CARE Committee

From: Jay Penniman <jayfp@hawaii.edu>
Sent: Tuesday, August 30, 2022 12:56 PM
To: CARE Committee; Axel I. Beers; Kelly King; James B. Forrest; Ellen B. McKinley
Subject: Bill 21 Testimony
Attachments: 2022_08_30_MNSRP_Testimony_Bill_21.doc; Untitled attachment 00090.htm; LED AMA Council on Science and Public Health.pdf; Untitled attachment 00093.htm; 2014_Mon 130pm-B. Brainard- Light at Night and Health.pdf; Untitled attachment 00096.htm; 2018_Israel_Coral_Reefs_srep42329.pdf; Untitled attachment 00099.htm; MARIO MOTTA.docx; Untitled attachment 00102.htm

Aloha,

Please find my testimony and additional references attached.

Mahalo,

Jay

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30 August, 2022

Testimony of Jay F. Penniman, Manager, Maui Nui Seabird Recovery Project

CLIMATE ACTION, RESILIENCE, AND ENVIRONMENT COMMITTEE

Wednesday, August 31, 2022 9:00 a.m.

BILL 21, CD1, FD1 (2022), SEABIRD AND BIODIVERSITY PROTECTION (CARE-74)

Aloha Chair King, Chair Lee, & Members of the CARE Committee, I am Jay Penniman and I manage the Maui Nui Seabird Recovery Project.

Thank you all for the care and effort you have taken in developing this bill for an ordinance. Committee chair King and her staff have taken a deep dive into the issues of light pollution and its impacts on our island home. They have provided the committee and the council with a well crafted outrdoor lighting ordinance proposal that will significantly improve the night environment when it is fully implemented. Concerns and issues have been raised by the administration and members of the public and the ammended ordinance effectively addresses these while maintaining the integrity of the light polution reducing improvements to Maui County‘s Outdoor lighting Ordinance.

The public works department recently commissioned an after the fact environmental assessment for the streetlights that were purchased to replace the high pressure sodium streetlights that are at the end of their life span and require much more energy to run than modern LED street lights. Unfortunately this environmental assessment has many inacuracies and fails to truely consider alternatives that would comply with the proposed bill 21 for an ordinance. I have submitted response to the draft EA and encourage all of you to read these as I presume you will also receive testimony citing the draft EA as rationale to eliminate the core of bill 21; the requirement for short wavelength spectra to be severely limited in nighttime lighting as it has been for the past ten years on Hawai‘i Island. Additionally, the LED streetlights that would comply with bill 21 also comply with the department‘s streetlight conversion goal of reducing the amount of electricity consumed and thus saving the county money. The issue of being unwilling to add filters to the streetlights because that would void the warrentee is mute because the warrentee on the power supply is either expired or will shortly expire.

I have included additional references in my submitted testimony that show the amount of reasearch documenting the detrimental effects of short wavelength light on wildlife, coral reefs, human health and dark nighttime skies for astronomical observations.

Thank you for your time and consideration of this bill and I encourage you all to vote it on to full council consideration.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-A-16

Subject: Human and Environmental Effects of Light Emitting Diode (LED) Community Lighting

Presented by: Louis J. Kraus, MD, Chair

Referred to: Reference Committee E
(Theodore Zanker, MD, Chair)

INTRODUCTION

With the advent of highly efficient and bright light emitting diode (LED) lighting, strong economic arguments exist to overhaul the street lighting of U.S. roadways.[1-3] Valid and compelling reasons driving the conversion from conventional lighting include the inherent energy efficiency and longer lamp life of LED lighting, leading to savings in energy use and reduced operating costs, including taxes and maintenance, as well as lower air pollution burden from reduced reliance on fossil-based carbon fuels.

Not all LED light is optimal, however, when used as street lighting. Improper design of the lighting fixture can result in glare, creating a road hazard condition.[4,5] LED lighting also is available in various color correlated temperatures. Many early designs of white LED lighting generated a color spectrum with excessive blue wavelength. This feature further contributes to disability glare, i.e., visual impairment due to stray light, as blue wavelengths are associated with more scattering in the human eye, and sufficiently intense blue spectrum damages retinas.[6,7] The excessive blue spectrum also is environmentally disruptive for many nocturnal species. Accordingly, significant human and environmental concerns are associated with short wavelength (blue) LED emission. Currently, approximately 10% of existing U.S. street lighting has been converted to solid state LED technology, with efforts underway to accelerate this conversion. The Council is undertaking this report to assist in advising communities on selecting among LED lighting options in order to minimize potentially harmful human health and environmental effects.

METHODS

English language reports published between 2005 and 2016 were selected from a search of the PubMed and Google Scholar databases using the MeSH terms "light," "lighting methods," "color," "photic stimulation," and "adverse effects," in combination with "circadian rhythm/physiology/radiation effects," "radiation dosage/effects," "sleep/physiology," "ecosystem," "environment," and "environmental monitoring." Additional searches using the text terms "LED" and "community," "street," and "roadway lighting" were conducted. Additional information and perspective were supplied by recognized experts in the field.

ADVANTAGES AND DISADVANTAGES OF LED STREET LIGHTS

The main reason for converting to LED street lighting is energy efficiency; LED lighting can reduce energy consumption by up to 50% compared with conventional high pressure sodium (HPS)

lighting. LED lighting has no warm up requirement with a rapid "turn on and off" at full intensity. In the event of a power outage, LED lights can turn on instantly when power is restored, as opposed to sodium-based lighting requiring prolonged warm up periods. LED lighting also has the inherent capability to be dimmed or tuned, so that during off peak usage times (e.g., 1 to 5 AM), further energy savings can be achieved by reducing illumination levels. LED lighting also has a much longer lifetime (15 to 20 years, or 50,000 hours), reducing maintenance costs by decreasing the frequency of fixture or bulb replacement. That lifespan exceeds that of conventional HPS lighting by 2-4 times. Also, LED lighting has no mercury or lead, and does not release any toxic substances if damaged, unlike mercury or HPS lighting. The light output is very consistent across cold or warm temperature gradients. LED lights also do not require any internal reflectors or glass covers, allowing higher efficiency as well, if designed properly.[8,9]

Despite the benefits of LED lighting, some potential disadvantages are apparent. The initial cost is higher than conventional lighting; several years of energy savings may be required to recoup that initial expense.[10] The spectral characteristics of LED lighting also can be problematic. LED lighting is inherently narrow bandwidth, with "white" being obtained by adding phosphor coating layers to a high energy (such as blue) LED. These phosphor layers can wear with time leading to a higher spectral response than was designed or intended. Manufacturers address this problem with more resistant coatings, blocking filters, or use of lower color temperature LEDs. With proper design, higher spectral responses can be minimized. LED lighting does not tend to abruptly "burn out," rather it dims slowly over many years. An LED fixture generally needs to be replaced after it has dimmed by 30% from initial specifications, usually after about 15 to 20 years.[1,11]

Depending on the design, a large amount blue light is emitted from some LEDs that appear white to the naked eye. The excess blue and green emissions from some LEDs lead to increased light pollution, as these wavelengths scatter more within the eye and have detrimental environmental and glare effects. LED's light emissions are characterized by their correlated color temperature (CCT) index.[12,13] The first generation of LED outdoor lighting and units that are still widely being installed are "4000K" LED units. This nomenclature (Kelvin scale) reflects the equivalent color of a heated metal object to that temperature. The LEDs are cool to the touch and the nomenclature has nothing to do with the operating temperature of the LED itself. By comparison, the CCT associated with daylight light levels is equivalent to 6500K, and high pressure sodium lighting (the current standard) has a CCT of 2100K. Twenty-nine percent of the spectrum of 4000K LED lighting is emitted as blue light, which the human eye perceives as a harsh white color. Due to the point-source nature of LED lighting, studies have shown that this intense blue point source leads to discomfort and disability glare.[14]

More recently engineered LED lighting is now available at 3000K or lower. At 3000K, the human eye still perceives the light as "white," but it is slightly warmer in tone, and has about 21% of its emission in the blue-appearing part of the spectrum. This emission is still very blue for the nighttime environment, but is a significant improvement over the 4000K lighting because it reduces discomfort and disability glare. Because of different coatings, the energy efficiency of 3000K lighting is only 3% less than 4000K, but the light is more pleasing to humans and has less of an impact on wildlife.

Glare

Disability glare is defined by the Department of Transportation (DOT) as the following:

> "Disability glare occurs when the introduction of stray light into the eye reduces the ability to resolve spatial detail. It is an objective impairment in visual performance."

Classic models of this type of glare attribute the deleterious effects to intraocular light scatter in the eye. Scattering produces a veiling luminance over the retina, which effectively reduces the contrast of stimulus images formed on the retina. The disabling effect of the veiling luminance has serious implications for nighttime driving visibility.[15]

Although LED lighting is cost efficient and inherently directional, it paradoxically can lead to worse glare than conventional lighting. This glare can be greatly minimized by proper lighting design and engineering. Glare can be magnified by improper color temperature of the LED, such as blue-rich LED lighting. LEDs are very intense point sources that cause vision discomfort when viewed by the human eye, especially by older drivers. This effect is magnified by higher color temperature LEDs, because blue light scatters more within the human eye, leading to increased disability glare.[16]

In addition to disability glare and its impact on drivers, many residents are unhappy with bright LED lights. In many localities where 4000K and higher lighting has been installed, community complaints of glare and a "prison atmosphere" by the high intensity blue-rich lighting are common. Residents in Seattle, WA have demanded shielding, complaining they need heavy drapes to be comfortable in their own homes at night.[17] Residents in Davis, CA demanded and succeeded in getting a complete replacement of the originally installed 4000K LED lights with the 3000K version throughout the town at great expense.[18] In Cambridge, MA, 4000K lighting with dimming controls was installed to mitigate the harsh blue-rich lighting late at night. Even in places with a high level of ambient nighttime lighting, such as Queens in New York City, many complaints were made about the harshness and glare from 4000K lighting.[19] In contrast, 3000K lighting has been much better received by citizens in general.

Unshielded LED Lighting

Unshielded LED lighting causes significant discomfort from glare. A French government report published in 2013 stated that due to the point source nature of LED lighting, the luminance level of unshielded LED lighting is sufficiently high to cause visual discomfort regardless of the position, as long as it is in the field of vision. As the emission surfaces of LEDs are highly concentrated point sources, the luminance of each individual source easily exceeds the level of visual discomfort, in some cases by a factor of 1000.[17]

Discomfort and disability glare can decrease visual acuity, decreasing safety and creating a road hazard. Various testing measures have been devised to determine and quantify the level of glare and vision impairment by poorly designed LED lighting.[20] Lighting installations are typically tested by measuring foot-candles per square meter on the ground. This is useful for determining the efficiency and evenness of lighting installations. This method, however, does not take into account the human biological response to the point source. It is well known that unshielded light sources cause pupillary constriction, leading to worse nighttime vision between lighting fixtures and causing a "veil of illuminance" beyond the lighting fixture. This leads to worse vision than if the light never existed at all, defeating the purpose of the lighting fixture. Ideally LED lighting installations should be tested in real life scenarios with effects on visual acuity evaluated in order to ascertain the best designs for public safety.

Proper Shielding

With any LED lighting, proper attention should be paid to the design and engineering features. LED lighting is inherently a bright point source and can cause eye fatigue and disability glare if it is allowed to directly shine into human eyes from roadway lighting. This is mitigated by proper

design, shielding and installation ensuring that no light shines above 80 degrees from the horizontal. Proper shielding also should be used to prevent light trespass into homes alongside the road, a common cause of citizen complaints. Unlike current HPS street lighting, LEDs have the ability to be controlled electronically and dimmed from a central location. Providing this additional control increases the installation cost, but may be worthwhile because it increases long term energy savings and minimizes detrimental human and environmental lighting effects. In environmentally sensitive or rural areas where wildlife can be especially affected (e.g., near national parks or bio-rich zones where nocturnal animals need such protection), strong consideration should be made for lower emission LEDs (e.g., 3000K or lower lighting with effective shielding). Strong consideration also should be given to the use of filters to block blue wavelengths (as used in Hawaii), or to the use of inherent amber LEDs, such as those deployed in Quebec. Blue light scatters more widely (the reason the daytime sky is "blue"), and unshielded blue-rich lighting that travels along the horizontal plane increases glare and dramatically increases the nighttime sky glow caused by excessive light pollution.

POTENTIAL HEALTH EFFECTS OF "WHITE" LED STREET LIGHTING

Much has been learned over the past decade about the potential adverse health effects of electric light exposure, particularly at night.[21-25] The core concern is disruption of circadian rhythmicity. With waning ambient light, and in the absence of electric lighting, humans begin the transition to nighttime physiology at about dusk; melatonin blood concentrations rise, body temperature drops, sleepiness grows, and hunger abates, along with several other responses.

A number of controlled laboratory studies have shown delays in the normal transition to nighttime physiology from evening exposure to tablet computer screens, backlit e-readers, and room light typical of residential settings.[26-28] These effects are wavelength and intensity dependent, implicating bright, short wavelength (blue) electric light sources as disrupting transition. These effects are not seen with dimmer, longer wavelength light (as from wood fires or low wattage incandescent bulbs). In human studies, a short-term detriment in sleep quality has been observed after exposure to short wavelength light before bedtime. Although data are still emerging, some evidence supports a long-term increase in the risk for cancer, diabetes, cardiovascular disease and obesity from chronic sleep disruption or shiftwork and associated with exposure to brighter light sources in the evening or night.[25,29]

Electric lights differ in terms of their circadian impact.[30] Understanding the neuroscience of circadian light perception can help optimize the design of electric lighting to minimize circadian disruption and improve visual effectiveness. White LED streetlights are currently being marketed to cities and towns throughout the country in the name of energy efficiency and long term cost savings, but such lights have a spectrum containing a strong spike at the wavelength that most effectively suppresses melatonin during the night. It is estimated that a "white" LED lamp is at least 5 times more powerful in influencing circadian physiology than a high pressure sodium light based on melatonin suppression.[31] Recent large surveys found that brighter residential nighttime lighting is associated with reduced sleep time, dissatisfaction with sleep quality, nighttime awakenings, excessive sleepiness, impaired daytime functioning, and obesity.[29,32] Thus, white LED street lighting patterns also could contribute to the risk of chronic disease in the populations of cities in which they have been installed. Measurements at street level from white LED street lamps are needed to more accurately assess the potential circadian impact of evening/nighttime exposure to these lights.

ENVIRONMENTAL EFFECTS OF LED LIGHTING

The detrimental effects of inefficient lighting are not limited to humans; 60% of animals are nocturnal and are potentially adversely affected by exposure to nighttime electrical lighting. Many birds navigate by the moon and star reflections at night; excessive nighttime lighting can lead to reflections on glass high rise towers and other objects, leading to confusion, collisions and death.[33] Many insects need a dark environment to procreate, the most obvious example being lightning bugs that cannot "see" each other when light pollution is pronounced. Other environmentally beneficial insects are attracted to blue-rich lighting, circling under them until they are exhausted and die.[34,35] Unshielded lighting on beach areas has led to a massive drop in turtle populations as hatchlings are disoriented by electrical light and sky glow, preventing them from reaching the water safely.[35-37] Excessive outdoor lighting diverts the hatchlings inland to their demise. Even bridge lighting that is "too blue" has been shown to inhibit upstream migration of certain fish species such as salmon returning to spawn. One such overly lit bridge in Washington State now is shut off during salmon spawning season.

Recognizing the detrimental effects of light pollution on nocturnal species, U.S. national parks have adopted best lighting practices and now require minimal and shielded lighting. Light pollution along the borders of national parks leads to detrimental effects on the local bio-environment. For example, the glow of Miami, FL extends throughout the Everglades National Park. Proper shielding and proper color temperature of the lighting installations can greatly minimize these types of harmful effects on our environment.

CONCLUSION

Current AMA Policy supports efforts to reduce light pollution. Specific to street lighting, Policy H-135.932 supports the implementation of technologies to reduce glare from roadway lighting. Thus, the Council recommends that communities considering conversion to energy efficient LED street lighting use lower CCT lights that will minimize potential health and environmental effects. The Council previously reviewed the adverse health effects of nighttime lighting, and concluded that pervasive use of nighttime lighting disrupts various biological processes, creating potentially harmful health effects related to disability glare and sleep disturbance.[25]

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopte , and the remainder of the report filed.

1. That our American Medical Association (AMA) support the proper conversion to community-based Light Emitting Diode (LED) lighting, which reduces energy consumption and decreases the use of fossil fuels. (New HOD Policy)

2. That our AMA encourage minimizing and controlling blue-rich environmental lighting by using the lowest emission of blue light possible to reduce glare. (New HOD Policy)

3. That our AMA encourage the use of 3000K or lower lighting for outdoor installations such as roadways. All LED lighting should be properly shielded to minimize glare and detrimental human and environmental effects, and consideration should be given to utilize the ability of LED lighting to be dimmed for off-peak time periods. (New HOD Policy)

Fiscal Note: Less than $500

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Acknowledgement: The Council thanks George Brainard, PhD (Thomas Jefferson University); Richard Stevens, PhD (University Connecticut Health Center); and Mario Motta, MD (CSAPH, Tufts Medical School) for their contributions in preparing the initial draft of this report, and the commentary by Travis Longcore, PhD, on the ecological impact of nighttime electrical lighting.

Light at Night and Human Health

George C. Brainard, Ph. D.
Professor of Neurology
Jefferson Medical College
Thomas Jefferson University
Philadelphia, PA

SALC September 14-17, 2014 Nashville, TN

Light at Night and Human Health

Learning Objectives

Participants will be able to:

1. Learn how human circadian, neuroendocrine and neurobehavioral responses are influenced by light.
2. Understand the basic neural and ocular elements that regulate the human circadian, neuroendocrine and neurobehavioral systems.
3. Review the evidence for how inappropriate exposure to light at night may be a risk factor for cancer and other disorders.
4. Discuss what is known and what is not known about the impact of outdoor lighting on human health.

Light at Night and Human Health

The presentation materials made available for the Illuminating Engineering Society of North America conference on Street and Area Lighting, September 14-16, 2014 in Nashville, TN include review articles and publications which are related to the presentation. They are:

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5) Stevens RG, Brainard GC, Blask DE, Lockley SW and Motta ME ., CA: Cancer Journal for Clinicians, 2014

Light at Night and Human Health

Lecture Notes

Light at Night and Human Health

Lecture Notes

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Lecture Notes

Light at Night and Human Health

Federal Support: NSF EEC-0812056, NASA: NSBRI through NASA NCC 9-58; National Institutes of Health (NINDS, NIMH, NCCAM, NCI); FDA; DOD; DOE

Industry Support: Panasonic Corporation and Panasonic Electric Works; Philips Lighting; OSRAM; Lighting Sciences Group; Apollo Light; Bio-Brite

Philanthropic Support: The Institute for Integrative Health: Keller Corporation; Philips Lighting; IESNA Philadelphia Chapter

Breast Cancer and Circadian Disruption From Electric Lighting in the Modern World

Richard G. Stevens, PhD[1]*; George C. Brainard, PhD[2]; David E. Blask, PhD, MD[3]; Steven W. Lockley, PhD[4]; Mario E. Motta, MD[5]

Breast cancer is the leading cause of cancer death among women worldwide, and there is only a limited explanation of why. Risk is highest in the most industrialized countries but also is rising rapidly in the developing world. Known risk factors account for only a portion of the incidence in the high-risk populations, and there has been considerable speculation and many false leads on other possibly major determinants of risk, such as dietary fat. A hallmark of industrialization is the increasing use of electricity to light the night, both within the home and without. It has only recently become clear that this evolutionarily new and, thereby, unnatural exposure can disrupt human circadian rhythmicity, of which three salient features are melatonin production, sleep, and the circadian clock. A convergence of research in cells, rodents, and humans suggests that the health consequences of circadian disruption may be substantial. An innovative experimental model has shown that light at night markedly increases the growth of human breast cancer xenografts in rats. In humans, the theory that light exposure at night increases breast cancer risk leads to specific predictions that are being tested epidemiologically: evidence has accumulated on risk in shift workers, risk in blind women, and the impact of sleep duration on risk. If electric light at night does explain a portion of the breast cancer burden, then there are practical interventions that can be implemented, including more selective use of light and the adoption of recent advances in lighting technology and application. **CA Cancer J Clin 2014;64:207-218.**

Keywords: breast neoplasms, circadian clock, melatonin production, shift work, sleep duration

Introduction

The Breast Cancer Burden

Breast cancer is the leading cause of cancer death among women worldwide.[1] Risk is highest in the economically developed societies and is increasing rapidly in those developing societies that historically showed low risk.[2] Until the 1980s, it was thought that the primary determinant of risk was a change in diet; in particular, a change from low-fat to high-fat content was extensively investigated in both rodent models and epidemiological studies. Considerable epidemiological evidence, however, has shown that fat content of adult diet has little or no effect on breast cancer risk, and the evidence for benefits of fruit and vegetable intake is weak.[3] In fact, other than alcohol intake, overall diet composition, at least in adulthood, has

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DISCLOSURES: This work was supported in part by the Institute for Integrative Health to G.C.B. and in part by grant 1R21CA129875 from the National Cancer Institute to D.E.B. This work was also supported by the National Space Biomedical Research Institute through grant NASA NCC 9-58 to G.C.B. and S.W.L. Dr. Brainard reports grants from the Institute for Integrative Health and the National Space Biomedical Research Institute during the conduct of the study; an unrestricted gift from Philips Lighting to his institution; and nonfinancial support from Lutron, Lighting Sciences Group, and Litebook outside the submitted work. In addition, Dr. Brainard has a patent titled "Portable Light Unit for Stimulating the Neuroendocrine System and Achieving Phototherapy for Depression" (Canada/Japan) licensed to G.C. Brainard; a patent titled "Photoreceptor System for Melatonin Regulation and Phototherapy" issued to G.C. Brainard and G. Glickman; a patent titled "Photoreceptor System for Melatonin Regulation and Phototherapy" pending to G.C. Brainard and G. Glickman; and a patent titled "Method for Modifying or Resetting the Circadian Cycle Using Short Wavelength Light" pending to C.A. Czeisler, G.C. Brainard, S.W. Lockley, and R.E. Kronauer. He reports speaking honoraria and/or travel expenses received in 2011 from Illuminating Engineers Society, National Aeronautics and Space Administration Behavioral Health and Performance Working Group (NASA BHPWG), and Abington Hospital; in 2012 from Illuminating Engineering Society, Parsons New School, Noche Zero, University of Michigan, National Space Biomedical Institute, AlCon, Longwood Gardens, and NASA BHPWG; and in 2013 from Illuminating Engineering Society, Philips Lighting, International Association of Lighting Design, and the Association of Research and Enlightenment. Dr. Lockley reports consultancy fees from Wyle Integrated Science and Engineering, Naturebright, Headwaters, PlanLED, Blackrock, Cowen & Company, Endurant Capital Management, Fidelity, Frankel Group, Impax Labs, Kearney Venture Partners, Lazard Capital Markets, New Horizon Capital, Perceptive Advisors, Polar Capital, ResearchWorks Inc., and Wyvern Funds; fees as an expert witness from Armstrong Management Lawyers, Rothstein Law Firm, Hicks Morley Hamilton Steward Storie LLP, and Cox & Palmer; grants to his institution from Philips Lighting and Biological Illuminations LLC; honorarium for seminar from Harvard University; patent through his institution for short-wavelength light; book royalties from Oxford University Press; payment from MediCom Worldwide Inc. for developing educational presentations; compensation for travel/accommodation/meeting expenses from Wyle Integrated Science and Engineering, Ontario Association of Fire Chiefs, the Eighth International Conference on Managing Fatigue, Rio Tinto, New England College of Occupational and Educational Medicine (NECOEM), the Connecticut Business & Industry Association Health and Safety Conference, Emergency Services Steering Committee, Cantifix, and the Illuminating Engineering Society Conference; and unrestricted gifts of lighting equipment from Philips Lighting, Bionetics Corporation, and Biological Illuminations LLC.

doi: 10.3322/caac.21218. Available online at cacancerjournal.com

very little impact, although body mass clearly does.[4] The published analyses that have attempted to adjust for changes in known risk factors have reported that less than half the risk in high-risk societies can be accounted for by changes in the established risk factors.[5-8] Recent evidence has also implicated physical activity in risk,[9] and changes in activity as societies industrialize was not taken into account in the cited studies; however, these changes would have to be massive to explain much of the differences among societies. This stands in stark contrast to most of the major cancers for which the primary causes are known (eg, lung cancer and smoking, liver cancer and hepatitis viruses, cervical cancer and human papillomavirus, stomach cancer and *Helicobacter pylori*, skin cancer and sun exposure).

Are the differences among societies in the risk of breast cancer, and the rising trends in risk in most societies, explained by a combination of many exposures working together? Or is there a major factor that has so far been overlooked[10]?

After diet, what else changes as societies industrialize? Of course, there are many changes (eg, physical activity, hormone-replacement therapy, many aspects of diet), but a hallmark of the modern world is the increasing use of electricity to light the evening and nighttime environment. Could increased exposure to light during the dark hours, which can disrupt melatonin, circadian rhythms, and sleep, be a problem?

Circadian Rhythms

Life on Earth has adapted over 3 billion years to the 24-hour cycle of light and dark from rotation of the planet as it circles the Sun. An endogenous circadian rhythmicity in physiology has developed that enables life to anticipate the change from day to night and night to day; this is true for virtually all life forms, from cyanobacteria[11] to human beings[12] and everything in between. The circadian system of cyanobacteria has yielded invaluable insight into the circadian systems of life forms in general; it is propelled by a three-gene cluster denoted KaiA, KaiB, and KaiC, with the cyclic phosphorylation of the latter apparently driving the physiological output of the clock.[13] This three-gene cluster controls global gene expression by alteration of DNA topology and controls specific gene transcripts via a feedback loop in vivo.[11] The circadian cycle of KaiC phosphorylation and dephosphorylation can be recapitulated in vitro,[14] making it easily amenable to study. In mammals, a more complex system operates, although the three core characteristics are the same: a self-sustaining, or endogenous, ~24-hour physiological oscillation; an input mechanism to signal environmental time of day; and an output mechanism to synchronize circadian-controlled behavior, physiology, and metabolism in the rest of the organism.

Human circadian biology is complex but is also generated by an interlocking molecular genetic loop designed to maintain circadian rhythmicity in cells and tissues at approximately, but not exactly, 24 hours, even in the absence of an external time cue from the Sun. In many organisms, including humans, the primary environmental time cue used to synchronize the circadian system is the daily light-dark cycle, which, in mammals, is detected by a parallel "nonvisual" light-sensing system in the retina that is anatomically and functionally distinct from vision and is devoted to measuring both the external time of day (day vs night) and the time of year or season (duration of night).

