts, J. E., R. Whitt, D. Lawless, J. S. Terman, M. Terman and J. Dillon (1992) Immune response to visible light treatment of SAD patients. *In Biological Effects of Light (Edited by M.F. Holick and A. M Kligman)* 125-132. Walter de Gruyter, New York.

30. Levi, F., C. Canon, M. Dipalma, I. Florentin and J. L. Misset (1991) When should the immune clock be reset? From circadian pharmacodynamics to temporally optimized drug delivery. *Ann N Y Acad Sci* **618**, 312-329.

31. Baldwin, W. S. and J. C. Barrett (1998) Melatonin: receptor-mediated events that may affect breast and other steroid hormone-dependent cancers. *Mol Carcinog* **21**, 149-155.

32. Levi, F. (2000) Therapeutic implications of circadian rhythms in cancer patients. *Novartis Found Symp* **227**, 119-136; discussion 136-142.

33. Lissoni, P., S. Barni, A. Ardizzoia, F. Brivio, G. Tancini, A. Conti and G. J. Maestroni (1992) Immunological effects of a single evening subcutaneous injection of low-dose interleukin-2 in association with the pineal hormone melatonin in advanced cancer patients. *J Biol Regul Homeost Agents* **6**, 132-136.

34. Maestroni, G. J. and A. Conti (1996) Melatonin and the immune-hematopoietic system therapeutic and adverse pharmacological correlates. *Neuroimmunomodulation* **3**, 325-332.

35. Filipski, E., F. Delaunay, V. M. King, M. W. Wu, B. Claustrat, A. Grechez-Cassiau, C. Guettier, M. H. Hastings and L. Francis (2004) Effects of chronic jet lag on tumor progression in mice. *Cancer Res* **64**, 7879-7885.

36. Schernhammer, E. S., B. Rosner, W. C. Willett, F. Laden, G. A. Colditz and S. E. Hankinson (2004) Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev* **13**, 936-943.

37. Pauley, S. M. (2004) Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypotheses* **63**, 588-596.

38. Conti, A. and G. J. Maestroni (1998) Melatonin rhythms in mice: role in autoimmune and lymphoproliferative diseases. *Ann N Y Acad Sci* **840**, 395-410.