Although managing fire became possible perhaps as long ago as 1.5 million years, and the candle was developed about 5000 years ago, it has only been since the advent of electric power a little over 100 years ago that it has become possible to pervasively and brightly light the night. Importantly as well, electric lighting as currently employed is rich in blue wavelengths, which are most effective at disrupting circadian rhythmicity; in contrast, fire light from candles and wood is rich in yellow and red, which are relatively less effective in disturbing circadian rhythms (see below).

Light, whether from the Sun or electric luminaires, is the most potent environmental exposure for functionally entraining and resetting the circadian system or for disfunctionally disrupting endogenous circadian rhythmicity.

Czeisler et al[15] conducted a landmark study designed to determine the intrinsic circadian period of humans. Eleven healthy young subjects (average age, 24 years) and 13 healthy older subjects (mean age, 67 years) were placed on a "forced desynchrony" protocol in which a 14-hour dark period was followed by a 14-hour dim light period (~15 lux). Based on measurement of melatonin, cortisol, and core body temperature, the intrinsic circadian period averaged 24.18 hours in both the young and older group, and the variance was very small in both groups. These results are important; before this work, reports of the intrinsic period ranged from 13 to 65 hours.

Circadian Rhythmicity in Physiology

In humans, the master pacemaker is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Through both neural and humoral transduction, the SCN communicates with peripheral organs and tissues to synchronize clock gene expression throughout the organism to generate endogenous circadian rhythmicity. The core circadian genetic loop consists of a remarkably small number of genes, at present believed to be about 10. Yet this core controls the expression of about 10% of the entire genome[16,17]; importantly, the gene expression under circadian control is tissue-specific, with only a minority that are common among tissues. These clock genes generate an endogenous

circadian rhythmicity in physiology, which means that, under constant dark conditions, humans will cycle intrinsically at a period slightly longer than 24 hours (by ~12 minutes on average, although the population range is from ~23.6 to 25.1 hours) for the rest of their lives.[15] While a seemingly small difference from 24 hours, the daily 12-minute synchronizing shift by light that we take for granted is essential; sun in the morning is detected by the retina, which sends this signal to the SCN, which, in turn, resets the clocks in the rest of the body. Without this resetting, we could not remain entrained to the 24-hour world. Unfortunately, this is exactly what is experienced by the majority of totally blind people, whose lack of light detection prevents a necessary resetting of their endogenous circadian clock each day to precisely 24 hours, and so it runs on a non-24-hour cycle. This can cause non-24-hour sleep-wake disorder, a highly disruptive and chronic circadian rhythm disorder characterized by cyclic episodes of good sleep, followed by poor nighttime sleep and excessive daytime napping, and then good sleep again as the internal clock runs in and out of synch with the 24-hour social day, in a never-ending cycle.[18] It is not just sleep that is affected, however; all circadian-controlled systems become desynchronized, including many hormones (eg, melatonin, cortisol, thyroid-stimulating hormone), glucose and lipid metabolism, temperature regulation, cell cycles, and more.

Haus and Smolensky[19] and Blask[20] provide succinct analyses of various potential physiological mechanisms that might link circadian disruption to cancer risk; these include consequences of melatonin suppression, disruption of sleep-wake patterns, cell cycle impairment, and altered clock gene function. In addition, the role of circadian control of steroid hormone secretion by the adrenal cortex is described by Ota et al[21]; the adrenal gland plays a crucial role in communicating the time of day information from the SCN to peripheral tissues through glucocorticoid secretion, and nocturnal light disrupts this process.

Bjarnason et al[22] demonstrated circadian expression of several circadian genes (human period circadian clock 1 [*hPer1*], human cryptochrome 1 [*hCry1*], and human brain and muscle Arnt-like protein 1 [*hBmal1*]) in oral mucosa in eight healthy, diurnally active males; expression profiles were as predicted based on rodent evidence. In addition, cell cycle markers of G and S phase were also circadian, raising the possibility that cell cycle regulation was under circadian gene control. This ground-breaking work has been followed by many new insights about the interconnections of circadian gene function and cell cycle regulation in cells and tissues in general.[23] Cell cycle regulation and loss of cell cycle control are central to our understanding of the carcinogenic process; increased normal cell turnover increases risk of mutations in general, and in tumor suppressor genes in particular, leading potentially to a transformed cell and the beginning of the path to a diagnosed cancer. Therefore, chronic disruption of clock gene expression that leads to cell cycle deregulation could provide a chronic stimulus, increasing DNA replication errors and resulting mutations. Many aspects of DNA damage response are also under circadian control,[24] thus potentially exacerbating the impact of disruption of circadian rhythmicity on cell cycle regulation and initiation of cancer. Studies in rodents and cell systems of the effect of "circadian disruption" by clock gene knockout (KO) (eg, *Per2*, *CLOCK*, *Cry1*) on cancer risk, however, are mixed.[25-28]

A further aspect of circadian impact is the investigation of a fundamental link between circadian gene expression and metabolism[29]; this connection opens a plethora of potential adverse effects of circadian disruption. In particular, CLOCK is a histone acetyltransferase (HAT) that appears to counterbalance sirtuin 1 (SIRT1), a histone deacetylase. Another clue on the circadian-metabolism connection is that the long sought ligand for nuclear receptor subfamily 1, group D, members 1 and 2 (REV-ERBα and REV-ERBβ, respectively), key elements of the circadian oscillator, is heme.[30] In our evolutionary history, what better single molecule could our endogenous circadian system use to assess the nutritional status of our mammal than heme?

Impact of Electric Light at Night on Circadian Rhythmicity

In 1980, the first clear evidence was published in *Science* that ocular exposure to bright white light during the night could suppress melatonin production in young adults.[31] Since that seminal report, great detail has emerged on the impact of wavelength, intensity, duration, and time of night on the acute suppression of melatonin production by light. Similarly, much more is understood about how light resets the timing of the circadian clock and the rhythms it controls, often measured from the timing of the melatonin rhythm but also including cortisol, core body temperature, and circadian gene expression.

Initially, it was thought that bright light, at least 2500 lux, was required for melatonin suppression in humans.[31] More recently, however, it has been shown that, under carefully controlled conditions, retinal exposure to illuminances of as low as 1 lux or less of monochromatic light at wavelength 440 to 460 (blue-appearing light) can significantly lower nocturnal melatonin,[32,33] as can <100 lux of broad-spectrum fluorescent light.[34-37] These same light levels can also elicit significant phase shifts of the circadian clock and directly enhance alertness[37-40]; approximately 100 lux exposure will cause about 50% of the maximum response. Such light exposure, when experienced in the evening at home from bedside lamps, TVs, computer screens, tablets, and other devices, causes suppression of melatonin, delays the

timing of circadian rhythms, and elevates alertness, all of which make it harder to fall asleep, make it harder to wake up in the morning, and restrict sleep.[36,41]

The physiological mechanism by which light exposure is conveyed to the circadian system is one of the more intriguing topics in modern biology[42]; a hitherto unknown intrinsically photosensitive retinal ganglion cell (ipRGC) was reported in 2002 in *Science*.[43-45] This novel photoreceptor is anatomically and functionally distinct from the rods and cones used for vision and is a more fundamental aspect of mammalian biology, having evolved before vision.[46] These ipRGCs, which represent <1% of ganglion cells, contain the photopigment melanopsin, which is maximally sensitive to blue light (λmax, ~480 nm). The cells are spread across the retina to provide a network of light detectors across the eye, which is further enhanced by the melanopsin contained in their dendritic fields, and are hardwired to areas of the brain involved in regulation of circadian rhythms and alertness.[47,48] While rods and cones play a role in light detection for the circadian system,[49,50] melanopsin is the primary photoreceptor by which light information is transduced to the circadian system.

It is now evident that, among other things, 1) bright light exposure at night suppresses melatonin in all sighted persons[31]; 2) shorter wavelength (blue) light is most effective and longer wavelength (red) is least effective in melatonin suppression, alerting the brain, and resetting the circadian pacemaker[32,40,51]; 3) there is a dose response in which, the greater intensity of the light, the greater percentage suppression of melatonin[37,52]; 4) there are differences in individual sensitivities to light-induced melatonin suppression[53-55]; and 5) characteristics of daytime lighting can alter sensitivity to light exposure during the night.[56-59] These and other properties of light that are under investigation have important implications for future research directions, design of epidemiological studies, and finally, for potential intervention and mitigation.

Sleep Disruption Versus Circadian Disruption

Adequate sleep is required for optimal cognitive function and for many other aspects of well-being that are not entirely understood. Inadequate or interrupted sleep has short-term safety consequences through increased sleepiness and potential longer term risks to chronic diseases, including cardiovascular disease, diabetes, and some cancers. Sleep is essential to health; however, it is not sufficient to synchronize the circadian clock: a strong daily cycle of light and dark is required (although, at least in mammals, the sleep-wake cycle gates light exposure to the retinae for entrainment of the circadian clock by the opening and closing of the eyes and, so, is an important practical consideration). The normal nocturnal rise in circulating melatonin is not affected by being asleep or awake but is severely attenuated by light exposure during the night.

Research on sleep and health cannot entirely separate effects of sleep duration from duration of exposure to dark, because the sleep-wake cycle gates light-dark exposure to the SCN and pineal[60]; therefore, the results of observational and laboratory experimental research are difficult to interpret. The distinction is important. A requirement for a daily and lengthy episode of darkness to maintain optimal circadian health has different implications than a requirement that one must be asleep during this entire period of dark; it may be normal to have wakeful periods in the middle of a dark night.[61]

Electric light exposure during the night can disrupt sleep as well as circadian rhythmicity. The long-term health effects of short sleep and circadian disruption are both increasingly receiving research attention.[62,63] Short or interrupted sleep has been shown in observational studies and in carefully controlled experiments to have marked impacts on markers of metabolic disorders.[64,65] Because dark and sleep are difficult to adequately disentangle in studies of diurnal animals such as humans, it is not clear whether the proximate cause of metabolic changes is sleep disruption itself, disruption of circadian physiology, and/or a direct effect of light exposure. For example, Taheri et al[66] examined sleep as determined by polysomnography in 1024 adults and found that sleep duration was significantly associated with morning levels of leptin in the blood. In the same group of subjects, however, total reported hours of sleep were more strongly associated. The mean reported sleep duration was 7.2 hours, whereas the mean of verified sleep was 6.2 hours, an entire hour shorter. Self-reported "sleep" probably relates to the number of hours between lights out in the evening and getting up in the morning, or, total hours of dark.

Another example is described by Moller-Levet et al.[67] In that experimental study, 26 subjects (12 female; mean age, 27 years) were exposed to 1 week of "sufficient sleep" and 1 week of "insufficient sleep" in a balanced cross-over design, and then a transcriptome analysis was performed; the authors reported that 711 genes were either up-regulated or down-regulated by "insufficient sleep." They also reported that restricted sleep altered melatonin by delaying its phase and blunting its amplitude. The restricted sleep protocol, however, required 18 hours of bright light (and the paper is surprising in its lack of detail on the lighting used in the experimental conditions), whereas the "control" condition required exposure to 14 hours of bright light. The authors designated the control condition as one in which there was an "opportunity" for 10 hours of sleep, and the restricted condition was the opportunity for only 6 hours. The longer lighted period for the restricted condition would be expected

to truncate melatonin production, but this does not mean that a person at home in 10 hours of dark who only actually sleeps for 6 hours has any impact on melatonin production or gene expression.

Buxton et al[68] attempted to disentangle the effects of circadian disruption from those of sleep disruption on metabolic disorders in humans. In their experiments, the combination of the two had large effects on the resting metabolic rate and plasma glucose concentrations, both in directions that would be expected to increase the risk of obesity and diabetes if maintained chronically. It is not yet clear which type of disruption, circadian or sleep, has the greater effect, or how they interact, however. Future research should attempt to distinguish the relative roles of circadian disruption, sleep disruption, melatonin suppression, or light itself on the interaction between electric lighting and adverse health effects, as these distinctions are vital to guide intervention strategies.

Animal Models of Light and Cancer

Investigation of light effects on mammary tumorigenesis in rodents began in the 1960s.[69-78] For both chemically induced and spontaneous tumors, most of these studies showed an increase in tumor incidence and number by exposure to a constantly lighted environment compared with a 24-hour alternating schedule of light and dark (eg, 24 hours of light vs 12 hours of light:12 hours of dark). Beginning in the 1980s, researchers focused more closely on the ability of melatonin to inhibit mammary carcinogenesis and on the impact of a constant light environment in animal rooms on mammary tissue development, and major effects were reported.[79,80] Because the stimulatory effects of constant light on mammary tumorigenesis mimicked the tumor-promoting effects pinealectomy, it was proposed that the light-induced suppression of melatonin production was specifically responsible for augmenting mammary carcinogenesis. At the time of these studies, light was used as a tool for melatonin suppression and, itself, was not considered as a human exposure of consequence. It is important to note that constant exposure to bright light not only suppressed melatonin synthesis in these experiments but also induced additional detrimental effects on the circadian activity of the SCN in general.

In the early 2000s Blask and colleagues began to examine the effect of various levels of light during the night on the growth of a human breast cancer xenograft in nude rats.[81,82] They predicted that nighttime light exposure would suppress melatonin and that this suppression would significantly increase an existing tumor's ability to utilize linoleic acid for its growth.[83] This prediction was based on previous work showing that nocturnal melatonin directly suppressed the growth of both estrogen receptor-positive and estrogen receptor-negative tumors and that linoleic acid, which is required for the growth of breast tumors, is also suppressed by nighttime levels of melatonin. Therefore, linoleic acid and its mitogenic metabolite can be used as markers of tumor growth rate in response to endogenous nocturnal melatonin signal and its suppression by light at night.[81-84]

Consistent with their prediction, Blask et al[81,82] found a dose-dependent suppression by nighttime fluorescent light exposure on blood melatonin levels in exposed rats, a significant increase in metabolism of linoleic acid in the human breast cancer xenografts, as well as a large increase in tumor growth rate; the estimated tumor weight (from palpation) attained 5 g at 30 days post-implantation in constant dark, whereas it attained 5 g at 15 days in the constant light condition. The dose response was dramatic; and, even at the lowest illumination level, there was a partial suppression of melatonin and a corresponding increase in tumor growth rate.

Blask et al[81] took this experimental design an important step further by perfusing the human xenografts growing in the nude rat with human blood taken from young women under three conditions: 1) during the day, 2) at night during the dark, and 3) at night after light exposure to the subject. Blood taken at night in the dark and, thus, high in melatonin, strongly inhibited the growth and metabolism of the xenografts; whereas blood taken at night from the same young women after light exposure and, thus, low in melatonin, did not slow the tumor growth at all. Moreover, the addition of melatonin to the blood taken after nighttime light exposure restored to it a strong tumor-inhibitory capacity; whereas the addition of a melatonin antagonist to the blood taken in the dark obliterated its tumor-inhibitory capability. These results clearly demonstrated that the tumor-inhibitory effect of blood taken at night was because of its melatonin content.

Other notable recent animal experiments also designed to test the idea that circadian disruption from electric light may increase cancer risk have shown that simulated jet lag stimulates cancer growth in mice[85,86]; the cell line used was Glasgow osteosarcoma. It must be noted that Filipski et al[85,86] deliberately chose a mouse strain that had a weak and inverted melatonin rhythm, with low circulating levels during the night and a daytime peak. Their goal was to identify a cancer-promoting effect of light that was not mediated by melatonin suppression.

Anticancer Mechanisms of Melatonin

There is strong experimental evidence that, in complete darkness, melatonin inhibits the growth of established, but extremely small, tumors; these tumors may never progress to become a clinically detectable neoplasm, in part because of the oncostatic effect of melatonin.[87,88] This inference is based on a series of experiments first using murine tumor

lines implanted into rats and then using human breast cancer xenografts implanted into the rat model. The theory that light at night may increase cancer risk was originally based on a light-induced suppression of melatonin.[89]

Melatonin may also aid in preventing cancer initiation as well because of its antiproliferative and antioxidant capacities, its ability to enhance immune surveillance, and its effects in modulating cellular and humoral responses and epigenetic alterations.[90-95]

Light and Breast Tissue Development

The important experiments by Blask and colleagues[81,82] focus on the growth of existing but small tumors that might never survive but for the melatonin suppression from exposure to light at night. There may be other potential mechanisms by which circadian disruption might induce cancer. Cancer development is believed to follow a multistage, or multihit, process in which an accumulation of mutations eventually results in a normal cell transforming into a malignant cell capable of growing into a clinically detectable neoplasm.[96] The mutations are believed to be essential; however, cancer-causing agents do not necessarily have to be directly mutagenic; altered growth and development of a tissue, such as breast, can have a profound impact on the chances that the essential mutations will occur over time. It is for this reason that estrogen levels, age at menarche, and child bearing are believed to play such an important role in risk of breast cancer; they all affect the normal growth and development of breast.[97]

The early experiments of Mhatre et al[79] and Shah et al[80] found that constant light had a measurable impact on breast tissue development in rats. When constant light was initiated in utero to pregnant dams,[80] tumor yield from dimethylbenzanthacene (DMBA) administration at age 55 days to the female offspring was substantially increased; the mammary tissue in exposed rats was also found to be rich in terminal end buds, the structures most susceptible to chemical mutagenesis.[79] In contrast, Anderson et al[98] initiated constant light when the female rats were 26 days old (having been on a 12:12 hour light:dark cycle until then) and found that tumor yield was actually reduced. Remarkably, Anderson et al[98] also found that the exposed rats had evidence of rapidly advanced terminal differentiation of breast tissue, and most began lactating though still virgin. This, the authors surmised, rendered their breast tissue refractory to malignant transformation by DMBA. The difference in timing of light exposure between the work of Shah et al[80] and Anderson et al[98] had a large effect on tumor yield. This area deserves vastly more investigation.

By these mechanisms, exposure to light at night early in life (even in utero from exposure of the pregnant mother[99]) may affect breast cancer risk throughout life.

Epidemiological Studies of Circadian Disruption and Breast Cancer

The first suggestion that light at night might explain a portion of the breast cancer pandemic was made in 1987.[10,100] The hypothesis was based on the idea that exposure to light at night would result in melatonin suppression, which, in turn, would increase breast cancer risk as described in the previous section. Since 1987, a series of predictions of this theory have been tested, including: that shift working women should be at higher risk[101]; blind women should be at lower risk[102]; risk would have an inverse association with sleep duration[103]; and, across societies, the incidence of breast cancer and nighttime ambient illumination, as measured by satellite image, should be correlated.[104] In general, predictions of the theory have been supported.[105]

Shift Work

The strongest evidence to date are data showing that women who work nights (shift work) are at higher risk of breast cancer. These data led the International Agency for Research on Cancer (IARC) to conclude that "shift work that includes circadian disruption is probably carcinogenic to humans (Group 2A)."[106] The American Medical Association then broadened the topic in a policy statement in 2012 on the health hazards of light at night in general.[107] Since the IARC classification, there have been more epidemiological studies in various settings and populations that have supported an association,[108-112] with one showing mixed results[113] and one that reported no association.[114] These and the previous studies are reviewed together in a meta-analysis by Jia et al,[115] who reported that, among the "high-quality studies," night work was associated with an increased risk of breast cancer (relative risk, 1.4; confidence interval, 1.13-1.73).

An issue for the interpretation and comparison of the published studies is that there has not been a uniform definition of "shift work" used across the studies. Some studies focused on rotating shifts, others on "graveyard shift," and others on any non-day shift; some studies analyzed risk according to duration in years of work, but not in the intensity (eg, the number of shifts per week or per month) over the working life, while others did examine intensity as well as duration. In 2009, the IARC convened a workshop of 23 experts in occupational medicine and epidemiology; the task was to attempt some sort of consensus on what are the most disruptive and what are the least disruptive features of non-day shift work.[116] The authors concluded that future epidemiological studies should attempt to quantify all three of these shift work features in exposure assessment: 1) shift schedule (eg, evening, night, rotating), 2) years on each shift schedule, and 3) shift intensity.

Shift work has been used as a surrogate for exposure to light at night and circadian disruption in the epidemiological studies of cancer. (This circadian disruption can include

melatonin suppression, clock gene disruption, and sleep disruption; the epidemiological studies to date cannot distinguish among these three.) The weight of evidence strongly supports a suppression of melatonin amplitude and disruption of its phase,[117-121] although not all studies have found this[122]; there is also one report that race or ethnicity may modify the impact of shift work on melatonin production.[123] If shift work is a surrogate for light at night exposure, then another important consideration in evaluation of these studies is that the comparison groups, day workers, are certainly not unexposed. Almost all persons in the modern world use electric lights in the evening and at night. The degree of melatonin suppression is a continuum, with shift workers likely to be the most suppressed and blind people the least (on average), but each and every day, people suppress their melatonin to some degree if they are not in the dark at dusk and stay there until dawn. Similarly, all people in the modern world experience some degree of circadian or sleep disruption because of electric light, and, again, the degree of disruption is distributed continually. The electric light exposures typically seen in the evening at home have strong effects on suppressing melatonin, shortening sleep, and disrupting circadian rhythmicity (see section above: "Impact of Electric Light on Circadian Rhythmicity").

Blindness

Hahn[102] published the first evidence that blind women may be at lower risk of breast cancer than sighted women. He reasoned that, if light during the night increased risk, then blind women should be at lower risk because they may have an inability to detect light and would not be inclined to use electric lighting at any time of day or night. There have been four studies since then that have each supported Hahn's prediction, albeit in small numbers of cases[105,124]; in 3 of these, the confidence interval for the reduced relative estimate for total blindness included 1.0; however, in one of these, the trend in lower risk with increasing degree of visual impairment was statistically significant. It must be noted that, on average, however, blind women have not been shown to exhibit greater 24-hour melatonin production[124]; what is different is that blind women cannot have their endogenous melatonin signal blunted or altered by electric lighting as it can be in sighted women.

Sleep Duration and Disruption

Another prediction of the theory that electric light exposure at night leads to circadian disruption and, hence, increases cancer risk is that short and/or disrupted sleep would be associated with elevated risk by exposing individuals to more light and/or suppressing melatonin to a greater extent. The first report to test this prediction was by Verkasalo et al.[103] Subsequent results have been mixed, so the evidence to date is inconclusive.[105] In particular, Girschik et al[125] reported on a case-control study of breast cancer from Australia that neither sleep duration nor sleep quality was associated with risk. However, for this particular exposure, sleep, the case-control design may be highly prone to bias, both recall bias but, more likely, bias by indication in which a development of breast cancer changes sleep habits.[126] These studies have not isolated sleep, because when sleep changes, so does light exposure, and many other metabolic changes occur. The physiological changes purported to be because of sleep restriction[64,65] may, in part, be because of light extension.

Ecological Analyses

If ocular exposure to light at night increases breast cancer risk, then communities with high levels of ambient nighttime light should be associated with higher incidence rates.[127] This was first tested by Kloog et al[104] using the Israeli National Cancer Registry and Defense Meteorological Satellite Program (DMSP) illumination data (ospo.noaa.gov/Operations/DMSP/index.html). Among 147 communities, the breast cancer incidence and the nighttime light level were significantly correlated; the highest lighted community had a 73% higher incidence compared with the lowest after controlling for demographic variables of ethnic makeup, birth rate, population density, and local income level. Lung cancer incidence was also analyzed as a "negative" control, and, in fact, there was no correlation of nighttime illumination and lung cancer incidence, as predicted.

Kloog et al[128] extended this analysis to 164 countries of the world using the GLOBOCAN 2002 database and again the DMSP database. Cancers of lung, colon, larynx, and liver were also analyzed with the expectation that they would not be correlated with nighttime illumination, and they were not. Breast cancer incidence was significantly associated with nighttime illumination, and it was estimated that the risk was 30% to 50% higher in the highest lighted countries compared with the lowest after controlling for fertility rate, per capita income, percent of urban population, and electricity consumption. In a similar approach, Bauer et al[129] conducted a case-referent analysis of geographic location of residence in the state of Georgia, USA. With breast cancer as the case and lung cancer as the referent, the odds ratio for the highest of three light level categories (constructed from the DMSP light level data) was 1.12 (confidence interval, 1.04-1.20), further supporting the association of higher levels of ambient nighttime light exposure and breast cancer risk.

Circadian Gene Polymorphisms

The initial suggestion that circadian gene polymorphisms might be related to breast cancer risk focused on CLOCK

and a possible interaction of it with cell cycle regulation, specifically cyclin D1[130]; these ideas were expanded upon a few years later.[131]

The first investigations into the effects of disruption of circadian gene function on risk were conducted by Yong Zhu and colleagues beginning with a report of a circadian gene polymorphism associated with breast cancer risk published in 2005.[132] These authors selected the variable number tandem repeat (VNTR) polymorphism in the coding region of Per3, one of the core circadian genes, because it had been previously reported to be associated with affective disorder and diurnal preference.[133] Loss of this gene has a more subtle phenotypic impact than loss of Per1 or Per2, in that Per3 KO in mice does not result in a complete loss of circadian control but, rather, results in a shortened circadian period by about 30 minutes.[134] Recently in humans, the less common 5/5 genotype was shown to be associated with self-reported sleep patterns that were different from persons with the 4/4 and 4/5 genotypes (ie, earlier wake time, bed time, and less daytime sleepiness) in a prospective study of 675 subjects aged 20 to 35 years in England.[135] The sleep assessments were based on a questionnaire. A smaller study using polysomnography on 22 healthy subjects did not show any difference in sleep behavior but did show differences in sleep architecture between 5/5 subjects compared with 4/4 subjects, such as more slow wave sleep.[136]

Zhu et al[132] reported an odds ratio of 1.7 (confidence interval, 1.0-3.0) for premenopausal women with the 5/5 or 5/4 genotype compared with the 4/4 genotype. Intriguingly, it has recently been reported that persons with the 5/5 genotype are more sensitive to the suppressive effect of blue-enriched light at night than those with the 4/4 genotype.[55] A limited number of further studies have been conducted of other circadian gene polymorphisms with mixed results.[137,138]

It is too soon to tell whether these efforts will lead to a coherent story that might result in some sort of screening or therapeutic benefit.

Circadian Gene Expression

There have been a limited number of studies showing differences in circadian gene expression in breast tumor tissue compared with surrounding normal tissue,[139] and those studies are difficult to interpret at present. Another approach has been to assess global differences in markers of circadian gene expression using peripheral blood lymphocytes (PBLs) in breast cancer cases and controls. For example, significant hypomethylation of the *CLOCK* promoter and hypermethylation of the *CRY2* promoter were found when comparing PBLs from breast cancer cases and controls.[140,141] This was followed by a study showing similar differences between day-working and night-working women in promoter methylation of these two genes,[142] which provides another possible mechanism for an increased risk in night workers. This is an exciting and emerging area of investigation.

Other epigenetic mechanisms may also connect circadian gene expression and breast cancer risk. Sahar and Sassone-Corsi[143] proposed that, because CLOCK has HAT activity, it may alter expression of cyclin D1, the gene product of which plays a critical role in cell cycle regulation and reportedly is associated with breast cancer risk.[144]

Future Directions—Intervention and Mitigation

It is now clear that electric lighting, including indoor evening light levels, has strong effects on human circadian rhythms in physiology, metabolism, and behavior. Recent experimental evidence in humans has shown, for example, that the lighting commonly used in the typical home in the evening is enough to delay melatonin onset and blunt its nocturnal peak.[36] Even the display screens of personal computers, which often emit light rich in the blue portion of the visible spectrum, can alter melatonin production in the evening.[41] It is not certain that these alterations, in fact, can increase breast cancer risk; that evidence is accumulating but is not yet conclusive. However, chronic disruption of circadian rhythmicity has the potential to yield serious long-term health consequences.

Nocturnal light exposure and circadian disruption may be particularly important for children,[145] and even exposure to the mother while pregnant may affect fetal exposure to altered hormone levels in utero. Wada et al[146] have reported one of the first studies of maternal circulating estradiol and testosterone levels; levels were higher among women who reported typically being awake at 1 AM, and there was an inverse relationship of reported sleep duration and hormone levels among these pregnant women. Much more study of the impact of the home light environment of children and pregnant women should be conducted.

An analogy exists between breast cancer in women and prostate cancer in men in the sense that both are considered primarily hormone-driven cancers, each is the most common cancer worldwide in each gender (after lung cancer in men), and for neither are there convincing explanations for their high incidence in the industrialized world. Much less research exists on circadian disruption in prostate cancer than breast cancer, but there is some limited evidence.[105] In a prospective study conducted in Iceland, Sigurdardottir et al[147] focused on sleep and found that men who reported poor-quality sleep at baseline were at about a 2-fold higher risk compared with men who reported good-quality sleep. The authors argued that disrupted and poor-quality sleep reflects circadian disruption as well. Flynn-Evans et al[148] exploited the 2005-2006 National Health and Nutrition Examination Survey (NHANES)

database for a cross-sectional study to determine whether men working non-day shifts had elevated prostate-specific antigen (PSA) levels, and they found a strong relationship. Men with PSA levels >4 ng/mL were more than twice as likely to also be non-day shift workers than men with PSA levels <4 ng/mL; men with PSA levels >10 were nearly 4 times as likely to be shift workers. The authors argue that this suggests an elevated risk of future prostate cancer.

Another area of research that demands attention is the effect of light-induced circadian disruption in breast cancer patients with respect to the progression of their disease and their responsiveness to chemotherapy, hormonal therapy, radiotherapy, and/or targeted biological therapy. For example, do breast cancer patients who are circadian disrupted exhibit increased resistance to, and toxicity from, various standard therapeutic modalities compared with "circadian-intact" patients? Many cancer patients experience circadian disruption and sleep disturbances because of the presence of disease and/or the effects of therapy in addition to an altered light exposure over the 24-hour daily cycle. Would chronic exposure of breast cancer patients to light at night throughout the course of their disease and treatment result in unnecessary treatment failures? Such treatment failures might lead to accelerated disease progression and increased morbidity/mortality, which could be avoided altogether by correcting the underlying circadian regulatory deficit by appropriate circadian-friendly lighting of their homes and, to the extent possible, in hospital. This not only might serve to slow down or even halt disease progression but conceivably could open the door for circadian-optimized cancer therapy, which might improve the chances of disease remission or even cure.

As research on a possible increase in breast cancer risk grows (and other health concerns, such as other cancers, metabolic disorders, and childhood development), so too has research on lighting technologies that remain visually effective yet support improved regulation of human circadian, neuroendocrine, and neurobehavioral systems; this research is both in photonics (ie, light-emitting materials) and in lighting applications. For example, the new solid-state lighting system being developed for installation on the International Space Station in 2015-2016, is designed to provide astronauts optimum visual support as well as improved sleep, circadian entrainment, and daytime alertness.[149] In another innovative approach, Jou et al[150] report on the development of a light-emitting diode that mimics the spectral irradiance of candle light, which would presumably have much less impact on the circadian system if used in the evening instead of a blue-enriched compact fluorescent light bulb.

An important direction for future research includes developing novel animal models and experimental strategies that can determine the relative contributions to breast cancer risk of circadian phase shifts, sleep deprivation, and nocturnal melatonin suppression within the spectrum of circadian disruption induced by light exposure at night. In particular, there is a need for extensive investigation of the impact of circadian disruption on sex hormone production, distribution, and function in humans (eg, estrogens), as these have known and strong effects on breast cancer risk. The interactions among these factors are undoubtedly complex, and parsing out their individual as well as relative contributions to breast cancer risk may be a formidable challenge—the whole, indeed, may be greater than the sum of its parts.

Lighting technology is rapidly advancing, and it could have pervasive adverse health effects if we do not understand its disruptive potential. But this same technology also allows for a more sophisticated control of lighting to much better accommodate circadian health in this increasingly lighted, industrialized world. ■

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Opinion

Cell PRESS

Measuring and using light in the melanopsin age

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Light is a potent stimulus for regulating circadian, hormonal, and behavioral systems. In addition, light therapy is effective for certain affective disorders, sleep problems, and circadian rhythm disruption. These biological and behavioral effects of light are influenced by a distinct photoreceptor in the eye, melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs), in addition to conventional rods and cones. We summarize the neurophysiology of this newly described sensory pathway and consider implications for the measurement, production, and application of light. A new light-measurement strategy taking account of the complex photoreceptive inputs to these non-visual responses is proposed for use by researchers, and simple suggestions for artificial/architectural lighting are provided for regulatory authorities, lighting manufacturers, designers, and engineers.

Light as a regulator of physiology and behavior

During the past three decades, empirical evidence has demonstrated that many aspects of human physiology and behavior are influenced by retinal illumination [1–4]. Such responses originate in the eye but are separate from other aspects of vision insofar as they are unrelated to particular spatial patterns of light exposure, and can survive even in some blind subjects. Consequently, these types of light responses have been commonly referred to as non-image-forming or non-visual.

These catch-all terms encompass a wide array of response types. The most influential is light-induced phase resetting of endogenous circadian clocks. Because circadian rhythmicity is a feature of nearly every physiological, metabolic, and behavioral system, this phenomenon brings a wide array of biological processes under indirect retinal control. Beyond this, the term non-visual response has come to encompass a growing list of more acute effects of light that together ensure a day-like physiological state. Thus, for example, light constricts the pupil, suppresses pineal melatonin production, increases heart rate and core body temperature, stimulates cortisol production, and acts as a neurophysiological stimulant (increasing subjective and objective measures of alertness and psychomotor reaction time, and reducing lapses of attention).

Appreciation of this basic biology has led to the development of a number of therapeutic applications. Light has been shown to have anti-depressant properties, particularly in the treatment of seasonal affective disorder (SAD) and its subclinical variant sSAD [3,4]. Appropriately timed light exposure has also been developed as therapy for circadian-rhythm sleep disorders and circadian disruption associated with jetlag, shift work, and space flight. Finally, light has been explored as a treatment for non-seasonal depression, menstrual-cycle-related problems, bulimia nervosa, and cognitive and fatigue problems associated with senile dementia, chemotherapy, and traumatic brain injury [3–6].

These effects of light on physiology and behavior evolved over millennia in which environmental illumination provided a reliable indicator of time of day. The advent of

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0166-2236/$ – see front matter
 http://dx.doi.org/10.1016/j.tins.2013.10.004

electrical lighting has disrupted this relationship, with patterns of light exposure now also reflecting personal tastes and social pressures. It is important therefore that non-visual effects of light are incorporated into considerations for lighting design. Thus, for example, one might ask to what extent a given architectural lighting replicates the biological effects of natural daylight; how lighting could be employed to minimize the deleterious effects of shiftwork while promoting alertness and safety; or how light therapy could be optimized.

The lighting industry and academic researchers have started to address these problems [7–9]. Progress in these endeavors, however, first requires appropriate quantification of how light impacts human physiology and behavior. There are two broad categories for light measurement techniques: radiometry and photometry [10]. Radiometry is based on characterizing the physical properties of light wavelength and energy. A radiometer quantifies radiant power over a defined bandwidth of electromagnetic energy. Photometry is a specialized branch of radiometry that takes into account the fact that biological photoreceptors are not equally sensitive to light at all wavelengths. A photometer is a radiometer that uses filters to weight the detector response to different wavelengths according to the spectral sensitivity of an aspect of human vision. Most commercially available photometers use a weighting function termed the photopic luminous efficiency function (or V_λ), which reflects the spectral sensitivity of long- and middle-wavelength-sensitive cones [11]. Depending on the geometric properties of interest, luminous intensity (units of lumens/sr or candelas, cd), luminance (cd/m^2), or illuminance (lm/m^2 or lux) can be determined from the output of these devices.

Between 1980 and 2000, the great majority of studies on human circadian, endocrine, behavioral, and therapeutic responses to light quantified stimuli in terms of photopic illuminance (lux) [1–3]. During that time, lux meters were readily available and inexpensive because they were the tool of choice in the lighting and photographic professions. Two related branches of investigation have since shown that this practice is inadequate.

First, during the last decade it was discovered that whereas the photoreceptive capacity of the retina is dominated by rods and cones, a few of the retinal output neurons (retinal ganglion cells) are also directly photosensitive [12,13]. These intrinsically photoreceptive retinal ganglion cells (ipRGCs) achieve this photoreceptive capacity through expression of melanopsin, an opsin photopigment [14–16]. ipRGCs comprise only a small fraction of the total ganglion cell population (1–5%, depending on the species and method of estimation), but project to all major retinorecipient parts of the brain, including those associated with non-visual responses [17–19]. Specific ablation of ipRGCs abolishes non-image-forming responses, identifying this cell class as the principal conduits of photic input to circadian and other systemic responses to light [20–22]. Furthermore, ipRGCs can detect light even when isolated from the rest of the retina, explaining why some photosensitivity survives loss of functional rods and cones [12,23–29]. This discovery of a new photoreceptor raises the possibility that the spectral sensitivity of non-image-forming responses could be fairly different from that of rod- or cone-based vision.

Second, empirical observations have shown that circadian and other behavioral and physiological responses can indeed have very distinct spectral sensitivity. Ten analytic action spectra and many investigations based on selected wavelength comparisons of such responses in humans, non-human primates, and rodents revealed peak sensitivity in the short-wavelength portion of the visible spectrum (from 447 to 484 nm) [12,30–45], fairly divergent from that predicted by V_λ (peak sensitivity at 555 nm).

Taken together, these data demonstrate that established photometric light measures that use the V_λ spectral weighting function, such as photopic lux, are inadequate for quantifying light intended to regulate non-visual physiology and behavior. Unfortunately, to date there is no established replacement. This omission has important practical consequences. For researchers, the absence of a suitable and agreed method of light measurement makes it difficult to compare findings or replicate experimental conditions. It also represents a significant barrier to relating laboratory findings to lighting applications, and makes it difficult for the lighting industry and regulators to predict the impact of different lighting regimes on behavioral and physiological systems. The fundamental problem in addressing this need has been the difficulty in determining a spectral weighting function (equivalent to V_λ) suitable for non-visual responses. To understand this challenge it is first necessary to review the basic neurophysiology of ipRGCs.

The response of ipRGCs to light

Melanopsin, the photopigment of ipRGCs, is structurally and phylogenetically more closely related to the opsins of invertebrate rhabdomeric photoreceptors than to rod and cone opsins [46,47]. In common with such invertebrate rhodopsins, the phototransduction cascade engaged by melanopsin results in cellular depolarization [48]. As a result, the fundamental light response of ipRGCs is an irradiance-dependent increase in firing [12].

The quantum efficiency of melanopsin is comparable to that of rod and cone opsins [49]. ipRGCs, however, lack specialized photopigment-concentrating organelles (such as rod/cone outer segments) to maximize the probability of photon capture. As a result, the probability of absorbing a photon is >1 million times lower than in rods or cones for a given area of photostimulation [49]. Consequently, even though the ipRGC phototransduction cascade has high amplification [49], melanopsin photoreception is much less sensitive than that of rods or cones. Once the threshold for melanopsin activation has been reached, however, the intrinsic light response scales with stimulus intensity over several decimal orders [12], and is remarkably persistent, being sustained over long durations of constant illumination [50].

Although melanopsin phototransduction is only engaged at moderate to high irradiance, ipRGCs and their downstream responses can be responsive to much lower levels of illumination [51]. For example, it was originally thought that illuminance of 2500 lux was required to

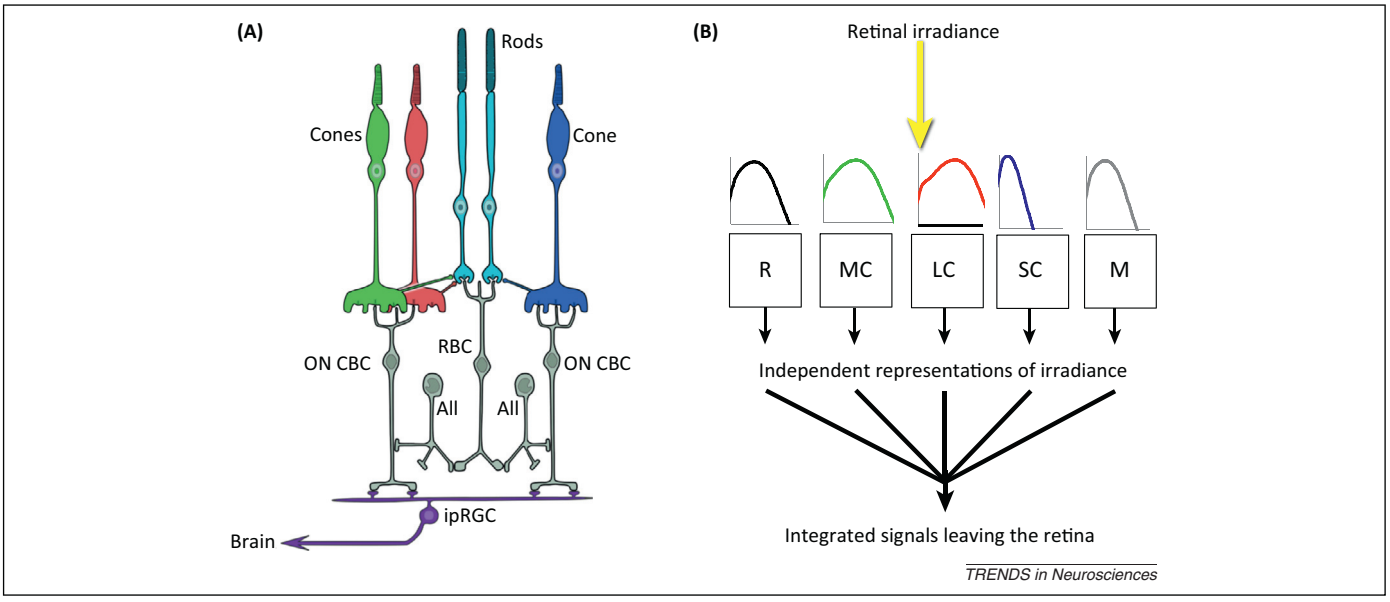

Figure 1. All retinal photoreceptor classes are upstream of circadian, neuroendocrine, and neurobehavioral responses to light. **(A)** Schematic of the relevant retinal circuitry in humans. Non-image-forming responses originate in the retina and have been attributed to a particular class of retinal ganglion cell (ipRGC). ipRGCs are directly photosensitive owing to expression of melanopsin, which allows them to respond to light even when isolated from the rest of the retina. *In situ* they are connected to the outer retinal rod and cone photoreceptors via the conventional retinal circuitry. The details of their intraretinal connections are not completely understood and probably vary between different subtypes. Shown here are major connections with on cone bipolar cells (on CBCs) connecting them to cone and, via amacrine cells (AII) and rod bipolar cells (RBC), rod photoreceptors. As a consequence, the firing pattern of ipRGCs can be influenced by both intrinsic melanopsin photoreception and extrinsic signals originating in rods and each of the spectrally distinct cone classes (shown in red, green, and blue). **(B)** This feature is conceptualized in much simplified form as a number of photoreceptive mechanisms (depicted as R for rod opsin; M for melanopsin; SC for S cone opsin; MC for M cone opsin; and LC for L cone opsin), each of which absorbs light according to its own spectral sensitivity profile (shown in cartoon form as plots of log sensitivity against wavelength from 400 to 700 nm) to generate a distinct measure of illuminance. These five input signals are then combined by the retinal wiring, and within the ipRGC itself, to produce an integrated signal that is sent to non-image-forming centers in the brain. As each of the five representations of weighted irradiance is produced by a photopigment with its own spectral sensitivity profile, their relative significance for the integrated output defines the wavelength dependence of this signal, and hence of downstream responses.

suppress nocturnal melatonin in humans [52], but later studies have shown that under certain conditions, as little as 1 lux or less can suppress melatonin in humans [53]. This sensitivity highlights an important feature of this photoreceptive system: ipRGCs receive input from the outer retina (Figure 1A). Thus, ipRGC dendrites are targets for synaptic input from bipolar and amacrine cells, as well as being sites for melanopsin-driven phototransduction. As a result, the ipRGC firing pattern is a composite, integrated signal consisting of the intrinsic light response (melanopsin photoreception) and incoming rod- and cone-driven signals [36]. This arrangement greatly extends the range of stimuli that can elicit circadian and neurophysiological responses, and explains why animals that are genetically null for melanopsin continue to exhibit non-image-forming responses to light [16,54,55].

Spectral sensitivity

At its very origin, the signal driving physiological and behavioral light responses (ipRGC firing) is defined by the combined influence of multiple photoreceptive processes: the melanopsin-driven phototransduction mechanism within the ipRGC itself, and remote photoreception in rods and cones (Figure 1B). Each of these mechanisms of light detection has a distinct spectral sensitivity, defined by the spectral efficiency of the photopigment expressed and the spectral transmission properties of the ocular media.

(i) Rods. Rod opsin, the photopigment of rod photoreceptors, shows peak sensitivity (λ_{max}) at approximately 500 nm in all mammalian species. Pre-receptoral filtering shifts this towards somewhat longer wavelength in the standard human observer (507 nm).

(ii) Cones. Mammalian genomes typically contain several genes encoding spectrally distinct cone opsins. Humans, and other old world primates, have three types of cones. Human S cones express a short-wavelength-sensitive cone opsin (cyanolabe), maximally sensitive to wavelengths at ~420 nm; M cones contain a different cone opsin (chlorolabe; peak sensitivity ~535 nm); L cones contain a red-shifted cone opsin (erythrolabe; peak sensitivity ~565 nm [56]). Other mammals lack the chlorolabe/erythrolabe distinction, and have a single cone opsin maximally sensitive in the middle of the human visible spectrum. There are also important species differences in the spectral sensitivity of the cyanolabe pigments. For example, many rodent retinas have a photopigment that is maximally sensitive to near-ultraviolet radiation [57]. In humans, pre-receptoral filtering shifts peak sensitivity of short- and medium-wavelength cones to longer wavelength (~440 and 545 nm, respectively).

(iii) Melanopsin. The available data indicate that the spectral sensitivity of melanopsin, the photopigment of ipRGCs, is similarly invariant across species, with λ_{max} at approximately 480 nm [58–62]. A potential complication in relating this estimate of the spectral sensitivity of melanopsin to the spectral response property of ipRGCs *in vivo* is the suggestion that like the rhabdomeric opsins of invertebrates, melanopsin may be bistable [58,60,63,64]. Bistability affords

rhabdomeric photopigments the capacity to regenerate the vitamin A-derived chromophore that is isomerized following light absorption through the absorption of another photon [65]. Because this regeneration event can be produced by different wavelengths, it could influence the spectral response properties of the receptor. Whether mammalian melanopsins are bistable and whether this bistability is biologically relevant remain to be determined [66–68]. In either event, studies on mice indicate that this factor does not significantly impact the spectral response properties of melanopsin under practical lighting regimes [69,70].

The firing rate of ipRGCs may thus be influenced by five (or four in the case of non-primates) spectrally distinct photoreceptors (Figure 1B). It follows that the spectral sensitivity of downstream responses (and thus the spectral weighting function that should be applied during light measurement) is determined by the manner in which these various channels are combined. In fact, the contribution of each photoreceptive input to evoked responses appears to be fundamentally context-dependent, a feature clearly illustrated by studies of a well-understood ipRGC-driven response, the pupillary light reflex (PLR).

Pupillary light reflex: a case study

The PLR controls the light intensity reaching the retina via a simple and well-characterized pathway that links a sensory signal, irradiance, to a motor output, pupil constriction. It originates with ipRGC innervation of the olivary pretectal nucleus [21,71–75]. Pupil area decreases with increasing irradiance over a ~9-$\log_{10}$ intensity range. A key feature of the light reflex is its tonic nature in bright light: constriction is held steady under continuous illumination [71–73,75,76]. Data from both laboratory animals and humans indicate that rods, cones, and melanopsin participate in the PLR, and that their relative contributions are variable, depending on stimulus intensity and spectral content, and change over time under constant illumination [16,29,33,37,76–78].

An abrupt step in illumination elicits rapid, robust pupil constriction predominantly driven by cones and/or rods. The amplitude of this initial response and the relative contribution of each photoreceptor type depend on the irradiance and wavelength of the light stimulus. Following this phasic pupil constriction, the pupil gradually relaxes to a more dilated state and, if the threshold for melanopsin activation is exceeded, it assumes a sustained steady-state diameter that persists throughout the light stimulation [37,76,77]. During this post-phasic response, the contribution from melanopsin increases and with extended illumination (>3 min) the response is predominantly driven by melanopsin. When the light is turned off, if the prior retinal irradiance has exceeded the threshold for melanopsin activation, constriction persists for many seconds, termed by some the post-illumination pupil response [79]. This response is considered to be predominantly melanopsin-dependent [37].

A consequence of this shifting reliance on rods, cones, and melanopsin is that the spectral sensitivity profile of the PLR is fundamentally labile. Thus, at low light levels below the melanopsin threshold, the pupil matches the spectral sensitivity of cone (or rod) photoreceptors. For higher irradiance, early components of pupil constriction are defined by cone spectral sensitivity, later components by melanopsin, and intermediate irradiance by a combination of the two (Figure 2).

Other non-visual light responses

Data for the PLR demonstrate that no single spectral efficiency function accounts for this response under all conditions. In addition, other findings indicate that the rules governing when and to what extent other non-image-forming responses rely on rods, cones, or melanopsin are not constant. Thus, different cone contributions have been observed across brain regions receiving ipRGC input, even under essentially identical experimental conditions [80,81]. Differences in central processing could explain such diversity, as could the fact that there are at least five different types of ipRGCs [17]. These various ipRGC types have distinct central projection patterns, implying diversity in their importance for various circadian and neurophysiological responses. ipRGC types also differ in morphology, melanopsin content, and intrinsic photosensitivity [17,82,83]. Although inputs to these ipRGC types have not been fully characterized, differences in dendritic morphology suggest that afferent connections are also likely to differ qualitatively and quantitatively [17,82–84], allowing significant diversity in the extent to which responses downstream from ipRGCs are reliant on rods, cones, and melanopsin.

Measuring light for circadian and neurobehavioral regulation

It would be desirable to be able to quantify light as experienced by non-visual systems using a single, one-dimensional unit (the equivalent of photopic lux). Achieving this for lights of divergent spectral content, however, awaits elucidation of a suitable spectral weighting function. There have been attempts to address this deficit [85–87]. The neurophysiology outlined above, however, reveals the challenges in producing a method of spectral weighting that would be suitable for all circadian, neuroendocrine, and neurobehavioral responses under all conditions. Evoked responses reflect input from all of the retinal photoreceptor classes, with the relative importance of each being highly labile within and between response types. As a result, the spectral sensitivity of this photoreceptive system is fundamentally context-dependent. This is no less true for other aspects of vision, and as this nascent field of research matures, a spectral response function derived from one or more of the individual photoreceptor inputs might be found to provide a reasonable approximation of relevant non-image-forming responses under many practical circumstances. Alternatively, a family of such functions to be used under different conditions and/or for different response endpoints may be developed. At present, however, there are insufficient data on which to base such strategies. What advice can then be given to those measuring and using light in experimental and practical applications?

Advice for researchers

The scientific literature contains a large number of studies relating circadian, neuroendocrine, and neurobehavioral

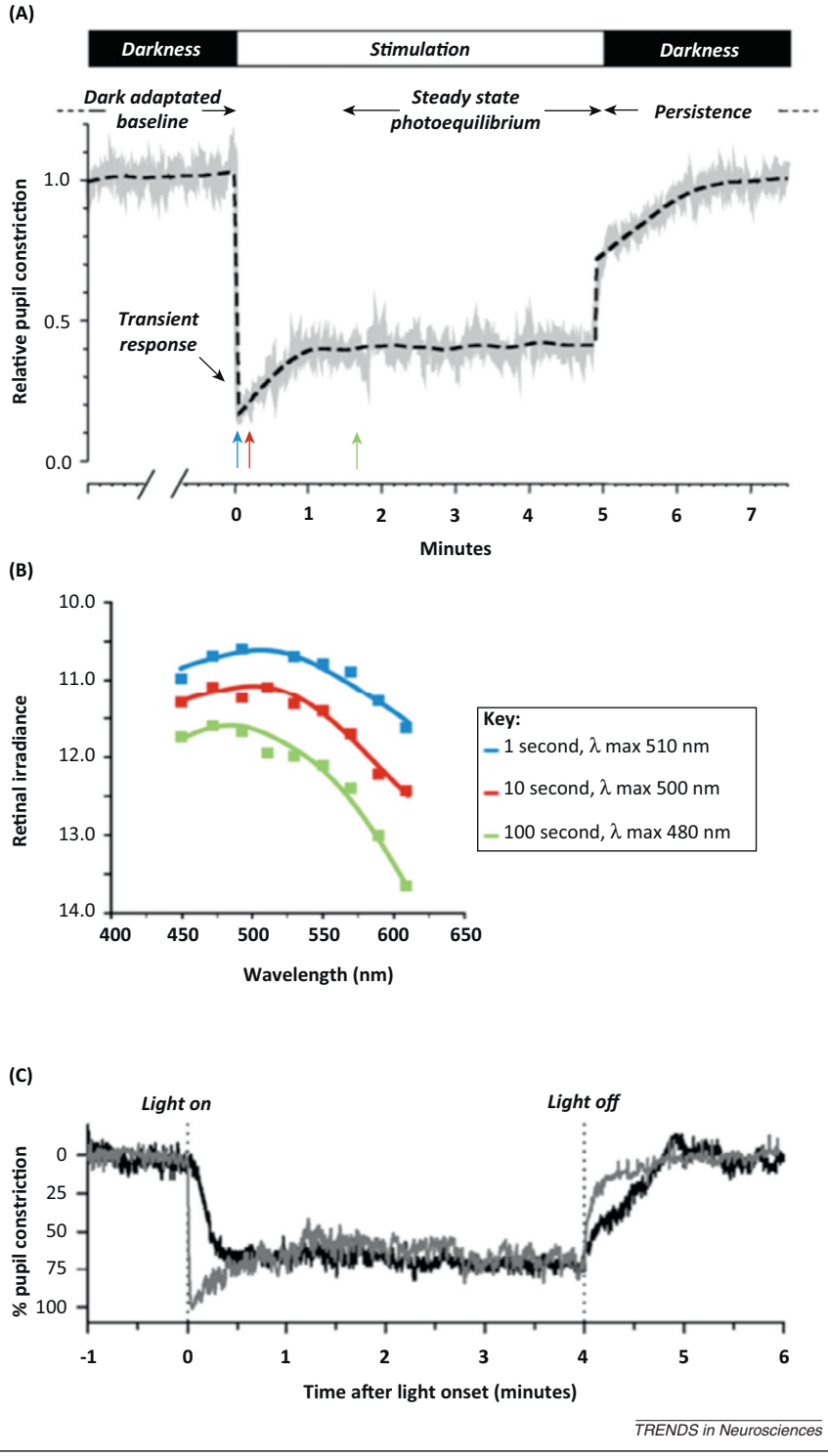

Figure 2. Spectral sensitivity of half-maximal pupillary constriction in humans. **(A)**. The pupillary light reflex response is composed of several different temporal components. At light onset, the pupil shows rapid, transient constriction during the first 1000 ms of light exposure. This is followed by redilation to a tonic or sustained pupil diameter that stabilizes to a steady-state constriction (photoequilibrium) even during prolonged constant illumination. When the light is turned off, there is slow, delayed redilation of the pupil back to the resting (dark-adapted) state that is melanopsin-driven. Graph adapted from [76]. **(B)** Mean spectral sensitivity is depicted as the retinal irradiance (log quanta/cm^2/s) required to elicit a criterion pupil response (half-maximal constriction) at nine wavelengths for three different stimulus durations of 1, 10, and 100 s (corresponding to the positions of blue, red, and green arrows in A). The smooth curve through the points represents the optimal fit to the data using a mathematical combination of rod, cone, and melanopsin spectral sensitivities. As the stimulus duration increases, the sensitivity of the response gradually decreases by more than one log unit and is shifted towards shorter wavelength, from 510 nm at 1 s to 500 nm at 10 s and 480 nm at 100 s. Graph derived from data in [77]. **(C)** Representative traces for pupillary constriction in a sighted participant (gray) and in a blind individual without rod and cone function (black). Pupillary constriction to 480 nm was sluggish and lacks the transient response after light onset in the blind individual, whereas the sustained steady-state pupillary light reflex (PLR) and the persistent response when the light is turned off are conserved. Graph reproduced, with permission, from [29].

responses to calibrated light exposures. The lack of a consistent and adequate method of quantifying light, however, makes it hard to replicate experimental conditions or to compare across studies. This represents a considerable barrier to scientific progress.

Given that we do not yet have an accepted spectral weighting function for non-image-forming responses, the best current advice is that researchers should record their light exposures in the most complete form, namely as corneal spectral power distributions. A range of low-cost spectroradiometers can be used to provide this information, if appropriately calibrated.

A major advantage of recording the spectral power distribution is that it can be used to derive any other unit of measure currently available or developed in the future. Currently, the most appropriate use of that capacity would be to calculate the effective irradiance experienced by each of the rod, cone, and melanopsin photoreceptors capable of driving non-visual responses. The inclusion of each of these photoreceptors in the efferent pathway implies that, at its earliest stages, incident light is encoded into five (or three or four in the case non-primate mammals) representations of irradiance by the activity of rods, melanopsin, and S, M, or L cones (Figure 1B). It can therefore be considered that non-visual responses are initiated by one or more of five distinct biological representations of irradiance: rhodopic, melanopic, cyanopic, chloropic, and erythropic illuminance (Table 1). Retinal and central wiring combines these distinct measures to provide an integrated representation of the light environment. Because this integration process is not completely understood, it is not yet possible to predict the relative reliance of a given circadian, neuroendocrine, or neurobehavioral response under particular circumstances on each.

At present, it is therefore recommended that quantities reflecting the activity of each of these individual inputs be reported. This does not achieve the ideal of describing light as a one-dimensional quantity that predicts non-image-forming responses. Nonetheless, reducing the spectral power distribution to a limited number of biologically meaningful quantities (five in the case of humans; four for most other mammalian species) makes the problem of comparing polychromatic lights of different spectral quality significantly more tractable. This helps in equating stimulus–response relationships described in different laboratories, and in relating those research findings to lighting conditions in the field. As studies using this measurement system accumulate, it will then become possible to generate and test hypotheses regarding the ability of one or more of the five qualities to predict a target physiological or behavioral response. Thus, it may become clear that the magnitude of a nominal response is best predicted by, for example, a simple linear summation of cyanopic and melanopic illuminance values over a variety of studies using spectrally divergent stimuli.

Full equations for calculating rhodopic, melanopic, cyanopic, chloropic, and erythropic illuminance values are provided in Table 1. The spectral efficiency functions used for these calculations (based on pigment absorbance profiles corrected for ocular filtering in a standard human observer) are provided as supplementary material online, where a toolbox for calculation of α-opic illuminance values from corneal spectral irradiance measures is also available. As noted above, some of these spectral efficiency functions are species-specific, and resources suitable for laboratory rodents are provided (at http://www.eye.ox.ac.uk/team/principal-investigators/stuart-peirson).

Advice for industry and regulatory authorities

The traditional objectives of architectural lighting include the provision of light that: (i) is optimal for visual performance; (ii) is visually comfortable; (iii) permits aesthetic appreciation of the space; and (iv) conserves energy [10,88]. As discussed above, light exposure has a broad range of effects on physiology and behavior. These non-visual effects of light should be an additional consideration in the design and operation of human environments, as well as those for domesticated animals.

An important note of caution here is that it is not always clear whether lighting design should aim to maximize or minimize non-visual responses. In many ways, light can be considered a drug, having the potential for both beneficial and deleterious effects. These conflicting effects can occur concurrently, and in a single individual and context. For example, for night-shift workers, bright workspace lighting may improve immediate job performance by enhancing visual perception and promoting alertness, but suppress melatonin and shift the circadian clock to an undesirable phase. Conversely, dimmer lighting may minimize effects on circadian timing, but may be detrimental to more immediate performance.

Balancing the desirable and undesirable impacts of light or darkness requires careful, informed consideration of the context and of the myriad effects of light on physiol-

Table 1. Photometric measures for each of the five potential photoreceptive inputs to circadian and neurophysiological light responses in humans

Photoreceptor	Photopigment	Spectral sensitivity function	Unit of measure[a]
Short-wavelength (S) cones	S-cone photopsin (cyanolabe)	Cyanolabe response function $N_{sc}(\lambda)$	Cyanopic illuminance (cyanopic-lux)
Medium-wavelength (M) cones	M-cone photopsin (chlorolabe)	Chlorolabe response function $N_{mc}(\lambda)$	Chloropic illuminance (chloropic-lux)
Long-wavelength (L) cones	L-cone photopsin (erythrolabe)	Erythrolabe response function $N_{lc}(\lambda)$	Erythropic illuminance (erythropic-lux)
ipRGCs (intrinsic photosensitivity)	Melanopsin	Melanopsin response function $N_z(\lambda)$	Melanopic illuminance (melanopic-lux)
Rods	Rod opsin	Rod opsin response function $N_r(\lambda)$	Rhodopic illuminance (rhodopic-lux)

[a]Each unit of measure (E_α, where α specifies the retinal photopigment) is derived by convoluting the spectral power distribution of incident light ($E_{e\lambda}$) with the relevant spectral sensitivity function, which in turn is defined by the photopigment spectral sensitivity adjusted for pre-receptoral filtering in a standard observer [$N_\alpha(\lambda)$; see the supplementary material online for full functions and a detailed description of their derivation] according to the equation $E_\alpha = 72\,983.25 \int E_{e\lambda}(\lambda)\, N_\alpha(\lambda)\, d\lambda$. Species-specific variants of the spectral sensitivity functions may be required for non-human applications to account for differences in pre-receptoral filtering and photopigment spectral sensitivity.

ogy, perception, and cognition. Such calculations can be a daunting challenge, all the more so because both basic and applied science in this area continues to evolve rapidly. Simple prescriptions are as likely to do harm as good, and even experts may have divergent ideas about best practice under some situations. Nevertheless, assuming that following deliberation a decision has been made to either maximize or minimize the non-visual effects of light, how can this be achieved?

For reasons outlined above, it is not yet possible to predict the non-image-forming impact of a given illuminant based on its intensity and spectral composition. However, some guidance is possible. If the broad objective is to minimize the activation of ipRGC outputs, the goal should be to keep retinal irradiance as low as possible. There is no established threshold below which these systems are completely blind to light, so total darkness during sleep may be ideal where practical. Likewise, with respect to the visible spectrum, any wavelength can, in principle, activate the system. However, given that the relative sensitivity of these non-visual responses is generally reduced in the longer visible wavelength range, light sources should be biased towards longer visible wavelengths, to the extent consistent with other demands. Conversely, if the objective is to promote ipRGC photoreception, retinal irradiance should be increased (within acceptable safety limits) and light sources may be biased towards the blue and blue/green regions of the visible spectrum, to which all photoreceptive inputs to this system are fairly sensitive.

Concluding remarks

Science and engineering rely on accurate measurement. The discovery of ipRGC photoreceptors, and our growing understanding of their role in setting physiological and behavioral state, has revealed that current methods of light measurement are incomplete. The question of exactly how they should be updated will no doubt be revisited as our understanding of this system evolves, as has happened for other aspects of photometry. Nevertheless, the science has reached a state at which it is sensible to take the first important steps in that process. We propose methods of light measurement that quantify effective irradiance for each of the photoreceptive inputs to this system independently. The goal is to provide a comprehensive description of light as experienced by the circadian, neuroendocrine, and neurobehavioral systems, on which future developments can build.

Acknowledgments

This review arose from discussions between the authors at a focused workshop held in Manchester, UK, in January 2013, which received financial support from the ZVEI (German Electrical and Electronic Manufacturer's Association) and administrative assistance from the University of Manchester. The authors are grateful to John Hanfin and Ben Warfield for technical support on the supplementary online material and manuscript figures.

Disclaimer statement

Of the 14 authors of this manuscript, Drs Berson, Cooper, Gamlin, Price, Provencio, and O'Hagan identify no potential conflicts of interest related to the manuscript, developed from the First International Workshop on Circadian and Neurophysiological Photometry. Dr Brainard reports that through Thomas Jefferson University, his laboratory has received equipment, advice, or financial support from the IESNA Philadelphia Chapter; Panasonic, OSRAM-Sylvania, Philips Lighting; Lutron, Lighting Sciences Group, Apollo Lighting; BioBrite Inc., and Litebook, and he holds two currently issued patents (USPTO #09/853,428 and #8,366,755) and two continuing patent applications (USPTO #09/853,428 and World PCT 2005/004948AZ). Dr Brown reports that he is currently contributing to a project funded by Philips Lighting and has received funding from Philips Lighting previously. Dr Czeisler reports that he has received consulting fees from or served as a paid member of scientific advisory boards to a number of companies such as: Cephalon, Inc. (acquired by Teva Pharmaceutical Industries Ltd); Koninklijke Philips Electronics, N.V.; Sleep Multimedia, Inc.; and Zeo, Inc.; owns equity interests or receives royalties from other companies such as Philips Respironics, Inc.; is the incumbent of an endowed professorship provided to Harvard University by Cephalon, Inc.; holds a number of process patents in the field of sleep/circadian rhythms (e.g., photic resetting of the human circadian pacemaker), has served as an expert witness on various legal cases related to sleep and/or circadian rhythms; and directs the Harvard Medical School Division of Sleep Medicine, which has received unrestricted research and educational gifts and endowment funds from companies such as Philips Respironics, Inc. and Cephalon, Inc. Dr Figueiro reports that the Lighting Research Center receives funding from GE Lighting, Philips Lighting, Philips Respironics, and OSRAM Sylvania, and has built a light meter used for collecting circadian light in the field. Dr Lockley reports having received consulting fees from a number of companies such as Apollo Lighting and Naturebright; unrestricted equipment gifts from Bioilluminations LLC, Bionetics Corporation, and Philips Lighting; a fellowship gift from Optalert in Australia; honoraria, travel, accommodation, and/or meals for invited presentations or teaching from companies such as Velux, Apollo Lighting, Illinois Coalition for Responsible Outdoor Lighting, Lighting Science Group Corp, and Philips Lighting; has received previous and ongoing research grants from Alcon Inc., Apollo Lighting, Illuminations LLC, and Philips Lighting; has received patent revenue from a patent assigned to the University of Surrey; and holds a pending patent assigned to the Brigham and Women's Hospital. Dr Lucas reports receiving project awards from Philips Lighting. Dr Peirson reports that his laboratory has a postdoctoral fellowship sponsored by Roche. Dr Skene reports having a patent (PHNL000507WO; EP 1317302B1); being the beneficiary of an agreement between the University of Surrey and Philips Lighting B.V. for patent assignment and receiving research grant support; receiving grant support from Philips Consumer Lifestyle B.V.; and being Co-director of Stockgrand Ltd, UK.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tins.2013.10.004.

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Action Spectrum for Melatonin Regulation in Humans: Evidence for a Novel Circadian Photoreceptor

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The photopigment in the human eye that transduces light for circadian and neuroendocrine regulation, is unknown. The aim of this study was to establish an action spectrum for light-induced melatonin suppression that could help elucidate the ocular photoreceptor system for regulating the human pineal gland. Subjects (37 females, 35 males, mean age of 24.5 ± 0.3 years) were healthy and had normal color vision. Full-field, monochromatic light exposures took place between 2:00 and 3:30 A.M. while subjects' pupils were dilated. Blood samples collected before and after light exposures were quantified for melatonin. Each subject was tested with at least seven different irradiances of one wavelength with a minimum of 1 week between each nighttime exposure. Nighttime melatonin suppression tests ($n = 627$) were completed with wavelengths from 420 to 600 nm. The data were fit to eight univariant, sigmoidal fluence–response curves ($R^2 = 0.81$–0.95). The action spectrum constructed from these data fit an opsin template ($R^2 = 0.91$), which identifies 446–477 nm as the most potent wavelength region providing circadian input for regulating melatonin secretion. The results suggest that, in humans, a single photopigment may be primarily responsible for melatonin suppression, and its peak absorbance appears to be distinct from that of rod and cone cell photopigments for vision. The data also suggest that this new photopigment is retinaldehyde based. These findings suggest that there is a novel opsin photopigment in the human eye that mediates circadian photoreception.

Key words: melatonin; action spectrum; circadian; wavelength; light; pineal gland; neuroendocrine; photoreception; photopigment; human

Light is the primary stimulus for regulating circadian rhythms, seasonal cycles, and neuroendocrine responses in many species, including humans (Klein et al., 1991; Wehr, 1991). Furthermore, clinical studies have demonstrated that light therapy is effective for treating selected affective disorders, sleep problems, and circadian disruptions (Wetterberg, 1993; Lam, 1998). Currently, the ocular photoreceptors that transduce light stimuli for circadian regulation and the clinical benefits of light therapy are unknown.

The retinohypothalamic tract, a distinct neural pathway that mediates circadian regulation by light, projects from the retina to the suprachiasmatic nuclei (SCN) (Moore, 1983). A neural pathway extends from the SCN to the pineal gland (Klein et al., 1991; Morin, 1994). By this pathway, light and dark cycles are perceived through the mammalian eyes, entrain SCN neural activity, and, in turn, entrain the rhythmic secretion of melatonin from the pineal gland. In virtually all species, melatonin secretion is high during the night and low during the day (Reiter, 1991; Arendt, 1998). In addition to entraining pineal rhythms, light exposure can acutely suppress melatonin secretion (Rollag and Niswender, 1976; Lewy et al., 1980). Acute, light-induced melatonin suppression is a broadly used indicator for photic input to the SCN, which has been used to elucidate the ocular and neural physiology for circadian regulation (Klein et al., 1991; Brainard et al., 1997).

Studies using rodents with retinal degeneration suggest that neither the rods nor cones used for vision participate in light-induced melatonin suppression, circadian phase shifts, or photoperiodic responses (Pevet et al., 1984; Webb et al., 1985; Foster et al., 1991). Furthermore, enucleation of rodless, coneless transgenic mice abolishes light-induced circadian phase shifts and melatonin suppression (Lucas and Foster, 1999; Freedman et al., 1999). Similarly, light-induced melatonin suppression and circadian entrainment have been demonstrated in humans with complete visual blindness (Czeisler et al., 1995) and with specific color vision deficiencies (Ruberg et al., 1996). Together, these studies on different forms of visual blindness suggest that melatonin regulation is controlled, at least in part, by photoreceptors that differ from the known photoreceptors for vision.

A recent study has shown that monochromatic light at 505 nm is approximately four times stronger than 555 nm in suppressing melatonin in healthy humans (Brainard et al., 2001). Those results confirmed that the ocular photoreceptor primarily responsible for pineal melatonin regulation in humans is not the three cone system that mediates photopic vision. The new data reported here extend this work by forming an action spectrum from fluence–response curves at multiple visible wavelengths.

Received March 22, 2001; revised May 17, 2001; accepted May 25, 2001.

This work was supported by National Institutes of Health Grant RO1NS36590 and NASA Cooperative Agreement NCC 9-58 with the National Space Biomedical Research Institute (to G.C.B.) and National Science Foundation Grant IBN9809916 and Department of Defense Grant R070HY (to M.D.R.). Input from many individuals was invaluable to this project. We gratefully acknowledge the support and technical assistance of Christine Alocillo, Jon Cooke, William Coyle, James Gardner, Frank Giunpa, Rick Guyer, Robert Glasgow, John McDevitt, John Monnier, Charles Nelson, Jeff Santman, and Donna Wittkowski. We also deeply appreciate the assistance from Laine Brainard, Dr. Ignacio Provencio, Dr. Britt Sanford, and Dr. William Thornton in assessing the data, developing graphs, and reviewing this manuscript. The inspiration for this work came from the 281 series of the Edgar Cayce readings.

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Developing an action spectrum is a fundamental means for determining the input physiology for the circadian system. This photobiological technique has high utility for (1) defining the relative effectiveness of photons at different wavelengths for eliciting a biological response and (2) identifying the specific photopigment involved in that response (Lipson, 1994; Coohill, 1999). The specific aim of the present study was to characterize the wavelength sensitivity of the photoreceptor system responsible for providing circadian input to the human pineal gland by establishing an action spectrum for light-induced melatonin suppression. The experiments defined an action spectrum that fits a retinaldehyde opsin template and identified 446–477 nm as the most potent wavelength region for regulating melatonin. Univariance among the eight fluence–response curves suggests that a single photopigment is primarily responsible for melatonin suppression. These results suggest that there is a novel photopigment in the human eye that mediates circadian photoreception.

Preliminary reports of this work have been presented previously (Brainard et al., 1999b-e, 2000b).

MATERIALS AND METHODS

Study design. Action spectra are determined by comparing the number of photons required for the same biological effect at different wavelengths (Lipson, 1994; Coohill, 1999). The melatonin suppression action spectrum described here was formed from fluence–response curves at eight wavelengths between 440 and 600 nm. A within-subjects design was used for each fluence–response curve. For each wavelength studied, a set of eight volunteers was exposed to a minimum of eight different light irradiances on separate nights with at least 6 d between exposures. At the completion of that work, it was determined that a probe of sensitivity to monochromatic light below 440 nm was needed. Consequently, a group of eight subjects was exposed to a single night of no light exposure and a single night of exposure to one irradiance of 420 nm light.

Subjects. Volunteers who were involved in shift work, planned long-distance jet travel before or during the study period, or had irregular sleeping schedules were excluded from this study. The subject drop-out rate was 7.9%. The ethnic distribution of the 72 subjects who completed this study included 55 Caucasians, 9 Asians, 4 African Americans, 3 Hispanics, and 1 individual of unknown ethnicity. Subjects who had a relatively stable daily sleeping pattern, passed a physical exam for general and ocular health, and signed an approved Institutional Review Board consent document were accepted into this study. A total of 37 females and 35 males between 18 and 30 years old (mean ± SEM age, 24.5 ± 0.3) completed the study. The self-reported mean ± SEM weekday wake-up time among subjects was 7:06 A.M. ± 18 min. All subjects were normal on the Ishihara and Farnsworth Munsell D-100 tests for color vision (mean ± SEM Farnsworth Munsell score, 51.4 ± 4.3).

Light exposure protocol. Each experiment began at midnight when subjects entered a dimly lit room (10 lux or less). One drop of 0.5% cyclopentolate HCl was placed in each eye to dilate the subjects' pupils, and blindfolds were placed over their eyes. Subjects remained sitting upright for 120 min and listened to music on headphones or engaged in quiet conversation. While still blindfolded and just before 2:00 A.M., a 10 ml blood sample was taken by venipuncture of the antecubital vein. Subjects' blindfolds were then removed, and the subjects were exposed to the monochromatic light stimulus from 2:00 to 3:30 A.M. During light exposure, each subject's head rested in an ophthalmologic head holder facing a ganzfeld apparatus that provided a concave, patternless reflecting surface encompassing each subject's entire visual field (Fig. 1). During this 90 min exposure, subjects sat quietly, kept their eyes open, and gazed at a fixed target dot in the center of the ganzfeld dome. Subject compliance for keeping their eyes open and the subjects' pupil size were monitored by a miniature video camera inside the ganzfeld dome. If the subjects began to close their eyes during the exposure period, the experimenters reminded them to keep their eyes completely open. At 3:30 A.M., a second 10 ml blood sample was taken by venipuncture, and the subjects were then permitted to leave the laboratory. Eight wavelengths were studied for this action spectrum (440, 460, 480, 505, 530, 555, 575, and 600 nm). Across these wavelengths, each subject was exposed to complete darkness from 2:00 to 3:30 A.M. on their control night and to a set of irradiances covering a 4 log unit photon density range of 10^{10} to 10^{14} photons/cm^2 on exposure nights. For the probe of sensitivity to monochromatic light at 420 nm, a group of eight subjects was exposed to a single night of no light exposure and a single night of exposure to 420 nm light at 31.8 μW/cm^2 (5.58×10^{13} photons/cm^2).

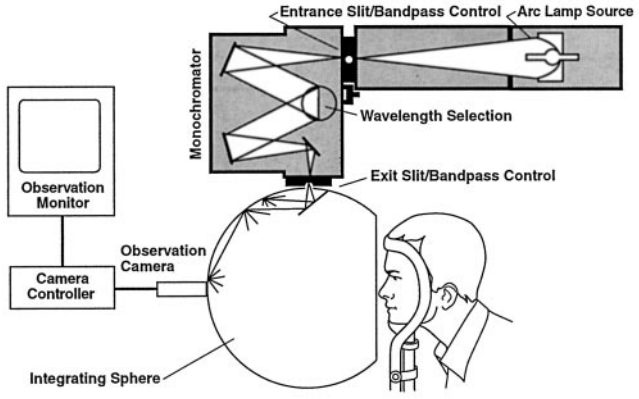

Figure 1. This diagram illustrates the experimental electronic, optic, and ganzfeld dome exposure array. This apparatus provides a uniform, patternless stimulus that encompasses the subject's entire visual field. For clarity, the subject's head is shown slightly withdrawn from the opening of the ganzfeld dome. During all light exposures, the subjects' bony orbits are completely enclosed in the dome walls, providing complete exposure of their visual fields.

Light production and measurement. As shown in Figure 1, experimental light stimuli were produced by a 450 or 1200 W xenon arc lamp (Photon Technology Inc., Princeton, NJ). Each lamp was enclosed in a light-proof chamber and cooled by water circulation. An exit beam of light from each source was directed by a parabolic reflector, and, for the 1200 W lamps, excess heat in the light beam was reduced by a water filter. Monochromatic wavelengths (10–14.5 nm half-peak bandwidths) were produced by a grating monochromator, and light irradiance was controlled by a manual diaphragm. The resulting light beam was directed into the top area of a ganzfeld apparatus and reflected evenly off the walls of the ganzfeld dome into volunteers' eyes. The entire reflecting surface of the dome was coated with a white material (Spectralite) with a 95–99% reflectance efficiency over the 400–760 nm range. Routine measurement of the light irradiance (in microwatts per square centimeter) was done with a Tektronix J16 Radiometer/Photometer with a J6512 irradiance probe (Tektronix, Beaverton, OR). Experimental light stimuli reflected from the ganzfeld dome were measured at volunteers' eye level immediately before and after the 90 min exposure. Additional measures were taken each 0.5 hr of the exposure to ensure stimulus stability and enable readjustment of the intensity if it varied. These spot measures were taken with an ft-1° meter (Minolta, Osaka, Japan). Spectroradiometric assessment of the monochromatic wavelengths at the level of subjects' corneas was done with a portable spectroradiometer with a fiber optic sensor (model S2000; Ocean Optics, Dunedin, FL). This equipment was calibrated with a standard lamp traceable to the National Institute of Standards and Technology.

In action spectroscopy, it is critical that the measured light stimuli are representative of the stimuli that actually reach the photoreceptors that mediate the photobiological response. In studies on light regulation of the circadian system, factors that can modify the measured stimulus before it reaches the photoreceptors include head and eye motion, squinting and eye closure, pupillary reflexes, and light transmission through the ocular media (Gaddy et al., 1993; Brainard et al., 1997). Most of these factors are controlled in the experimental technique described above. Concerning light transmission through ocular media, the cornea and aqueous and vitreous humors normally transmit nearly 100% of visible wavelengths to the retina and do not change substantively as the eyes age (Boettner and Wolter, 1962). In contrast, the aging human lens develops pigmentation that attenuates the transmission of shorter visible wavelengths to the retina (Lerman, 1987; Brainard et al., 1997). In the present study, restricting the age of volunteers to 18–30 years controlled this factor. Measurements of mean transmittance of 36 postmortem human lenses in this age range showed relatively even transmission from 440 to 600 nm. In contrast, there was a mean 45% reduction in lens

transmission at 420 nm compared with 460 nm (Brainard et al., 1997). Consequently, measured corneal light irradiances at 420 nm had to be adjusted to compensate for reduced stimulus transmission to the retina even in this relatively young study group.

Blood samples and melatonin assay. Blood samples were collected in glass vacutainers that contained EDTA. Plasma was separated by refrigerated centrifugation, aliquoted into cryogenic vials, and stored at −20°C until assay. Melatonin concentrations were assayed by radioimmunoassay using antiserum described by Rollag and Niswender (1976). Radiolabeled ligand was prepared by adding 10 μl of a dioxane solution containing 1 μmol of 5-methoxytryptamine and 1 μmol of tri-*N*-butylamine to 250 μCi (0.1 nmol) dried Bolton–Hunter Reagent (NEN, Boston, MA). The reaction was allowed to proceed for 1 hr before adding 50 μl of aqueous sucrose (16 gm/ml electrophoresis buffer) and purifying product by disc gel electrophoresis. Duplicate aliquots of 200 μl of each unknown and control sample were extracted into 2 ml of chloroform. The chloroform was removed in a SpeedVac centrifuge (Savant Instruments, Holbrook, NY) and resuspended in 200 μl of assay buffer (PBS, pH 7.4, containing 0.1% gelatin with 100 mg/l thimerosal as a preservative). The extracts were washed twice with 3 ml of petroleum ether and then evaporated to dryness in a SpeedVac before being resuspended in 200 μl of deionized water. Approximately 50,000 cpm of radiolabeled ligand and a 1:256,000 dilution of antiserum (R1055; bleeding date of 9/16/74) was added to each unknown and a triplicate twofold geometric series of standards ranging in concentration from 0.201 to 200 pg per 200 μl of assay buffer. The final assay volume of buffer in each tube was 400 μl. At the end of the 48 hr incubation period, 3 ml of 95% ethanol (4°C) was added to each assay tube, and the bound radioactivity was precipitated by centrifugation at 2000 × *g* for 30 min. The supernatant was decanted, and radioactivity in the precipitate was quantified. The quantity of melatonin immunoreactivity in the samples was calculated with the use of a computer program (M. L. Jaffe and Associates, Silver Spring, MD) (Davis et al., 1980). All solutions were maintained at 4°C throughout the radioimmunoassay procedure. Assay results were not corrected for recovery (which has proven to be >95% in independent trials). The minimum detection limit of the assay is 0.5–2.0 pg/ml.

Statistics. Two-tailed, paired Student's *t* tests were used to assess statistical significance of raw melatonin change from 2:00 to 3:30 A.M. Percent melatonin change scores were determined by the following formula:

$$\text{percent melatonin change score} = 100 \times \frac{\text{03:30 hr melatonin} - \text{02:00 hr melatonin}}{\text{02:00 hr melatonin}}.$$

Percent melatonin change scores then were normalized to percent control-adjusted change scores by subtracting the control (no light) condition percent change scores for each subject from that same subject's light exposure score. This technique accounts for the normal individual rise or fall in plasma melatonin levels with respect to the light-induced changes (Gaddy et al., 1993; Brainard et al., 1997). For data from each wavelength, complete sets of preexposure melatonin values, percent melatonin change scores, and percent control-adjusted melatonin change scores were analyzed with one-way, repeated-measures ANOVA. Significant differences between groups were assessed with *post hoc* Scheffe *F* tests with α set at 0.05. The group of single fluence–response curves (one for each wavelength) was fitted to a parametric model in which the melatonin response (Y) to a photon dose (X) is predicted by the following: the theoretical initial *Y*-response (0 dose) for the curve (A_1); the theoretical final *Y*-response ("infinite" dose) for the curve (A_2); the dose producing a response halfway between A_1 and A_2 (X_{50} or ED_{50}); and the slope estimator (p) for the slope of the curve between A_1 and A_2. The equation is as follows:

$$Y = \frac{A_1 - A_2}{1 + (X/X_{50})^p} + A_2.$$

The computer program Origin 6.0 (Microcal, Northampton, MA) was used to fit the fluence–response curves to the data. From extensive experience in our laboratory, a saturating 90 min light exposure produces a maximum mean percent control-adjusted plasma melatonin suppression ranging from 60 to 80% depending on the particular group of subjects being tested (Gaddy et al., 1993; Ruberg et al., 1996; Wang et al., 1999; Brainard et al., 2000a, 2001). To form an analytical action spectrum, it is necessary to determine whether all fluence–response curves can be fit to a univariant sigmoidal curve (Coohill, 1991; Lipson, 1994, 1999). To do this, sigmoid curves were fitted to the five fluence–response curves between 440 and 530 nm, which reached a mean percent control-adjusted melatonin suppression of 60–80% by constraining the A_1 factor (theoretical initial *Y*-response) to 0 because no light exposure should yield a 0% control-adjusted plasma melatonin suppression. From this set of curves, a mean A_2 (theoretical final *Y*-response or "infinite" dose for the curve) and a mean p (slope estimator) was calculated. Subsequently, all eight data sets (including the data sets that did not reach saturation) were then fitted to sigmoid curves that constrained A_2 and p to these means and constrained A_1 to 0. Each calculated curve was tested for goodness-of-fit of the data by coefficient of correlation.

Melatonin action spectrum. This action spectrum was formed from the photon density, which elicited the half-saturation constant (ED_{50}) of the percent control-adjusted melatonin suppression for each of the eight wavelengths. These half-saturation constants were derived from the eight univariant fluence–response curves described above. The half-saturation constants were then normalized to the maximum response and plotted as relative sensitivity. The relative quantum sensitivity from each group of subjects was then graphically plotted (quanta/wavelength) to illustrate the resultant action spectra for melatonin suppression in humans. A predicted peak sensitivity for this action spectrum was determined by fitting a vitamin A_1-retinaldehyde photopigment template to the data by a modification of the method described by MacNichol et al. (1983). Specifically, the long wavelength limb of vitamin A_1-based photopigments can be considered linear within the 10–90% sensitivity range when plotted on a frequency abscissa. To select the best fit vitamin A_1 template, the normalized 10–90% long wavelength melatonin ED_{50} data were fitted to a series of vitamin A_1-based templates within the 10–90% sensitivity range of the long-wavelength limbs of the templates (Partridge and De Grip, 1991). Pearson correlation coefficients derived from fitting the melatonin data to the templates indicated the optimum fitting template.

RESULTS

Variations in pupillary dilation, exposure time, and melatonin assay

Individuals vary slightly in their pupil size and response to mydriatic agents. Mean ± SD pupillary dilation was 7.19 ± 0.88 mm for all 72 subjects across all nights of exposures. There were no significant pupil size changes during the light exposures. Similarly, there is a small degree of variability in exact light exposure durations attributable to slight experimental delays. Across 627 single-subject experiments, the mean ± SD exposure duration was 90.6 ± 2.1 min. A total of 53 assays were run to quantify melatonin in plasma samples collected during this project. Coefficients of variation calculated from control samples assayed as 19.2 and 90.0 pg/ml had 10.8 and 4.0% for intra-assay coefficients of variation, respectively. The inter-assay coefficients of variation were 13.5 and 10.2%.

Fluence–response data at 460 nm

Given that the predicted peak of the final action spectrum is 464 nm, the full data complement, from raw melatonin values to a final fluence–response curve for the nearby monochromatic stimulus at 460 nm, is illustrated in Figure 2. This fluence–response study at 460 nm was done with eight subjects (four males and four females). Across these subjects on all nights of testing, there were no significant differences ($F = 0.70$; $p = 0.69$) between sets of preexposure values, indicating that baseline nocturnal melatonin levels were consistent across the different nights of study. The *top graph* in Figure 2 shows the mean + SEM preexposure and postexposure (2:00–3:30 A.M.) melatonin values (mean range, 72.1–29.3 pg/ml). At 460 nm, exposure to irradiances of 2.3 $\mu W/cm^2$ and lower did not significantly suppress plasma melatonin. In contrast, exposures of 3.1 $\mu W/cm^2$ and higher elicited significant melatonin suppressions ($p < 0.03$ or less).

For comparative purposes, all melatonin data were converted

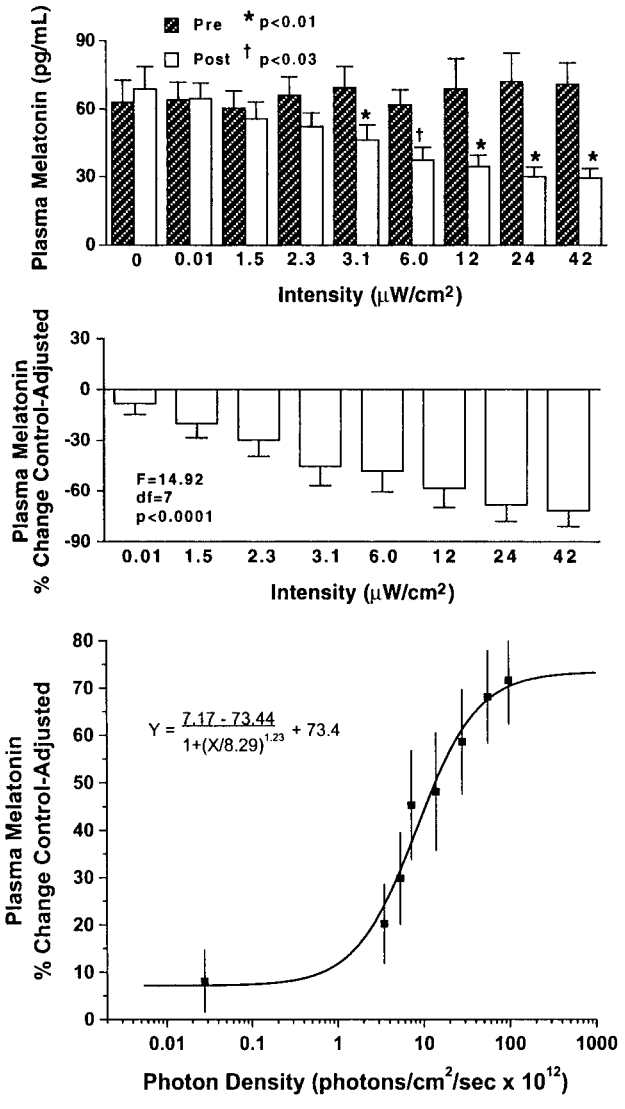

Figure 2. In the *top two graphs*, the *bars* represent group mean + SEM values of plasma melatonin relative to 460 nm monochromatic light exposure at different irradiances in one group of eight healthy subjects. The *top* shows plasma melatonin values before and after light exposure. There were no significant differences ($F = 0.70$; $p = 0.69$) across preexposure mean melatonin values. Light irradiances at or above 3.1 $\mu W/cm^2$ elicited significant melatonin suppression. The *middle* illustrates the subjects' plasma melatonin percent control-adjusted change scores. Progressively higher irradiance exposures at 460 nm produce progressively greater plasma melatonin percent control-adjusted change scores ($p < 0.0001$). The *bottom* demonstrates the best-fit fluence–response curve for 460 nm exposures and percent control-adjusted melatonin suppression ($R^2 = 0.97$). Each *data point* represents one group mean ± SEM.

to plasma melatonin percent control-adjusted change scores. As illustrated in the *middle graph* of Figure 2, one-way, repeated-measures ANOVA showed a significant effect of light intensity on plasma melatonin percent control-adjusted change scores ($F = 14.92$; $p < 0.0001$). *Post hoc* tests on plasma melatonin percent control-adjusted scores demonstrated that all intensities at or above 3.1 $\mu W/cm^2$ significantly suppressed melatonin more than the 0.012 $\mu W/cm^2$ stimulus ($p < 0.05$ or less). Similarly, all irradiances at or above 12.1 $\mu W/cm^2$ significantly suppressed melatonin more than the 1.5 $\mu W/cm^2$ stimulus. Finally, both 24.2 and 42.2 $\mu W/cm^2$ exposures elicited significantly higher plasma melatonin percentage of control-adjusted change scores compared with an irradiance of 2.3 $\mu W/cm^2$.

The data from the *middle graph* of Figure 2 can be mathematically converted into a best-fit, sigmoidal curve that plots melatonin suppression against stimulus photon density. The specific formula for this curve is shown below and has a 0.97 coefficient of correlation (R^2):

$$y = \frac{7.17 - 73.4}{1 + (x/8.29)^{1.23}} + 73.4.$$

As shown in the *bottom illustration* in Figure 2, this curve illustrates the fluence–response interaction between mean ± SEM melatonin percent control-adjusted change scores and the photon density of the monochromatic light.

Fluence–response data for all eight wavelengths

As shown in Figure 2, there is a clear, fluence–response relationship between graded photon densities of monochromatic 460 nm light and melatonin suppression. Data from each of the eight wavelengths tested in this study fit four-parameter sigmoidal curves with high coefficients of correlation. Specifically, wavelengths at 440, 460, 480, 505, 530, 555, 575, and 600 nm had respective coefficients of correlation (R^2): 0.99, 0.97, 0.95, 0.97, 0.98, 0.92, 0.96, and 0.97. As described in Materials and Methods, to form an analytical action spectrum, all fluence–response curves must be fit to a univariant sigmoidal curve (Lipson, 1994; Coohill, 1999). The univariant curve model for the data in this study has the factors of $A_1 = 0$, $A_2 = 66.9$, and $p = 1.27$. Figure 3 illustrates all eight univariant fluence–response curves from this study. As with previous circadian analytical action spectra (Takahashi et al., 1984; Provencio and Foster, 1995; Yoshimura and Ebihara, 1996), full-range fluence–response curves were not elicited above 550 nm. Despite this, standard photobiological curve-fitting methods could be used to fit the data from all eight wavelengths in the present study to univariant, sigmoidal functions. When fit to a univariant fluence–response curve with these factors, the data from exposures to 440, 460, 480, 505, 530, 555, 575, and 600 nm have high coefficients of correlation of 0.91, 0.95, 0.93, 0.94, 0.92, 0.90, 0.95, and 0.81, respectively.

Melatonin suppression response to 420 nm at a single intensity

Given the high sensitivity of subjects to short-wavelength light, as shown in Figure 4, it was determined that a probe of sensitivity to monochromatic light below 440 nm was needed. On the control night when the eight volunteers were exposed to darkness only, their raw mean melatonin levels at 2:00 and 3:30 A.M. were 69.4 and 76.0 pg/ml, respectively. That small increase was not statistically significant ($t = -1.15$; $p = 0.29$). As shown in Figure 4, when these volunteers were exposed to 420 nm light at 31.8 $\mu W/cm^2$ (5.58×10^{13} photons/cm^2), raw mean melatonin levels at 2:00 and 3:30 A.M. were 76.4 and 47.6 pg/ml, respectively. That decrease in melatonin was statistically significant ($t = 4.67$; $p < 0.003$). For comparative purposes, this single melatonin suppression response was fitted to the univariant fluence–response curve formula used for all of the data in Figure 3. The resulting curve estimated a half-maximum (X_{50} or ED_{50}) melatonin suppression response for 420 nm of 1.83×10^{13} photons/cm^2.

Action spectrum for melatonin suppression

Action spectra are determined by comparing the number of photons required for the same biological effect at different wave-

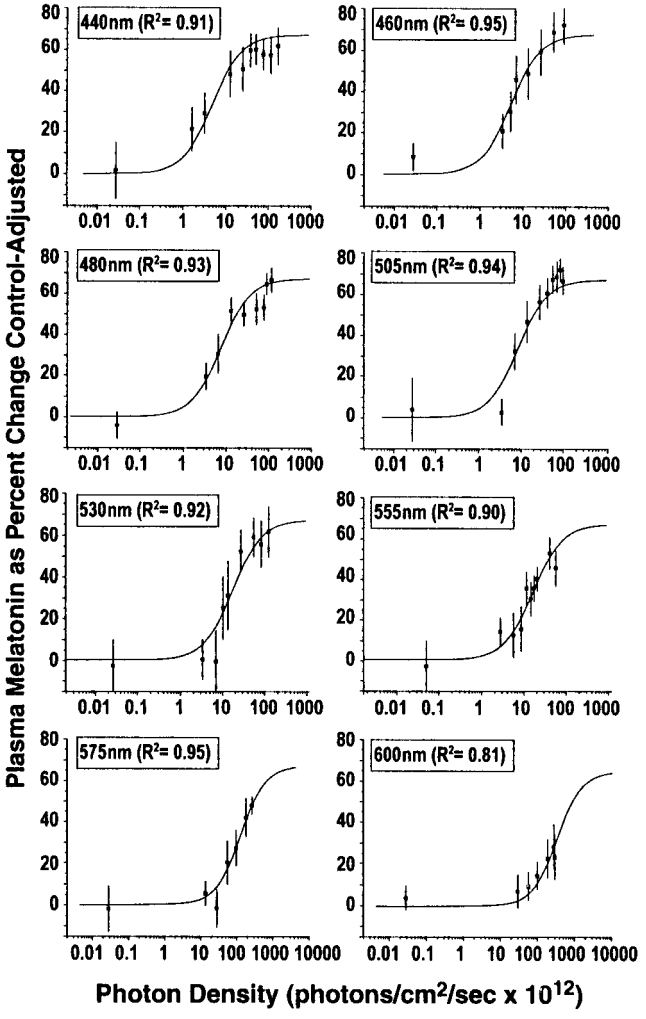

Figure 3. This figure illustrates the fitted univariant fluence–response curves for monochromatic light exposures and percent control-adjusted melatonin suppression for eight wavelengths of visible light. Each fluence–response curve is derived from eight healthy volunteers who participated in a complete, within-subjects experimental design. In each graph, the *data points* represent group means ± SEM. Each *curve* has a high coefficient of correlation (0.95–0.81).

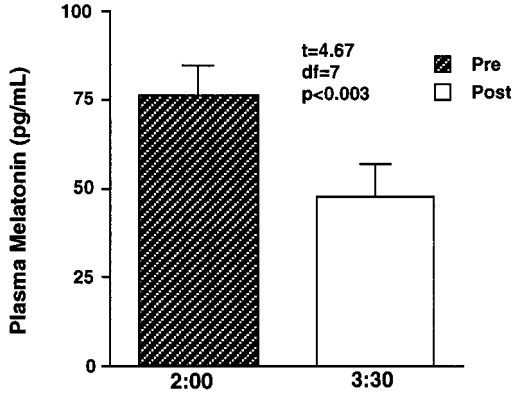

Figure 4. In this graph, the *bars* represent group mean ± SEM plasma melatonin values before and after exposure to 31.8 μW/cm^2 monochromatic light at 420 nm in eight healthy subjects. This light irradiance induced a significant melatonin suppression ($p < 0.003$).

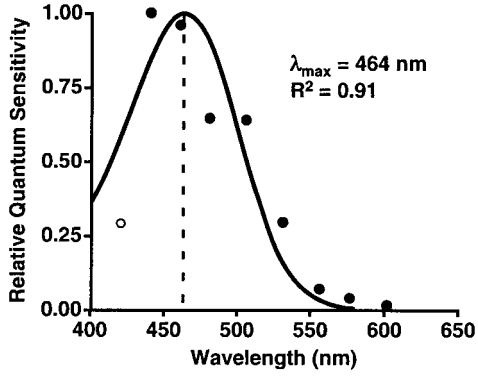

Figure 5. This graph demonstrates the action spectrum for percent control-adjusted melatonin suppression in 72 healthy human subjects. The *filled circles* represent the half-saturation constants of eight wavelengths from 440 to 600 nm that were normalized to the maximum response and plotted as log relative sensitivity. The *open circle* represents the estimated half-saturation constant derived from the 420 nm data. The *solid curve* portrays the best-fit template for vitamin A_1 retinaldehyde photopigments, which predicts a maximal spectral absorbance (λ_{max}) of 464 nm (Partridge and De Grip, 1991). There is a high coefficient of correlation for fitting this opsin template to the melatonin suppression data ($R^2 = 0.91$).

lengths (Smith, 1989; Coohill, 1999). For this experiment, the action spectrum was formed from the photon density that elicited the half-saturation constant (X_{50} or ED_{50}) of the percent control-adjusted melatonin suppression for each of the eight wavelengths. The half-saturation constants were derived from the eight univariant fluence–response curves shown in Figure 3 and the one estimated half-saturation constant from the data shown in Figure 4. The relative quantum sensitivity from each group of subjects was plotted in Figure 5 (quanta/wavelength) to illustrate the resultant action spectra for human melatonin suppression. When the data were aligned to the best-fit template for vitamin A_1-retinaldehyde photopigments, this action spectrum predicted a peak spectral sensitivity (λ_{max}) of 464 nm. There was a strong coefficient of correlation between the data and this fitted opsin nomogram ($R^2 = 0.91$).

Comparison of action spectra

The action spectrum for the photoreceptor system that provides input to the pineal gland appears to be distinct from the action spectra for the classical human visual photoreceptor systems. To illustrate this, the maximal spectral absorbencies and long wavelength limbs of the human rod and cone photoreceptors that support vision (Stockman and Sharpe, 1999) are illustrated in Figure 6, along with the maximal spectral absorbance and long wavelength limb of the melatonin action spectrum. The *shaded area* around the melatonin action spectrum illustrates ±SD for this function.

DISCUSSION

The action spectrum presented here is based on univariant fluence–response curves for melatonin suppression by eight monochromatic light wavelengths in healthy subjects. These data fit a vitamin A_1 opsin template with 446–477 nm, providing the strongest circadian input for melatonin regulation. These results suggest that a novel photopigment in the human eye may be primarily responsible for melatonin regulation and may be distinct from the individual rod and cone photoreceptors for vision.

In developing a fluence–response curve, a complete within-subjects experimental design produces the most reliable results. When subjects are studied over a 2–4 month period, however,

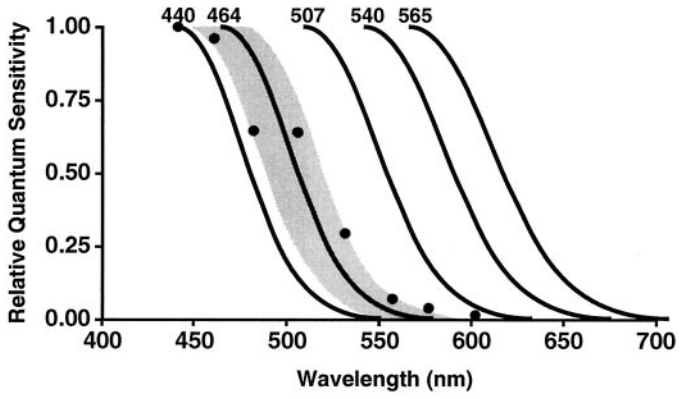

Figure 6. This figure illustrates a comparison of the melatonin suppression and visual action spectra. The maximal spectral response and long wavelength limb of the melatonin suppression template is plotted along with the maximal spectral response and long wavelength limbs of the human rods and cones that support vision (Stockman and Sharpe, 1999). The *shaded area* around the 464 nm template represents ±SD from the data presented above.

lack of stability in the subjects' circadian entrainment can introduce variability in light-induced melatonin suppression. This study accepted only volunteers who reported regular bed and wake times, and their melatonin rhythms appeared to have been stable during the course of the study. As shown in the 2:00 A.M. melatonin values (Fig. 2, *top*), there were no significant differences between sets of preexposure values, indicating that baseline melatonin levels were consistent across the different study nights. This phenomenon has been documented for the 505 nm fluence–response group, as well as in other similarly controlled studies (Brainard et al., 1997, 2000a, 2001; Wang et al., 1998). This within-subject stability of the melatonin rhythm over time has been confirmed frequently in the literature (Waldhauser and Dietzel, 1985; Arendt, 1988, 1998).

The data from each of the eight wavelengths between 440 and 600 nm fit a univariant four-parameter sigmoidal curve with a high coefficient of correlation. The univariance of these curves is consistent with, but does not prove, the hypothesis that melatonin suppression is modulated by a single photoreceptor type. At this time, it is not certain that there is a univariant fluence–response function at 420 nm because only one intensity has been tested. It will be important to test for a full fluence–response curve at 420 nm to (1) clarify the precise sensitivity of the melatonin system to this wavelength and (2) determine if this wavelength is univariant with the fluence–response curves of the other eight wavelengths. Previous studies with animals and humans have illustrated similar fluence–response relationships for melatonin suppression and other circadian responses with monochromatic and broad-spectrum light (Brainard et al., 1983, 1988; Podolin et al., 1987; McIntyre et al., 1989; Nelson and Takahashi, 1991; Dkhissi-Benyahya et al., 2000; Zeitzer et al., 2000). The initial attempts to define circadian and neuroendocrine responses to photons of different wavelengths began with polychromatic action spectra, which tested single irradiances of broader light bandwidths in various rodent species. These polychromatic action spectra were reasonably consistent in indicating that the spectral region between 450 and 550 nm provides the strongest stimulation of circadian and neuroendocrine responses in rodents (for review, see Brainard et al., 1999a). Analytic action spectra, based on sets of fluence–response curves at different monochromatic wavelengths, are superior for identifying photoreceptors that mediate photobiological responses (Lipson, 1994; Coohill, 1999).

There are four analytic action spectra for circadian and neuroendocrine regulation in hamsters, rats, and mice (Takahashi et al., 1984; Bronstein et al., 1987; Provencio and Foster, 1995; Yoshimura and Ebihara, 1996). Data from these action spectra have been fitted to spectral sensitivity curves for retinal-based visual photopigments. This curve fitting is predicated on the assumption that a retinal-based molecule transduces light stimuli for circadian regulation and allows the prediction of the shape of the photopigment absorption spectrum, as well as its peak sensitivity (λ_{max}). Across these studies, which used different circadian endpoints, the predicted λ_{max} ranges from 480 to 511 nm and is surrounded by a broad region of high sensitivity. From these results, different photopigments have been suggested to be responsible for circadian regulation, including rhodopsin, a rhodopsin-like molecule, a middle wavelength cone photopigment, or an ultraviolet cone photopigment.

It is commonly believed that the photopic visual system has a peak wavelength sensitivity of ~555 nm (Rodieck, 1998). Many investigators have hypothesized that the photopic visual system mediates circadian and neuroendocrine responses, because this part of the visual system is responsive to "bright" daytime levels of illumination. Previous data (Brainard et al., 2001) and those presented above do not support this hypothesis. The results clearly demonstrate that 555 nm is significantly weaker in suppressing melatonin compared with an equal photon density of 460 nm. Thus, the photopic system is not likely to be the primary input for circadian regulation. Demonstrating that the photopic visual system is not the principal phototransducer for melatonin regulation does not preclude it from having any role in circadian input. Indeed, recent studies suggest that visual cones may be involved in circadian regulation. Recordings from SCN neurons in rats indicate that the visual rods and cones provide input to cells of the rat SCN (Aggelopoulos and Meissl, 2000). Similarly, a human phase-shifting study suggests that, under some circumstances, the visual long wavelength-sensitive cone may also mediate circadian vision in humans (Zeitzer et al., 1997).

The data presented here do not support the hypothesis that any of the known visual photoreceptors provide the primary input for melatonin regulation. Figure 6 shows that none of the action spectra for individual visual photoreceptor systems match the action spectrum for melatonin suppression. If the photoreceptors that mediate vision in humans are not the primary photoreceptors for circadian regulation, what are the alternative candidates? Recent studies with various vertebrate species have identified several new molecules that may serve as circadian photopigments. These putative photopigments include both opsin-based molecules, such as vertebrate ancient opsin (Soni and Foster, 1997), melanopsin (Provencio et al., 1998), and peropsin (Sun et al., 1997), as well as non-opsin molecules, such as bilirubin (Oren, 1996) and cryptochrome (Miyamoto and Sancar, 1998). Among these new photopigments, only melanopsin has been specifically localized to the human neural retina (Provencio et al., 2000), and cryptochrome has been localized to the mouse neural retina (Miyamoto and Sancar, 1998). Cryptochromes have been studied extensively as circadian photoreceptors in plants and insects (Ahmad and Cashmore, 1993; Stanewsky et al., 1998) and have been proposed as circadian photoreceptors in mammals (Miyamoto and Sancar, 1998; Thresher et al., 1998). The contention that cryptochromes serve as circadian photoreceptors in humans

or other mammals, however, remains controversial (Griffin et al., 1999; van der Horst et al., 1999; von Schantz et al., 2000).

The action spectrum presented here matches a vitamin A_1-retinaldehyde photopigment template that supports the hypothesis that one of the new opsin photopigment candidates provides primary photic input for melatonin regulation in humans. The molecular identification of candidate opsin or non-opsin photoreceptors and their localization in the retina and/or neural components of the circadian system make them well suited to act as circadian phototransducers. However, functional data confirming any of these molecules as having a direct role in mammalian circadian photoreception is currently lacking. Furthermore, caution should be exercised in generalizing results from plants, insects, fish, amphibians, and rodents to humans.

Are the effects of light on melatonin suppression relevant to general circadian regulation? Studies have shown that hamsters have a higher intensity threshold for light-induced phase-shifts of wheel-running rhythms than for melatonin suppression (Nelson and Takahashi, 1991). Recently, however, a study on humans showed that the 50% response sensitivity for circadian phase shifting (119 lux) was only slightly higher than that for melatonin suppression (106 lux) with white light (Zeitzer et al., 2000). It is possible that there are separate photoreceptors for mediating circadian entrainment versus acute suppression of melatonin. It is reasonable, however, to hypothesize that a variety of nonvisual effects of light, such as melatonin suppression, entrainment of circadian rhythms, and possibly some clinical responses to light, are mediated by a shared photoreceptor system. Additional experiments are needed to test this hypothesis.

In general, relatively high light illuminances ranging from 2500 to 12,000 lux are used for treating winter depression, selected sleep disorders, and circadian disruption (Wetterberg, 1993; Lam, 1998). Although these light levels are therapeutically effective, some patients complain that they produce side effects of visual glare, visual fatigue, photophobia, ocular discomfort, and headache. Determining the action spectrum for circadian regulation may lead to improvements in light therapy. Total illuminances for treating a given disorder can be reduced as the wavelength emissions of the therapeutic equipment are optimized.

Modern industrialized societies use light extensively in homes, schools, work places, and public facilities to support visual performance, visual comfort, and aesthetic appreciation within the environment. Given that light is also a powerful regulator of the human circadian system, future lighting strategies will need to provide illumination for human visual responses, as well as homeostatic responses. The action spectrum presented here suggests that there are separate photoreceptors for visual and circadian responses to light in humans. Hence, new approaches to architectural lighting may be needed to optimally stimulate both the visual and circadian systems.

In conclusion, this study characterizes the wavelength sensitivity of the ocular photoreceptor system for regulating the human pineal gland by establishing an action spectrum for light-induced melatonin suppression. The results identify the 446–477 nm portion of the spectrum as the most potent wavelengths providing circadian input for regulating melatonin secretion. These data suggest that the primary photoreceptor system for melatonin suppression is distinct from the rod and cone photoreceptors for vision. Finally, this action spectrum suggests that there is a novel retinaldehyde photopigment that mediates human circadian photoreception. These findings open the door for optimizing the use of light in both therapeutic and architectural applications.

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Acta Astronautica 92 (2013) 21–28

Contents lists available at ScienceDirect

Acta Astronautica

journal homepage: www.elsevier.com/locate/actaastro

Solid-state lighting for the International Space Station: Tests of visual performance and melatonin regulation

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ARTICLE INFO

Article history:
Received 23 November 2011
Accepted 10 April 2012
Available online 26 April 2012

Keywords:
International Space Station
Solid-state lighting
Vision
Melatonin
Circadian
Neuroendocrine

ABSTRACT

The International Space Station (ISS) uses General Luminaire Assemblies (GLAs) that house fluorescent lamps for illuminating the astronauts' working and living environments. Solid-state light emitting diodes (LEDs) are attractive candidates for replacing the GLAs on the ISS. The advantages of LEDs over conventional fluorescent light sources include lower up-mass, power consumption and heat generation, as well as fewer toxic materials, greater resistance to damage and long lamp life. A prototype Solid-State Lighting Assembly (SSLA) was developed and successfully installed on the ISS. The broad aim of the ongoing work is to test light emitted by prototype SSLAs for supporting astronaut vision and assessing neuroendocrine, circadian, neurobehavioral and sleep effects. Three completed ground-based studies are presented here including experiments on visual performance, color discrimination, and acute plasma melatonin suppression in cohorts of healthy, human subjects under different SSLA light exposure conditions within a high-fidelity replica of the ISS Crew Quarters (CQ). All visual tests were done under indirect daylight at 201 lx, fluorescent room light at 531 lx and 4870 K SSLA light in the CQ at 1266 lx. Visual performance was assessed with numerical verification tests (NVT). NVT data show that there are no significant differences in score ($F=0.73$, $p=0.48$) or time ($F=0.14$, $p=0.87$) for subjects performing five contrast tests (10%–100%). Color discrimination was assessed with Farnsworth-Munsell 100 Hue tests (FM-100). The FM-100 data showed no significant differences ($F=0.01$, $p=0.99$) in color discrimination for indirect daylight, fluorescent room light and 4870 K SSLA light in the CQ. Plasma melatonin suppression data show that there are significant differences ($F=29.61$, $p<0.0001$) across the percent change scores of plasma melatonin for five corneal irradiances, ranging from 0 to 405 $\mu W/cm^2$ of 4870 K SSLA light in the CQ (0–1270 lx). Risk factors for the health and safety of astronauts include disturbed circadian rhythms and altered sleep–wake patterns. These studies will help determine if SSLA lighting can be used both to support astronaut vision and serve as an in-flight countermeasure for circadian desynchrony, sleep disruption and cognitive performance deficits on the ISS.

1. Introduction

Known risk factors for the health and safety of astronauts and ground control workers include disturbed circadian rhythms and sleep loss [1,2]. Sleep and circadian

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0094-5765/$ - see front matter © 2013 IAA. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.actaastro.2012.04.019

problems have been documented in space flight missions as short as 10 days [3]. An analysis of pharmaceutical use during 79 space flight missions showed that sleeping pills or hypnotic compounds accounted for 45% of all medications taken by 219 astronauts [4]. Despite the use of these drugs, studies of more than 60 astronauts on space shuttle (Space Shuttle Transport System or STS) missions showed that approximately half of them slept 6 h or less per 24-hour mission day, even though they are scheduled to sleep for 8 h [5]. Chronic partial sleep loss can pose a considerable threat to the success of a mission by diminishing alertness, cognitive ability and psychomotor performance [3,6–10].

The International Space Station (ISS) uses General Luminaire Assemblies (GLAs) that house fluorescent lamps for illuminating the astronauts' working and living environments [11]. Solid-state light emitting diodes (LEDs) are attractive candidates for replacing the fluorescent lighting system on the ISS. The advantages of LEDs over conventional fluorescent light sources include lower up mass, power consumption and heat generation, as well as fewer toxic materials, greater resistance to damage and long lamp life [12]. A prototype Solid-State Lighting Assembly (SSLA) was developed at Kennedy Space Center and successfully installed on the ISS during Expedition 18. Since then, NASA has developed a set of specifications for the solid-state lighting system that will replace the existing fluorescent lighting system onboard ISS [13]. This new lighting system will provide multiple settings that can support astronaut vision and potentially serve as a lighting countermeasure for performance decrements due to sleep and circadian disruption aboard the ISS.

It is crucial to characterize the new solid-state lighting units for their circadian, neuroendocrine and neurobehavioral efficacy as well as their capacity to support astronaut vision. Non-visual information about light is detected by the eyes and transmitted by the retinohypothalamic tract, a neural pathway which projects to both visual and non-visual regions of the human brain [14,15]. These neural centers receive environmental photic input from a specialized subset of photoreceptive retinal ganglion cells containing the photopigment melanopsin [14,16–18]. It has been demonstrated that more light is required for circadian, neuroendocrine and neurobehavioral regulation than is needed for vision [19–21]. Further, a different wavelength sensitivity has been identified for the non-visual regulation of physiology and behavior compared to stimulating visual responses [22]. For example, studies have shown that exposing humans to light of sufficient intensity and duration at night suppresses the pineal gland hormone melatonin, with the strongest response occurring between 446 and 477 nm, the portion of the spectrum that has a blue appearance [23,24]. Further research has shown that blue monochromatic light at 460 nm is more effective than longer wavelength light at 550–555 nm for phase-shifting circadian rhythms and enhancing alertness levels [25–27]. In contrast, daytime vision has a peak sensitivity to light at 555 nm [28].

The broad aim of the ongoing work is to test light emitted by prototype SSLAs for supporting astronaut vision and assessing neuroendocrine, circadian, neurobehavioral and sleep effects. Three initial ground-based studies were conducted inside of a high-fidelity replica of the ISS Crew Quarters (CQ). The four CQs onboard ISS are acoustically quiet, visually isolated areas for crewmember sleep, relaxation and private retreat [29,30]. The studies presented here include experiments on visual performance, color discrimination, and acute plasma melatonin suppression in cohorts of healthy, human subjects under different SSLA light exposure conditions.

2. Materials and methods

2.1. Light production

The experimental light exposure system used in this study, the Solid-State Lighting Module-Research (SSLM-R), was based on the SSLA prototype installed on ISS in terms of mechanical and electronic connectivity. The SSLM-R, however, was developed as a research tool with significantly expanded capacity for variable light outputs. The SSLM-R was developed at Kennedy Space Center (Bionetics Corporation, Cape Canaveral, FL) and contained LED arrays of 294 white LEDs and 254 RGB LEDs behind a lens diffuser. Although the SSLM-R has a broad capacity for emitting different blends of polychromatic illumination, the experiments reported here only utilized light emitted by the white LEDs that have a spectral power distribution as shown in Fig. 1. Light intensity emitted by the SSLM-R was adjusted by a built-in current-controller. For the visual tests, comparisons were made with (1) indirect daylight from a window on a laboratory counter top that averaged 7042 K CCT and 221 lx (163 $\mu W/cm^2$) at the middle of the test site; and (2) overhead fluorescent room light at an average of 3531 K CCT and 531 lx (168 $\mu W/cm^2$) at the middle of the test site.

2.2. Light measurement

The spectral power distribution measurement, shown in Fig. 1, was taken using a Model FSHH 325-1075P FieldSpec handheld spectroradiometer (Analytical Spectral Devices, Inc., Boulder, CO). Routine light measures were taken using an ILT-1400BL radiometer/photometer (International Light Technologies, Inc., Peabody, MA). For irradiance measures the meter had a Model SEL033 detector with a silicon photodiode (#8376) with wide-eye diffuser input optic W#11990 and a flat response filter F#28875. Illuminance

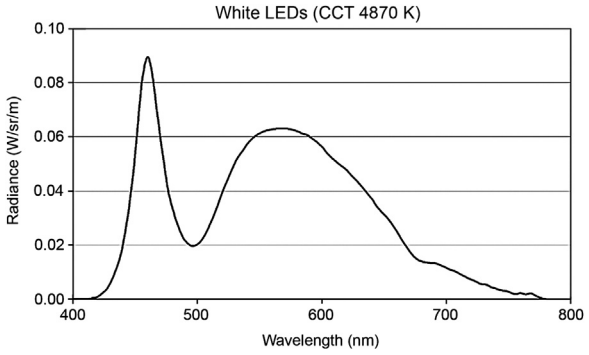

Fig. 1. Graph shows the spectral power distribution corresponding to the 4870 K polychromatic white light emitted by the SSLM-R.

measures were taken with a Model SEL033 detector with a silicon photodiode (#8977) with wide-eye diffuser input optic W#13152 and a photopic response Y#29960 filter. All meters received annual scanned calibrations between 200–1100 nm, were received in tolerance when calibrated during the course of running this protocol, and all calibrations were traceable to the US National Institute of Standards and Technology. Target irradiance and illuminance measures were taken at a fixed position within the CQ using a meter holder facing the center of the light emitting surface of the SSLM-R at a distance of 63.5 cm (25 in.). Correlated color temperatures (CCT) were measured with a Chromameter CL-200A (Konica Minolta Sensing, Inc., Ramsey, NJ). Importantly, the test subjects, like astronauts during space flight, were allowed free behavior within the CQ which could greatly amplify or attenuate the target irradiance/illuminance at their eye level.

2.3. The Crew Quarters

The Crew Quarters (CQ) that has been built in Thomas Jefferson University's Light Research Laboratory is a very close replica of the CQ's used by the astronauts aboard the ISS. The replica CQ at Jefferson was fabricated after careful study of NASA's documentation on the CQ [29,30] and direct measuring of a flight-certified CQ at Johnson Space Center (Houston, TX). Three modifications were needed including: (1) fabrication of a larger access door than the "hatch" that the astronauts use in microgravity; (2) installation of a ventilation fan for air flow in the unit; and (3) placement of a stool with a back support in the CQ for the use and comfort of the subjects during ground-based studies. These modifications did not change the interior dimensions compared to the flight-certified CQs. Importantly, the interior of the entire CQ at Jefferson is lined with the identical white materials used in the CQ's on the ISS (Architectural Fabric #V112671, Gore and Associates, Elkton, MD and woven tapes #840, Aplix Inc., Moorpark, CA). This assures high fidelity duplication of surface reflectance of light that the astronauts experience during space flight while in the CQ.

2.4. Visual tests

2.4.1. Subjects

Healthy astronaut-aged males, 31–53 years, were recruited for this study using advertisements on Craigslist and posters on the Jefferson campus. Subjects were first screened via a phone interview to verify age and availability. Exclusion criteria included abnormal color vision or abnormal eye health, as determined by the study neurophthalmologist. All vision tests were run between 9 AM and 3 PM. Eight subjects participated in all of the visual tests (mean age 39.7 ± 2.8 years).

2.4.2. Visual performance tests

Numerical Verification Testing (NVT) is a standardized test for determining how different lighting environments and contrast changes can affect the ability to perform a visual task [31]. To perform the task, subjects are given a sheet of paper displaying 2 columns of 20 rows of numbers (5 digits each). The columns are nearly identical except for random differences between the numbers in some rows. The study is proctored with a stopwatch and subjects are asked to place a mark on each row of numbers that do not match. Subjects are instructed to perform this task as quickly and as accurately as possible, without sacrificing accuracy for speed. Each set of tests contains 3 sheets each at 5 different printed contrasts (100%, 80%, 50%, 30%, and 10%). Subjects are scored based on both the accuracy and speed of their responses using a scoring model described elsewhere [31]. Three separate series of NVT tests were given under three different lighting conditions: indirect daylight at 221 lx, fluorescent room light at 531 lx and 4870 K SSLA light in the CQ at 1267 lx.

2.4.3. Color discrimination tests

The Farnsworth-Munsell 100 Hue test (FM-100) is a method for testing color discrimination [32]. The test consists of four trays of 25 colored disks, each tray representing a specific color gradient range of the visible spectrum (X-Rite, Inc., Grand Rapids, MI). Before testing, the color disks for a given tray are shuffled into a random pile. Subjects are then seated in front of a flat work surface and are asked to sort each tray of colored disks from the left fixed end to the right fixed end by shades of color. This test is done one eye at a time, with the subject wearing an eye patch over the eye not being tested. Subjects are scored based upon accuracy of arranging the disks in the proper sequence. Scoring is done using software provided with the trays. The higher the score, the more errors were made in terms of color discrimination. Separate FM-100 tests were given under three different lighting conditions: indirect daylight at 221 lx, fluorescent room light at 531 lx and 4870 K SSLA light in the CQ at 1267 lx.

2.4.4. Statistical analysis of visual test data

For the NVT test results, repeated measures, mixed-model ANOVAs were performed separately on the adjusted score data and the adjusted time data for contrast and light condition (SAS 9.0, SAS Institute Inc., Cary, North Carolina). For the FM-100 test results, a one-way ANOVA was run for FM-100 score versus lighting condition.

2.5. Melatonin suppression study

2.5.1. Subjects

The healthy females ($N=3$) and males ($N=5$) in this study had a mean $\pm$ SEM age of 26.4 ± 0.7 years and signed an approved IRB consent document before participating. All subjects demonstrated normal color vision by both the Ishihara test and the more extensive Farnsworth-Munsell D-100 color vision test (mean $\pm$ SEM score of 95.8 ± 12.8). All subjects were in good ocular and physical health as determined by an exam from a neuroophthalmologist, good mental health as determined by an assessment from a clinical psychologist, and free of signs of substance abuse as determined by a urinary toxicological screen. Sleep–wake stability was confirmed through either 10 day of actigraphy (Octagonal Sleepwatch;

Ambulatory Monitoring, Inc., Ardsley, NY), filling out daily sleep–wake logs at home and calling into a voice mailbox leaving a message both upon going to bed and upon awakening for subjects who had not done studies with this laboratory previously ($N=3$) or through phone interview for subjects who had participated in a study in this laboratory within the previous year ($N=5$).

2.5.2. Melatonin protocol

Subjects arrived for each study night at approximately 11:45 PM. As described in detail elsewhere, each experiment began at midnight when subjects were blindfolded and remained awake and sitting upright in darkness for 120 min [23]. While blindfolded, a blood sample was taken just prior to 2:00 AM. The blindfold was then removed, and subjects were transferred to the CQ to be exposed to a 90 min light stimulus from 2:00 to 3:30 AM. Subjects were seated in the CQ during light exposure, facing the SSLM-R. Subjects were not required to be gazing at the SSLM-R during the exposure, and were allowed to be performing other tasks. The most popular tasks were reading books or magazines and drawing. Devices that emit light, such as laptops, were not permitted inside the CQ. At 3:30 AM, a second blood sample was taken. Each subject was exposed to complete darkness from 2:00 to 3:30 AM on their control night and was tested with at least 6 day between each nighttime exposure. The plasma samples were assayed for melatonin using a radioimmunoassay (RIA) with assay sensitivity of 2.9 pg/mL [33].

2.5.3. Statistical analysis of melatonin data

Two-tailed, Students' *t*-tests were used to assess significance of raw melatonin change from 2:00 to 3:30 AM. The raw melatonin data were then converted to % melatonin change scores and % control-adjusted change scores as described elsewhere [23]. Sets of pre-exposure melatonin values, % melatonin change scores, and % control-adjusted melatonin change scores were analyzed with one-way, repeated measures ANOVA. Significant differences between groups were assessed with post-hoc Fisher PLSD test with alpha set at 0.05.

3. Results

3.1. Visual results

3.1.1. Visual performance test results

ANOVA showed no significant differences between lighting conditions for time ($F=0.13$, $p=0.88$) or score ($F=0.34$, $p=0.72$). Significant differences were found between contrast levels for both time ($F=27.93$, $p<0.0001$) and score ($F=18.38$, $p<0.0001$). Using a Dunnett's *t*-test post hoc analysis, it was found that 10% contrast differed significantly from all other contrasts for both time and score ($p<0.005$; Fig. 2).

3.1.2. Color discrimination tests

ANOVA showed no significant differences for FM-100 score between the three lighting conditions ($F=0.01$, $p=0.99$; Fig. 3).

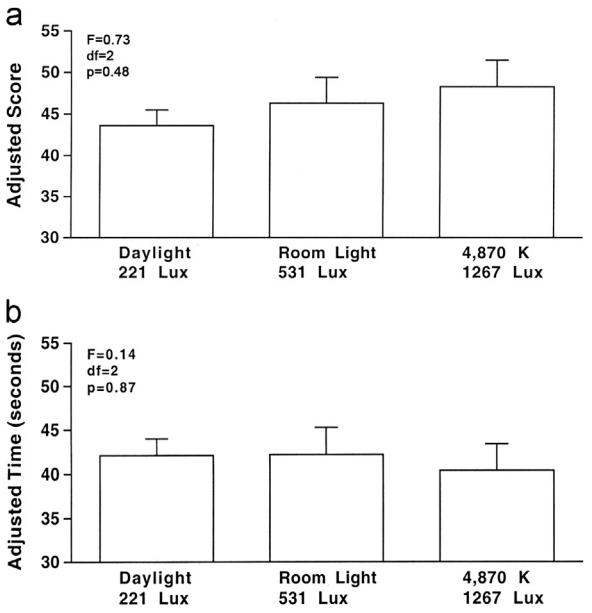

Fig. 2. In the two graphs, results are shown across three lighting conditions: indirect daylight, fluorescent room light, and 4870 K SSLM-R light in the CQ. (a) In this graph, the bars represent group mean+SEM adjusted score values ($N=8$) for the NVT testing at 10% contrast. No significant differences ($F=0.73$, $p=0.48$) were found between light conditions. (b) In this graph, the bars represent group mean+SEM adjusted time values ($N=8$) for the NVT testing at 10% contrast. No significant differences ($F=0.14$, $p=0.87$) were found between light conditions.

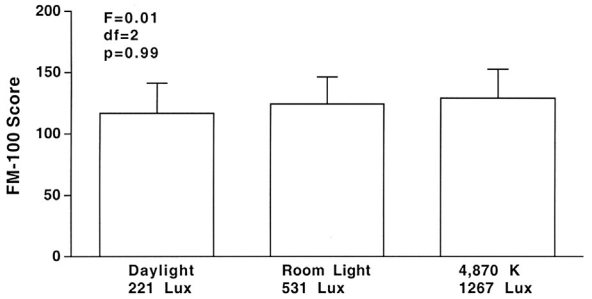

Fig. 3. In this graph, the bars represent group mean+SEM adjusted score values ($N=8$) for the FM-100 done under indirect daylight, fluorescent room light, and 4870 K SSLM-R light in the CQ. No significant differences were found between light conditions ($F=0.01$, $p=0.99$).

3.2. Melatonin assay and suppression results

Coefficient of variation calculated from control samples assayed averaged 4.8% for intra-assay coefficient of variation. The inter-assay coefficient of variation from the 4 assays run for this experiment averaged 4.7%. The raw plasma melatonin data for pre- and post-light exposure plasma melatonin levels were analyzed using paired, two-tailed *t*-tests. Fig. 4a presents a comparison of the mean (+SEM) pre- and post- melatonin values for each study night. The figure shows that corneal irradiance values at or above 211 μW/cm^2 of 4870 K white-appearing SSLM-R light significantly suppressed melatonin ($p<0.005$). Neither the control condition, nor the groups of exposure nights to

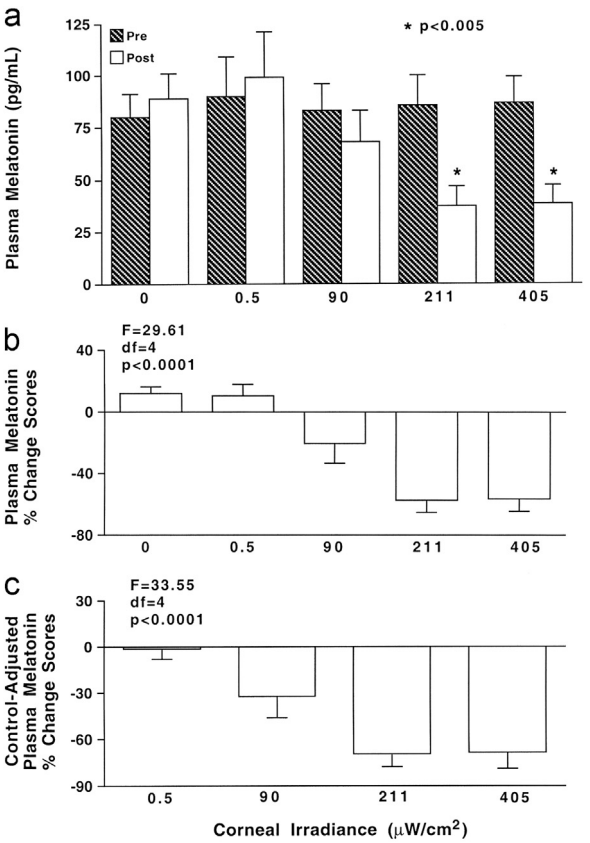

Fig. 4. (a) In this graph the bars represent group mean+SEM plasma melatonin values ($N=8$) before and after four irradiances from the SSLM-R at 4870 K and the control night (0 μW/cm^2). Irradiances shown in the figure correspond to illuminances of 0, 1.3, 279, 670 and 1270 lx. Paired, two-tailed *t*-tests indicated which conditions elicited statistically significant melatonin suppression. (b) This graph represents group mean+/−SEM percent melatonin change scores ($N=8$) for control and four irradiances from the SSLM-R at 4870 K. Increases in the light irradiance produced an increased suppression of melatonin levels, compared to control melatonin values. (c) This graph represents group mean−SEM percent control-adjusted melatonin change scores ($N=8$) for four irradiances from the SSLM-R at 4870 K. Increases in the light irradiance produced an increased suppression of melatonin levels.

the lower corneal irradiances of 4870 K white-appearing SSLM-R light (0.5 and 90 μW/cm^2) elicited a statistically significant change in plasma melatonin levels.

ANOVA demonstrated that there were no significant differences between mean pre-exposure melatonin values for each study night ($F=0.27$, $df=4$, $p=0.90$). As shown in Fig. 4b, mean percent changes in melatonin values exhibited increased suppression concurrent with increased corneal irradiance of 4870 K white-appearing SSLM-R light. ANOVA indicated that the effect of the light irradiance on percent change scores was significant ($F=29.61$, $df=4$, $p<0.0001$). The Fisher PLSD test detected a significant difference between percent change in melatonin values for the control night and exposures at or above 90 μW/cm^2 of 4870 K white SSLM-R light. The Fisher PLSD test also detected significant differences between percent change in melatonin values for the 90 μW/cm^2 and exposures at or above 211 μW/cm^2 of 4870 K white-appearing SSLM-R light.

Percent control-adjusted melatonin change scores are presented in Fig. 4c. ANOVA showed that there was a significant effect of light irradiance on melatonin suppression ($F=33.55$, $df=4$, $p<0.0001$). Increasing corneal irradiances of 4870 K white SSLM-R light exposure evoked progressively larger melatonin suppressions. Specifically, the Fisher PLSD test showed that the highest corneal irradiances of 4870 K white-appearing SSLM-R light (405 and 211 μW/cm^2) elicited a significantly stronger melatonin suppression than the lower irradiances (90 and 0.5 μW/cm^2). The corneal irradiance 90 μW/cm^2 of 4870 K white SSLM-R light elicited a significantly stronger melatonin suppression than the lowest irradiance (0.5 μW/cm^2).

4. Discussion

The present data demonstrate that bright white 4870 K SSLM-R light inside of the CQ supports visual performance and color discrimination equivalently to typical indoor exposures to indirect daylight and overhead fluorescent light. In addition, increasing irradiances of this white solid-state light inside the CQ elicit increasingly stronger melatonin suppressions in healthy volunteers. These findings demonstrate the feasibility of doing controlled studies on visual, neuroendocrine and circadian responses in a high fidelity replica of an ISS component.

There has been an acceleration of fluorescent lamp failure on the ISS, and a deficiency of flight-certified fluorescent lamp replacements. The new solid-state lighting technology specified by NASA provides an important opportunity for re-lamping of the ISS with an energy efficient lighting system that has a significantly longer life span and does not contain mercury [12,13]. That lighting retrofit is currently estimated to begin in the range of 2014–2016 and is intended to provide improved visual illumination for NASA astronauts to navigate their environment and accomplish their work. In addition, the new ISS lighting system is intended to provide light as an inflight countermeasure to help overcome the sleep and circadian disruption that some astronauts experience during spaceflight [1,5]. Specifically, NASA identifies the "Risk of performance errors due to fatigue resulting from sleep loss, circadian desynchronization, extended wakefulness, and work overload" as a major risk for humans during current and future human exploration class spaceflight missions [1]. The studies reported here represent a start towards quantifying the broader range of visual, biological and behavioral responses to light that will be supported within the ISS once the current fluorescent lighting system is replaced by solid-state luminaires.

To prepare for manned space missions, NASA utilizes Earth-based research in specific environments with elements that are similar or analogous to some of the conditions of spaceflight. Analog research environments can be in extreme locations such as Antarctica, rugged deserts, the ocean floor or inside of a volcano [34]. The work reported here represents a middle ground between research done in highly controlled laboratory conditions and NASA's experimental field environments. In creating a high fidelity replica of the CQ in the laboratory, an analog of this portion of the ISS can be used for testing astronaut

vision and potential lighting countermeasures for sleep and circadian disruption.

As expected, there were no significant differences across the three lighting conditions for either color discrimination or visual performance. Based on NASA's specifications for the new ISS solid-state lighting system, however, there will be the capacity for much dimmer light output as well as significant shifts in the balances of emitted wavelengths meant to serve as lighting countermeasures. Currently, visual tests are being done in the CQ with solid-state lighting stimuli that are not as likely to support equivalent visual performance and color discrimination. Ultimately, it will be important to balance the application of lighting countermeasures with the need for good visual stimulation.

Measurement of acute melatonin response to light has been used extensively as a tool to examine the ocular, neural, and biochemical physiology of melatonin regulation and circadian rhythms [35–37]. Similarly, studies of the melatonin responses to light have been used to develop light as a treatment for circadian disruption, jet lag, shiftwork, sleep disturbances, and mood disorders [38–40]. The melatonin suppression data reported here is being used as an initial approach to the development of lighting countermeasures for astronauts. These data demonstrate that increasing light irradiances inside the CQ elicit increasing plasma melatonin suppression in healthy human subjects. Compared to prior melatonin suppression studies that used 90 min nighttime exposures to either monochromatic, narrow bandwidth or broad bandwidth white light, the 211 and 405 $\mu W/cm^2$ irradiances of 4870 K SSLA light in the CQ appeared to elicit a full or saturating melatonin suppression response [24,41,42]. In contrast, the 90 $\mu W/cm^2$ exposure elicited roughly half the melatonin suppression compared to the higher irradiances. These data show that it is possible to quantify a photobiological response inside the CQ with a solid-state lighting system. Extensive work remains, however, in characterizing the broader range of neuroendocrine, circadian and neurobehavioral responses in this and other portions of ISS. Further, such ground testing is only a prelude to the development and validation of systematic inflight lighting countermeasure strategies for spaceflight operations.

The data reported here begin to address an intersection of two frontiers: (1) the long duration exploration of space, and (2) the rapid development of solid-state lighting that will ultimately revolutionize how our public facilities, work places and homes are illuminated in the coming decades. Similar to some of the astronauts, a significant portion of the global population suffers from chronic sleep loss or circadian-related disorders. By refining multipurpose lights for astronaut safety, health and well-being in spaceflight, the door is opened for new lighting strategies that can be evolved for use on Earth.

Acknowledgments

This work is supported by the National Space Biomedical Research Institute through NASA NCC 9-58 and NASA #NNX09AM68G. Special thanks to Daniel Schultz of Kennedy Space Center, Matthew Regan and Trevor Murdock of Bionetics Corporation, and Fred Maxik and Robert Soler of the Lighting Sciences Group for the development of the SSLM-Rs used in this research. Additional thanks to Dennis Grounds and Lauren Leveton, Ph.D. of Johnson Space Center for donation of the SSLM-Rs to our laboratory. Many thanks also to Ellen Dougherty for development of the high fidelity reflectant interior and exterior coverings of the CQ, Benita Middleton at the University of Surrey, UK for performing the RIA, and Kat West, Donna Hasher, Michael Downes, Alan Kubey, Nicholas Kurczewski, Jessica Treadway, and Iesha Mathis for technical assistance.

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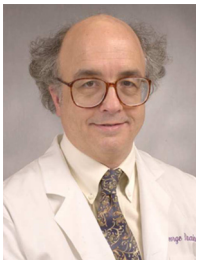

George C. Brainard, is a Professor of Neurology and the Director of the Light Research Program at Jefferson Medical College of Thomas Jefferson University in Philadelphia, PA. His academic work has been concerned with the effects of light on biological and behavioral responses of animals and humans for over thirty years. He currently serves as the National Space Biomedical Research Institute Team Leader for Human Factors and Performance that involves five universities working collectively to develop solutions for health risks during spaceflight.

William Coyle, has over 30 years experience as a cabinetmaker, woodworker and general remodeler. His work includes fabricating and installing custom cabinetry in homes and offices as well as general remodeling activities. He has also assisted the Jefferson Light Research Lab at Thomas Jefferson University in Philadelphia, PA for over 25 years fabricating and installing custom cabinetry to support and assist the Light Lab team in their research activities. He designed and built the CQ used in the current study.

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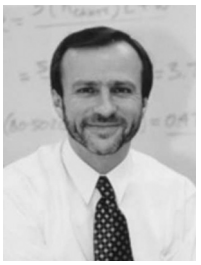
Benjamin Warfield, has been a part of the Jefferson Light Research Program for over 8 years, initially contributing on imaging and archival work for the 2003 NSBRI grant, then moving into a full time research technician post working on nighttime melatonin studies. He is now the lab operations support specialist, developing scientific posters and assisting with the lab's applied space research and dark-sky awareness projects while continuing to archive pineal research from the past.

James Maida, has been at Johnson Space Center for over two decades. In that time, he has been a technical monitor for the JSC Graphics Research and Analysis Facility (GRAF), the JSC Lighting Environment Test Facility (LETF), and the Anthropometry and Biomechanics Facility (ABF). He has also worked on the development and integration of the lighting analyses capability into the Shuttle and ISS programs. He has also served as real-time mission support with lighting analyses for crew timelines during berthing for ISS assembly using SVS.

Charles Bowen, Ph.D., previously designed analog, digital, and power electronics primarily for commercial seismic data acquisition systems for 19 years. This experience afforded practical insights into the operation and limitations of semiconductors and power system components that have applications for practical LED lighting. For the past 8 years, he performed the role of human factors design engineering specialist in the Lighting Environment Test Facility (LETF) at NASA/Johnson Space Center's Habitability and Environmental Factors Division. This position has afforded many opportunities to investigate technical aspects of a variety of lighting systems proposed for/used in NASA spacecraft.



Craig Bernecker, Ph.D., FIESNA, LC, has directed the lighting program at Penn State University, and developed lighting education programs in distance education, as well as served on the policy-advising body for the Penn State World Campus. He has published more than forty articles on lighting and is known for his work on the psychological aspects of lighting. He maintains an active consulting practice and regularly serves as a peer reviewer for the U.S. Department of Energy. Dr. Bernecker has served the Illuminating Engineering Society (IES) of North America in several capacities, including President for 2004-2005. He was named an IES Fellow in 1991.

Steven W. Lockley, Ph.D., is a neuroscientist at Brigham and Women's Hospital, and an associate professor of medicine at Harvard Medical School. His research focuses on human circadian biology. Specifically, his research includes the effects of timing, duration, intensity and wavelength of light exposure on circadian resetting, melatonin suppression and the acute alerting effects of light, as well as the visual impairments and the effects of the severity and type of blindness on circadian photoreception, the periodicity of the circadian pacemaker and development of circadian rhythm sleep disorders.

John P. Hanifin, M.Phil, Over the past 24 years, he has been an active contributor to the field of pineal research as evidenced by authorship on 2 and co-authorship on 20 peer-reviewed papers in the field. As the laboratory manager for the Jefferson Light Research Program of Thomas Jefferson University, he coordinates and integrates lab staff; assists in grant and manuscript writing; maintains policies and procedures involving human subjects; oversees subject recruitment, testing, and scheduling for ongoing light research studies; and manages government and industry grant support. He is currently in a Ph.D. collaborative program in Biochemical Sciences at the University of Surrey.

Light & Engineering
Vol. 16, No. 1, pp. 5-18, 2008

Svetotekhnika
No. 1, 2008, pp. 6-13

PHOTORECEPTION FOR THE NEUROBEHAVIORAL EFFECTS OF LIGHT IN HUMANS

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1. INTRODUCTION

Four traditional objectives of architectural lighting have been to provide light that: 1) is optimum for visual performance; 2) is visually comfortable; 3) permits aesthetic appreciation of the space; and 4) conserves energy [1-2]. During the past three decades, scientific evidence has led to a growing appreciation that, relatively separate from vision and visual reflexes, light perceived by the eye can be a potent biological, behavioral, and therapeutic stimulus in humans [3-7]. Recently, there has been an upheaval in the understanding of photoreceptive input to the circadian and neuroendocrine systems of humans and other mammalian species. A study on healthy human subjects confirmed that the three-cone system that mediates human photopic vision is not the primary photoreceptor system that transduces light stimuli for acute melatonin suppression [8]. This discovery was rapidly followed by the elucidation of two action spectra in healthy human subjects that identified 446-477 nm as the most potent wavelength region for melatonin suppression [9,10]. Those data suggested that a novel photosensory system, distinct from the visual rods and cones, is primarily responsible for regulating melatonin in humans.

Studies using both animal and human models are beginning to clarify the neuroanatomy and neurophysiology of the photosensory system that provides input for circadian, neuroendocrine, and neurobehavioral regulation. A recently discovered photopigment, named melanopsin, has been localized both in the retinas of rodents and humans [11,12]. More specifically, melanopsin is found in a subtype of intrinsically photoreceptive retinal ganglion cells (ipRGCs) [13-15].

These seminal discoveries and further clarification of the biochemistry, anatomy, and physiology of melanopsin and the ipRGCs have been significant achievements.

The professional communities of lighting manufacturers, lighting designers and architectural engineers have opened the door to understanding this emergent physiology and are considering the development of appropriate applications that might develop out of these discoveries [16-19]. The Commission Internationale de l'Eclairage (CIE) is broadly devoted to the science and art of lighting. In turn, the international lighting community relies on the CIE to provide standards and guidelines for the development of future lighting strategies. More specifically, Division 3 of the CIE is concerned with lighting for building interiors based on visual factors of occupants. Ultimately, lighting based on the classical design objectives will need to accommodate the relatively recent discoveries about the role that light may play in optimizing human health and well being.

2. CIRCADIAN, NEUROENDOCRINE, AND NEUROBEHAVIORAL ACTION SPECTRA

An action spectrum is one of the principal tools for identifying the photopigment that initiates a light-induced response. A photopigment's pattern

of wavelength sensitivity, or its absorbance spectrum, is like a fingerprint - it is unique to that molecule. Photobiologists define an action spectrum as the relative response of an organism to different wavelengths of visible and near-visible electromagnetic radiation. Over the years, a set of approaches for determining action spectra that are applicable to all light responsive organisms has been refined [20,21].

In the photobiological literature, there are two basic types of action spectra: polychromatic and analytic [21]. Generally investigators begin exploring light sensitive biological reactions by determining polychromatic action spectra. Such action spectra are developed by employing broader bandwidth light stimuli that either have half-peak bandwidths greater than 15 - 20 nm or by emphasizing particular wavelengths against backgrounds of "white" artificial or natural light. Polychromatic action spectra are useful for: 1) identifying interactions of biological responses to multiple wavelengths; 2) clarifying how organisms respond to light in more natural settings; and 3) guiding the development of the more sophisticated analytic action spectra. Polychromatic action spectra, however, have limited utility for identifying the specific photopigments that initiate light-sensitive responses [21]. As in other fields of photobiology, the earliest action spectrum studies on neuroendocrine and circadian responses to light utilized polychromatic stimuli. From 1972 through 2004, a set of published polychromatic action spectra developed in both rodents and humans consistently indicated that the spectral region between 450 nm and 550 nm provides the strongest stimulation of circadian and neuroendocrine responses [22, for review].

In 1984, the first circadian analytic action spectrum tested the effects of monochromatic light on wheel-running behavior of hamsters [23]. Soon, other circadian and neuroendocrine researchers began employing monochromatic wavelengths and increasingly sophisticated photobiological techniques for determining analytic action spectra. Since then, fourteen different analytic action spectra examining different circadian, neuroendocrine, and neurobehavioral responses in rodents, monkeys and humans have been published [22, for review]. Concurrent with the remarkable discovery of melanopsin and ipRGCs, eight recent analytical action spectra have demonstrated the wavelength sensitivity of some of the physiological responses mediated by these newly characterized sensory cells. Those action spectra are presented in Table 1.

Clearly, circadian and neuroendocrine researchers have steadily advanced in employing rigorous analytic action spectroscopy techniques for identifying the estimated peak photosensitivity (λ_{max}) for a variety of responses. It is significant that each of the studies in Table 1 indicate a λ_{max} ranging from 459 nm to 483 nm in the short wavelength portion (blue) of the visible spectrum [9,10,14,2428]. That shift to shorter wavelength sensitivity was first demonstrated in 1996 when Yoshimura and Ebihara showed that circadian phase shifting of *rd/rd* mice had a peak response at 480 nm [24]. Given the dif-

Table 1. Each of the above action spectra are based on fluence response curves at 6 to 10 wavelengths. Each λ max is derived from a best fit opsin nomogram. The table is adapted from a review article [43].

Analytical Action Spectra Studies Showing Peak Sensitivity to Blue Light for Circadian, Neuroendocrine, and Neurobehavioral Responses

Peak (λ Max)	Species	Response	Citation
480	Mouse *rd/rd*	Circadian Phase-shifting	[24]
464	Human	Melatonin Suppression	[8,9]
459			[10]
479	Mouse *rd/rd*	Pupillary Light Reflexes	[25]
483	Human	Cone Cell ERG –wave	[26]
483	Rat	Ganglion Cell Depolarization	[14]
481	Mouse *rd/rd cl*	Circadian Phase-shifting	[27]
482	Monkey	Ganglion Cell Depolarization	[28]

ferences in laboratories, animal models, physiological end points and specific investigative techniques, this consistent identification of peak responses across the blue portion of the spectrum is remarkable. It is also notable that the data from each of the action spectra in Table 1 were fit to single opsin nomograms with relatively high coefficients of correlation. Although full analytic action spectra have yet to be developed, a set of studies have confirmed that shorter wavelength monochromatic light is more potent than equal photon densities of longer wavelength light for evoking circadian phase shifts, suppressing melatonin, enhancing subjective and objective correlates of alertness, increasing heart rate, increasing body temperature, and inducing expression of the circadian clock gene *Per2* in humans [29-35]. Together, the full analytic action spectra along with the selected wavelength testing indicate that a novel photoreceptor system is primarily involved in circadian, neuroendocrine, and neurobehavioral responses mediated by the eyes of humans and other mammals.

It is important to note that not all analytic action spectra identify a λmax in the blue part of the spectrum. Analytic action spectra with wild type mice and hamsters showed peaks in the 500 nm to 511 nm range for phase shifting locomotor activity and pupillary constriction [23-25,36]. It may be that the intact rodent retina combines input from ipRGCs and classical visual photoreceptors for circadian phase shifting and pupillary responses. In contrast, when mice do not have functioning visual photoreceptors (such as in the *rd/rd* and *rd/rd cl* models), their retinas appear to shift to the shorter wavelength sensitivity for circadian and pupillary responses [23-25].

Independent of the research done with monochromatic wavelengths, studies have investigated a variety of neurobehavioral changes relative to correlated color temperature (CCT) of broad spectrum, polychromatic, fluorescent lights [37, for review]. In general, higher color temperature lamps emit more energy in the blue part of the visible spectrum than lower color temperature lamps. Lamps with higher CCT were found to evoke a stronger melatonin suppression compared to lamps with lower CCT in healthy humans [38-40]. Additionally, fluorescent lamps with a higher color temperature were observed to have a more potent effect on core body temperature than low color temperature lamps [38,41]. Furthermore, blood pressure and EEG frequency have been shown to increase under high CCT as compared to lower CCT [42,43]. Finally, when examining the effects of illumination prior to sleep, deep sleep was reduced under high CCT compared to low CCT during the first half of sleep [44]. Together, this literature is consistent in demonstrating that higher correlated color temperature lamps induce stronger neurobehavioral effects than lower correlated color temperature lamps in healthy subjects. Those findings are generally consistent with the analytical action spectra shown in Table 1. Several of the contributions to this book further explore the role of correlated color temperature in neurobehavioral responses to light, including the possibility that color temperature may not always be a sufficient predictor of lamp potency for biological and behavioral effects [45-47].

3. THE DISCOVERY OF MELANOPSIN AND A NEW OCULAR SENSORY SYSTEM

Optimization of lighting strategies requires a detailed understanding of the photoreceptive systems that are impacted. The development of modern lighting has been driven largely by a working knowledge of the photopic visual system. The relatively recent discovery of ipRGCs in the mammalian retina indicates that current approaches to lighting have been developed within the context of an incomplete understanding of the photoreceptive capacity of the retina [12,14,15,48].

For many years, a finding incongruous with their understanding of retinal photoreception has perplexed those investigating the photic regulation of circadian rhythms. This finding showed that mutant rodents with retinas nearly devoid of rods and cones, retained the ability to photically reset circadian activity rhythms [49,50]. This was quite surprising, given that behavioral and electrophysiological tests demonstrated that these animals were completely visually blind. Importantly, bilateral surgical removal of the eyes rendered them incapable of resetting their circadian clock, thereby indicating that the photoreceptors responsible for circadian resetting in eye-intact blind mice, must be ocular, but not rods or cones [49]. At the time, rods and cones were the only known ocular photoreceptors, leading to the paradox of photoreception occuring in an eye without photoreceptors. Similar to the findings in rodents, circadian entrainment and melatonin suppression studies in complete-

ly blind humans, partially blind humans and humans with color vision deficiencies suggested that a novel non-rod, non-cone photoreceptor was primarily involved in circadian regulation in humans [51-54].

The discovery of a novel vertebrate photopigment in 1998 initiated a series of studies that eventually led to the identification of a previously unrecognized photoreceptor class in the retina of vertebrates, including humans [11,12]. This photopigment, melanopsin, was initially identified in the pigmented skin cells of the African clawed frog, *Xenopus laevis*. Its expression was also observed in the retina of this frog [11]. Interestingly, the retinal cells expressing melanopsin were not the classical visual photoreceptors (rods and cones), but rather, neurons of the inner retina, cells not previously believed to be inherently light-sensitive. Mammalian homologs of melanopsin were subsequently cloned from mice and humans [12]. The predicted secondary structure of human melanopsin (hOPN4) is shown in Fig. 1.

1. In mammals, melanopsin expression was restricted to a small, widely distributed subpopulation of retinal ganglion cells (RGCs) [15,28,48,55,56]. The number and distribution of these cells was reminiscent of the RGCs known to project to the hypothalamic suprachiasmatic nucleus (SCN), the primary circadian pacemaker driving activity rhythms [57-59]. Follow-up studies have confirmed that the vast majority of SCN-projecting RGCs do indeed express melanopsin [13,55,56]. Taken together, these findings suggested that melanopsin-expressing RGCs may be intrisically photoreceptive, and may account for the circadian photosensitivity observed in blind mice and humans.

To determine whether this new cell class is photosensitive, Berson and colleagues labeled SCN-projecting RGCs by injecting a tracer into the SCN of rat [14]. They found these retrogradely labeled retinal ganglion cells to be intrinsically photosensitive, subsequently naming them ipRGCs. As shown in Table 1, the spectral sensitivity of rat ipRGCs peaks in the blue wavelengths (λmax = 483 nm). As expected, this sensitivity is consistent with that of melanopsin, which has been shown to be the necessary molecular entity responsible for conferring photosensitivity upon ipRGCs [60].

To establish the function of ipRGCs, several teams independently generated lines of melanopsin "knock-out" mice that lack functional copies of the melanopsin gene [15, 61,62]. These knock-out mice exhibited a deficiency in their ability to photically reset circadian locomotor rhythms [61,62]. Perhaps more interesting was the unexpected observation that these mice did photoregulate the circadian axis, albeit at a reduced sensitivity. This finding led several labs to cross melanopsin-null mice with visually blind mice [27,63]. The resulting offspring that lacked functional rods, cones and ipRGCs were "visually" and "circadianly" blind, behaving as though both eyes had been surgically removed. In addition to the inability to photoentrain circadian rhythms, these offspring were unable to demonstrate any light-induced suppression of the melatonin biosynthetic pathway, any light-dependent inhibition of nighttime locomotor activity, and any pupillary light reflex [27,63]. Taken together, these studies were critical in establishing that rods, cones, and ipRGCs all play a role in circadian photoentrainment and these other forms of non-visual photophysiology.

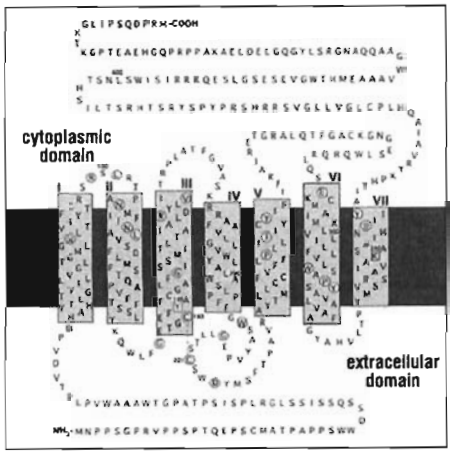

Fig. 1. This illustrates the predicted secondary structure of human melanopsin (hOPN4). The transmembrane domains have been predicted based upon homology with bovine rhodopsin. The crystal structure of bovine rhodopsin has been resolved to 2.8 angstroms [132]. Residues highly conserved among type 2 rhodopsins are indicated in green circles. The predicted site of chromophore linkage is indicated with a red square. Shown with a yellow square is the tyrosine residue occupying the site corresponding to glutamate-113 of bovine rhodopsin. A putative disulfude bridge is indicated as a red dashed line

Generally, the sensory membranes of invertebrate photoreceptors are composed of microvilli organized in an elongated structure called the rhabdomere [64,65]. This is in contrast to the sensory membranes of vertebrate photoreceptors which are modified, nonmotile cilia [66, for review]. Perhaps the most intriguing aspect of melanopsin is its greater resemblance at the molecular level to the opsins of rhabdomeric photoreceptors typical of invertebrates rather than the ciliary photoreceptors common to the vertebrates [11,67]. Melanopsin appears to share a more recent common ancestor with rhabdomeric opsins as compared to ciliary opsins, suggesting that the melanopsin-based non-visual photoreceptive system is "primitive". The rhabdomeric character of melanopsin also predicts that the transduction pathway activated by this photopigment should be rhabdomeric in nature. Several studies have confirmed this [68-70].

Opsins require a photolabile vitamin A-derived chromophore to be functional [66, for review]. In the vertebrate visual photoreceptors, opsins must be regenerated after photobleaching. Regeneration involves the active transport of the "spent" chromophore to the retinal pigment epithelium, a tissue juxtaposed to the rods and cones, and subsequent return of the "recharged" chromophore to the photoreceptors. By contrast, the opsins of the rhabdomeric photoreceptors of invertebrates can be photoregenerated *in situ* by a wavelength of light distinct from the wavelength that initiates transduction. Again, the rhabdomeric nature of melanopsin suggests that it may employ a photopigment regeneration scheme like that of the invertebrates. A study has suggested this [71]. This will be of significance to lighting designers, because knowledge of the peak spectral sensitivity of melanopsin may be insufficient to produce optimal light sources. Understanding the photodynamics of chromophore regeneration in ipRGCs will also be necessary to achieve maximum optimization of lighting.

In primates, melanopsin-containing RGCs may play a role in vision [28]. Melanopsin is expressed in "giant" RGCs which project to the visual relay center in the thalamus of the brain. The dendritic arbor diameters of these cells approach 1 mm and are the largest of the identified primate RGC classes. Only 3000 giant cells exist in the primate retina, representing 0.2% of all RGCs. As shown in Table 1, these cells are intrinsically photoreceptive, displaying a peak spectral sensitivity in the blue wavelengths (482 nm). Giant RGCs also are activated by rods and cones. Although much less sensitive than rods and cones, the intrinsic photosensitivity of giant RGCs is highly correlated with the intensity of the stimulus, thereby indicating precise irradiance coding. At irradiances subthreshold to the intrinsic sensitivity, giant cells receive irradiance-dependent information from rods and cones. Therefore, giant cells are capable of integrating and transmitting irradiance information across the entire dynamic range (scotopic, mesopic, and photopic) of the visual system. The morphology of melanopsin-containing RGCs is consistent with their function as irradiance detectors [48]. As illustrated in Fig. 2, the expansive, photosensitive arbors indicate a wide photon capture radius inappropriate for the formation of images, but seemingly optimal for broad spatial integration of environmental light. Furthermore, the sluggish electrophysiological dynamics of these cells ensures broad temporal integration as well, consistent with a function of irradiance detection [14].

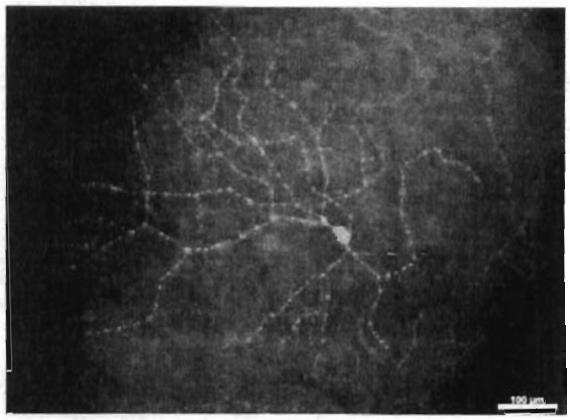

Fig. 2. An ipRGC immunolabeled with an anti-melanopsin antiserum in a flat-mounted human retina. Note the localization of melanopsin in the cell body and throughout the dendritic arbor rendering the entire cell photosensitive. Also note the characteristic varicosities decorating the dendrites. (Photo credit: A.M. Castrucci)

The relative contributions of rods, cones, and ipRGCs to the various non-visual responses to light remains to be determined. The nature of knock-out mouse models precludes such an assessment; the elimination of a critical signaling component early in development may result in developmental compensation that obscures the true contribution of the protein in question. Future studies using conditional knock-out schemes, where rods, cones, or ipRGCs can be disabled in the adult, will provide a better

insight into their roles in physiological responses to light. Fig. 3 provides a simplified summary of the ocular and neural anatomy that support vision and circadian, neuroendocrine and neurobehavioral responses.

4. FROM BASIC SCIENCE TO APPLICATIONS OF LIGHT THERAPY

Following the discovery that bright white light exposure at 2,500 lux induced a suppression of melatonin released from the pineal glands of healthy humans, researchers quickly determined that light could be used therapeutically to treat Seasonal Affective Disorder (SAD or winter depression) and to phase-shift human circadian rhythms [6,7,73-77]. Since then, light therapy has proven to be an effective therapeutic intervention for SAD patients and its subclinical variant, sSAD [78-80]. A variety of light treatment devices have been tested for treating these affective disorders, including light boxes, dawn simulators, and head mounted delivery systems (i.e. light visors). Although there is not a current consensus about the etiology and pathophysiology of SAD, a number of investigators postulate that there is a circadian component related to this disorder. The current standard practice is for patients to try a trial of 10,000 lux white fluorescent light for 30-60 minutes in the morning upon awakening [78-80]. As with many medical disorders, patients vary in their responsiveness to light therapy. Although a majority of clinical trials employing light therapy have been concerned with the treatment of SAD, additional clinical applications have been explored. These include light treatment of non-seasonal depression, various sleep disorders, menstrual cycle related problems, bulimia nervosa, and problems associated with senile dementia [6,7,81,87]. In addition, the utility of light therapy for resolving circadian disruption associated with intercontinental jet travel and shift work has been studied [5-7,88,90]. A chapter in this volume addresses recent studies and perspectives on the utility of light treatment for resolving shift work problems [91].

Over the past 15 years, light has been tested as a countermeasure for disruption of circadian rhythms and sleep-wake patterns in astronauts during space flight. Disturbed circadian rhythms and altered sleep-wake patterns are major risk factors for the health and safety of astronauts [92]. Associated behavioral changes include decreased alertness, diminished concentration, and performance decrements, all of which can compromise the safety of personnel and the objectives of space missions. Studies of astronauts have shown light treatment to be an effective tool for supporting circadian entrainment [93-97]. Ground-based studies continue to investigate the optimization of light as a countermeasure for circadian and sleep disruption in space flight missions [98,99]. The aerospace community is evaluating how lighting can be engineered properly for supporting vision, circadian regulation, and alertness of astronauts in advanced human environments, such as the International Space Station and the planned lunar habitat. Such work is likely to be relevant to general architectural lighting design on earth for civilians with specific clinical disorders as well as problems associated with shift work and jet lag.

How does the seminal discovery of a novel photosensory system in the human eye with a high sensitivity to blue light intersect with the further development of therapeutic and architectural lighting ap-

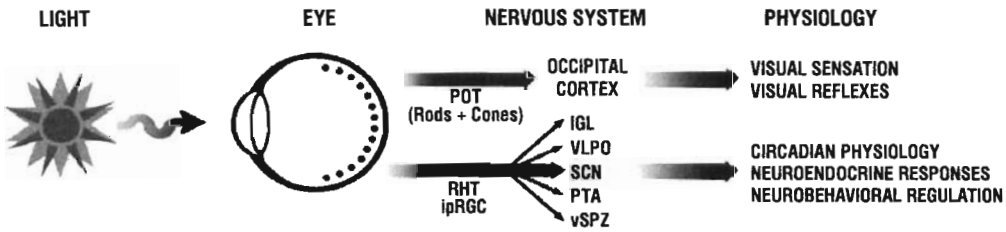

Fig. 3. The diagram above provides a simplified schematic of the neuroanatomy responsible for mediating both the sensory capacity of the visual system and the non-visual regulation of circadian, neuroendocrine and neurobehavioral functions. Abbreviations: POT - primary optic tract; RHT -retinohypothalamic tract; ipRGC - intrinsically photosensitive retinal ganglion cell; IGL - intergeniculate leaflets; VLPO -ventrolateral preoptic nuclei; SCN - suprachiasmatic nuclei; PTA -pretectal areas; vSPZ -ventral subparaventricular zones. This figure was modified from an earlier publication [72]

plications? One recent thrust has been to test shorter wavelength (blue) light treatment for improved efficacy to evoke circadian phase shifts and enhance acute alertness in healthy individuals [29-34]. Some of those data are reviewed more extensively in this volume [100]. Similarly, a Phase I clinical study tested prototype light panels with arrays of light emitting diodes (LEDs) for clinical efficacy in treating SAD [101]. In that study, the light therapy panels measured 31 x 58 cm and emitted either narrow-band blue light (468 nm, at 607 $\mu W/cm^2$ or about 400 lux) or dimmer narrow-band red light panels (an intended placebo light of 652 nm, at 34 $\mu W/cm^2$ or about 25 lux). Study results showed that symptom improvement was significantly better ($p<0.02$) in the group treated with the blue 468 nm light compared those treated with 652 nm light. Furthermore, the remission rates of the patients treated with the blue LED panel (55% remission) were comparable to the remission rates typically reported in patients utilizing current standard bright light treatment [101]. Although these data show that narrow band blue LED panels have promise as an effective treatment for SAD, larger scale studies are needed with other comparison conditions such as narrow bandwidth blue, green, and red lights at an equal photon density compared to broad spectrum white light. It is important to note that portable blue LED panels (much smaller than the panels described above) are commercially available, but have not yet been tested in a formal clinical trial. Together, these recent studies on phase-shifting, alertness, and SAD therapy suggest that short wavelength light may be more potent than broad spectrum white light, which, to date, is the standard tool of light treatment. More work must be done, however, before there is any certainty about the optimum blend of wavelengths for these types of applications. Furthermore, as new lighting devices are developed, caution must be exercised in not only assuring the efficacy, but also the safety of such technologies.

5. LIGHT EXPOSURE SAFETY AND MEASUREMENT

Inappropriate exposures to light can damage the human eye. Indeed, ultraviolet radiation, blue light, green light, white light, and infrared radiation all have the capacity to damage ocular tissues when exposures exceed the appropriate limits [102-105]. Fortunately, there are national and international guidelines for determining safe exposures to both broad spectrum and narrow bandwidth light [106–109]. The Blue Light Hazard Function is relevant to the light exposures used for specifically stimulating the melanopsin/ipRGC sensory system. This function relates to photochemically induced retinal injury resulting from optical radiation exposure at wavelengths primarily between 400 nm and 500 nm. The action spectrum for this adverse effect has a peak activity in the violet/indigo part of the spectrum (435-440 nm wavelength range) with short and long wavelength limbs that drop rapidly with lesser and greater wavelengths , respectively [106–109]. Among the human studies reported here that employed monochromatic or narrow bandwidth blue light, most, if not all had an independent hazard analyses of light exposures according to the published guidelines for photobiological safety [8,9,29,33,101 for examples]. In considering new experiments and applications with blue enriched light, it is prudent that ocular safety be assured. Another chapter in this volume discusses this safety concern further [110].

In addition to potential problems of direct phototoxic effects, exposure to light at night has been proposed as a possible cancer risk factor [111,112]. This theory is based, in part, on the well-established suppressive effects of nocturnal light on circulating melatonin in humans [113,114]. It has been demonstrated that industrialized nations that have an abundance of indoor and outdoor night lighting also have disproportionately high prevalence of breast cancer. It is suggested that nocturnal light exposure decreases melatonin and ultimately increases risk of breast cancer [111,112]. Epidemiological studies support this hypothesis with observations of decreased breast cancer in blind women and increased breast and colon cancer in women who do shift-work [115-121]. A range of human, animal, and *in vitro* studies also indicate an apparent relationship between light, melatonin, and cancer, although the dynamic is still not fully understood [124-128]. Although it is premature to make definitive conclusions regarding the possibility that nighttime light exposure is a risk factor for cancer in humans, it may become necessary to adjust standards for nighttime lighting as the relationships between light, melatonin regulation, circadian disruption and tumor development are clarified. Further discussion of this topic can be found in this volume [129].

The discovery of the melanopsin containing ipRGCs along with the new action spectra for cir-

cadian photoreception, make it very clear that a new system for measuring light needs to be developed. Early human studies on light-induced melatonin suppression, light treatment of winter depression, and light-induced circadian phase shifting, employed photopic measurements of light (lx) based on the responsiveness of the human visual system to quantify light. Although using that measurement system was serviceable, it implied that these responses are mediated by the three-cone photopic visual system. At least in terms of human melatonin suppression, phase-shifting and acute alerting responses, this is not true [8-10,29-34]. Based on those recent studies, it is likely to be shown that photopic measurements are inappropriate for optimally characterizing light for all responses principally mediated by the human retinohypothalamic tract. In the end, a new metric for quantifying light for circadian, neuroendocrine, and neurobehavioral regulation needs to be determined. Preliminary work, some of which is presented in this volume, is beginning to address this issue [130,131]. Ultimately, such a metric must be based on a collective understanding of the photoreceptive physiology of the retinohypothalamic tract and its specific spectral sensitivity. Development of this metric will require international collaboration across the circadian and visual science communities, perhaps under the leadership of the CIE. Until that is achieved, light employed in circadian and neuroendocrine studies or applications should be quantified in terms of irradiance or photon densities with a clear determination of the light source spectral power distribution.

6. CONCLUSION

Exploring the physics of light and the physiology of vision has been a passion for philosophers and scientists for at least two millennia [133]. In sharp contrast, the empirical study of the circadian, neurobehavioral, and therapeutic effects of light is relatively recent - spanning only a few decades. Despite its relative youth, this field of study is critically important in understanding how to optimize lighting in places where people live and work. The discovery and characterization of a new photosensory system in the human eye opens the door to significant challenges and innovation in the field of architectural lighting. These advancements create opportunities for pioneering new lighting technologies and design strategies that optimize illumination for vision, well being, and health.

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ACKNOWLEDGMENTS

The authors gratefully acknowledge the dedicated support of John Hanifin (referencing, editorial review and final formatting), Benjamin Warfield (development of Figure 3 and final formatting), Ana Maria Castrucci (contributing the photomicrograph in Figure 2), and Melissa Thiessen, Kathleen West and Mary James (editorial comments). With permission from the CIE, portions of this manuscript were adapted and updated from an earlier report [72]. The work was supported, in part, by grants from NIH RO1NS36590, NSBRI under NASA Cooperative Agreement NCC 9-58, NIMH1R43 MH066453-01, NCI 1RO1CA85408-01A2, NIEHS R21ES11659 and the Philadelphia Section of the Illuminating Engineering Society to GCB, and NIH RO1NS 052112 to IP.

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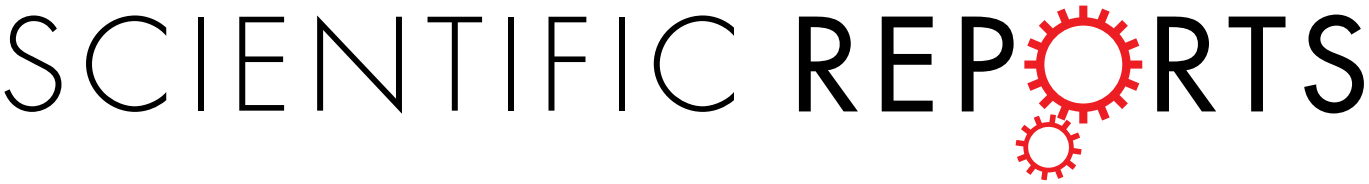

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The spectral and spatial distribution of light pollution in the waters of the northern Gulf of Aqaba (Eilat)

Received: 13 June 2016
Accepted: 10 January 2017
Published: 10 February 2017

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The urbanization of the shores of the Gulf of Aqaba has exposed the marine environment there, including unique fringing coral reefs, to strong anthropogenic light sources. Here we present the first *in situ* measurements of artificial nighttime light under water in such an ecosystem, with irradiance measured in 12 wavelength bands, at 19 measurement stations spread over 44 square km, and at 30 depths down to 30-m depth. At 1-m depth, we find downwelling irradiance values that vary from 4.6×10^{-4} μW cm^{-2} nm^{-1} 500 m from the city to 1×10^{-6} μW cm^{-2} nm^{-1} in the center of the gulf (9.5 km from the city) in the yellow channel (589-nm wavelength) and from 1.3×10^{-4} μW cm^{-2} nm^{-1} to 4.3×10^{-5} μW cm^{-2} nm^{-1} in the blue channel (443-nm wavelength). Down to 10-m depth, we find downwelling irradiance values that vary from 1×10^{-6} μW cm^{-2} nm^{-1} to 4.6×10^{-4} μW cm^{-2} nm^{-1} in the yellow channel and from 2.6×10^{-5} μW cm^{-2} nm^{-1} to 1.3×10^{-4} μW cm^{-2} nm^{-1} in the blue channel, and we even detected a signal at 30-m depth. This irradiance could influence such biological processes as the tuning of circadian clocks, the synchronization of coral spawning, recruitment and competition, vertical migration of demersal plankton, feeding patterns, and prey/predator visual interactions.

One of the most dramatic changes stemming from the growth in human population and the availability of electricity is the global spread of nighttime illumination[1]. The potential damages of this "light pollution" or "ecological light pollution" phenomenon to ecological systems such as the marine environment are indicated in the very term light pollution[2,3]. Due to the increase in human population, coastal habitats adjacent to populated areas have become particularly vulnerable to light pollution[4–6].

The main sources of anthropogenic light pollution are direct artificial light and sky glow. Sky glow is caused by the scattering of artificial light by the atmosphere and is strongly enhanced by dust, particulate pollution, and reflection by clouds. A prominent component of sky glow is the emission line at a wavelength of 589 nm[7], mainly from low pressure sodium vapor lighting, which became widespread in the 1960s and 1970s[5]. In addition to sodium vapor lighting, other types of light sources, such as mercury vapor, metal halide, fluorescence, and recently LED based systems, are also in common use (Fig. 1). These sources differ with respect to the spectral distribution of their light emission and consequently with respect to the biological systems they may affect[5,7,8]. In recent decades, the spectral diversity of artificial light sources has grown, and the trend towards adopting lighting technologies with a broader spectrum of 'white' light is likely to increase the potential for ecological impact[5,9]. Lighted buildings and towers, streetlights, security lights, boats, flares on off-shore oil platforms, and even lights on undersea research vessels, can all disrupt the ecosystem to varying degrees[2]. The most noticeable effects occur in areas where such lights are close to natural habitats, but even remote areas are exposed to increasing illumination from sky glow, whose impacts are just beginning to be quantified[2,9].

The spread of electric lighting has caused a major perturbation to natural nocturnal light fields and regimes, disrupting the natural cycle of light and darkness, and as a consequence has added a novel environmental stressor, affecting biochemical, physiological, and behavioral patterns that are synchronized with natural diel light/dark field properties. These include, for example, the synchronization of biological clocks[5,10,11] and reproductive timing[2,12–14]. The ability of artificial light sources to perturb biochemical, physiological, and

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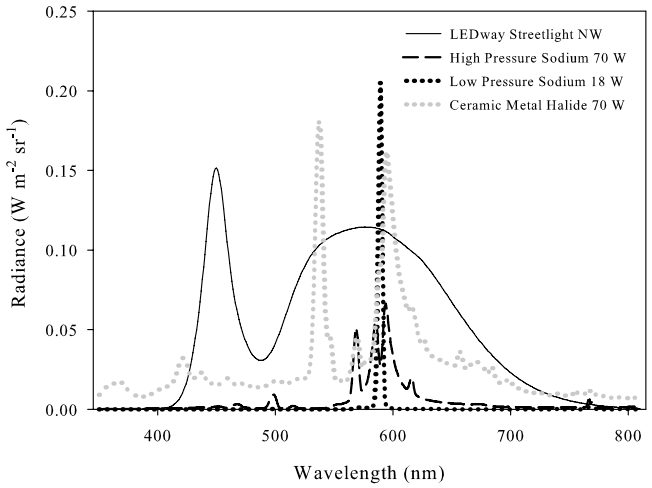

Figure 1. Spectra of different artificial light sources in use: LEDway - white LED (solid black line), high pressure sodium (dashed black line), low pressure sodium (black dotted line), and ceramic metal halide (gray dotted line). The spectra were obtained from http://ngdc.noaa.gov/eog/night_sat/spectra.html.

behavioral patterns is thought to be related to the overlap between the emission spectra of artificial light sources and the absorption spectra of light sensing cryptocromes. (Compare Fig. 1 to http://www.ledgrowlightshq.co.uk/chlorophyll-plant-pigments/). For example, such pigments have been shown to be involved in temporal synchronization processes in corals[10]. It has been suggested that the effects of light pollution on the reproductive physiology, migration, and foraging of marine species could possibly lead to changes in biodiversity[15] and in the composition of epifaunal communities[8]. Though some ecologists previously acknowledged the potential of artificial nighttime light to disrupt ecological systems in general[2] and coastal and marine environments in particular[16–19], the phenomenon has only recently become widely recognized as an environmental issue[20], and *in situ* measurements of light pollution and its biological and ecological consequences are lacking.

The natural cycle of light and darkness in the marine environment includes the wax and wane of moonlight, as well as the diel and seasonal patterns of sunlight. The subtle spectral changes in sunlight that take place prior to sunset have recently attracted particular interest as a result of their role in determining the hour of coral spawning[21]. Moonlight is of particular importance, since some marine animals display behavior patterns that are correlated with the synodic monthly phases of the moon[22]. Marine zooplankton have been shown to utilize moonlight for navigation[19,23], for migration[3], and as a trigger for biological process such as reproduction[11,21,24], predator-prey visual interaction[25], and photosynthesis[26]. Therefore, any perturbation of the natural illumination patterns to which aquatic organisms have adapted in the course of evolution can disrupt their fine-tuned life cycles, behavioral patterns, and physiological mechanisms[2,10,27]. Anthropogenic light sources constitute a particularly significant perturbation to nighttime underwater illumination, since they operate primarily at night (rather than during the day), and since their light intensity is comparable to that of moonlight (as opposed to that of sunlight).

Particularly vulnerable are light sensitive processes and behavioral patterns of the gulf's marine organisms, such as the lunar timing of coral spawning, as described by Atoda[28] and as confirmed in several subsequent studies[29–33], the diel expansion and contraction of tentacles[32], the diel vertical migration of zooplankton[34], and the feeding of diurnal corallivorous fishes[35]. Anthropogenic disturbances of the natural light patterns to which organisms have evolved to be attuned to may accelerate the decline of coral reefs that are already stressed by ocean warming, acidification, and eutrophication[36–38].

The contribution of corals to the primary structural composition of the reef and to the ecology of the reef via their providing an environment for breeding and protection of various organisms, along with the economic value of the corals, has been investigated over the course of a few decades[39,40]. However, the extent and potential impacts of light pollution on corals have not been investigated. Functional processes that are affected by environmental light conditions, such as the spawning phase of coral reproduction[10,41], may be disturbed as a result of changes in the levels of light reaching the seabed, which in turn may lead to a lack of synchronization in reproductive processes. In addition, changes in the intensity and spectral quality of artificial light may affect planulae settlement and recruitment patterns of corals in the vertical zonation region of the seabed[16,42], as well as the distribution of coral colony morphology over the area of the reef[43].

Given that corals are highly photosensitive, with a photoreception sensitivity threshold of blue light of $\sim 1.2 \times 10^{15}$ photons $m^{-2} s^{-1}$ [24], and given previous studies showing that reef structure can be strongly influenced by illumination[44], there is a definite potential for artificial nighttime lighting to have harmful effects on reef functions and reef health[45].

Clearly, an understanding of the impact of anthropogenic light sources is crucial for the very survival, sustainable use, management, protection, and bioremediation of important tropical ecosystems, such as coral reefs. As a primary step in this direction, the light field of these sources needs to be mapped in space and time. Previous efforts in this direction have included modeling[46], remote sensing[6,47], and mapping with geographic information systems (GIS)[48]. However, to the best of our knowledge, the full intensity and spectral composition of nighttime

light over the surface of the water and its bathymetric distribution in the water column in a coastal ecosystem have not been previously mapped. The spectral composition of the light is especially important, since different organisms sense light differently, including some organisms that have the ability to sense wavelengths outside of the visible spectrum[2,17].

Here we report for the first time the spatial and spectral distribution of nighttime light in the waters of the Gulf of Aqaba, a complex shoreline containing sectors of industry, commerce, and tourism, and surrounding one of the northernmost flourishing coral reefs on Earth which is protected and managed by the National Parks Authority of Israel.

The study area

The Gulf of Aqaba (Eilat) is an arm of the Red Sea, surrounded by two cities, Eilat, Israel (34°95′/29°55′), and Aqaba, Jordan (35°00′/29°50′), each with a population of tens of thousands of residents (~60,000 and ~160,000, respectively). In addition, these cities contain industrial complexes along the shores and commercial and military ports, as well as recreational marinas and a thriving tourist industry. As the northern reef destination closest to Europe, the coral reef is the main tourist attraction, with an extremely high number of divers per unit area of reef[49].

The Gulf of Aqaba is located in a (semi-arid) desert area with strong solar insolation, clear skies throughout most of the year (only ~30 cloudy days yr^{-1}, less than 30 mm rain yr^{-1}; http://www.iui-eilat.ac.il/Research/NMPMeteoData.aspx), very minimal river runoff, low water turbidity, low re-suspension of sediments[50,51], low nutrient concentration[52], and low plankton biomass[50,52]. These natural conditions allow natural light, as well as different forms of artificial light, to reach and penetrate the water body to considerable depths, with 1% of the subsurface irradiance reaching depths exceeding 110 m[53]. Correspondingly, the vertical attenuation coefficient for underwater downwelling irradiance of photosynthetically active radiation (K_d PAR) is low, ranging between 0.04 and 0.065 m^{-1} [50,54,55]. As such, the water in the Gulf of Aqaba may be categorized as open ocean, oligotrophic, case I waters[50,56]. We also note that the nature of the clear sky in this gulf area may reduce the extent of sky glow[9], though scattering of artificial light by the atmosphere will still occur to some extent.

Due to the uniquely steep shoreline, the fringing reefs in the gulf skirt the shoreline at the unusually close range of a few meters[57]. Thus, they are particularly exposed to the impact of artificial light sources from the densely populated surrounding urban conglomerations. This is in addition to the combination of tourism, pollution, intensive diving, and shoreline modification, all of which have contributed to the degradation of the gulf's reefs and the marine ecosystems that are supported by the reefs, as has been observed over the past few decades[57,58].

Materials and Methods

The underwater downwelling irradiance (*Ed*) in the Gulf of Aqaba was measured on the night of September 9th, 2014 at 23:00 local time and on the night of August 12th, 2015 at 22:00 local time (GMT + 3.0), using a SeaWiFS-compliant, high resolution, profiling reflectance radiometer (PRR-800; Biospherical Instruments Inc., San Diego) with 19 spectral channels in the 300–900-nm wavelength range. Irradiance in each of the 19 channels, as well as the total irradiance of photosynthetically active radiation (PAR), was measured. The PRR-800 was deployed at nighttime on moonless nights, from a boat, using the free fall technique[59] in order to avoid shade or reflectance from the boat and in order to keep the light sensor in a vertical posture.

We chose the PRR-800 and its downwelling irradiance mode, because of the ease of deployment, relatively rapid measurement rate for measurements in series at different depths, stability, and compatibility, as well as its highly sensitive sensor. We note that while downwelling irradiance might be the most appropriate variable for estimating the effect of light pollution on corals that live on the sea bed, it is not the most comprehensive measurement for estimating the effect of light pollution on species that detect light incident from all angles (e.g., zooplankton). Nevertheless, since our emphasis in conducting these first measurements of their kind is in evaluating the penetration depth of the light, the downwelling irradiance mode is the most useful for this purpose. Furthermore, since downwelling irradiance is an integral quantity, it is more likely to exhibit stable numbers above the measurement threshold (see more on the measurement threshold in this section) than radiance measurements would.

Measurements taken with a value of pitch or roll greater than 10 degrees were removed from the data analysis, in a similar fashion to Wang and Zhao[60]. The instrument was lowered with a velocity of ~0.7 m s^{-1}, and irradiance was recorded with a sampling frequency of 5 Hz. Sampling points were distributed throughout the Israeli part of the gulf (Fig. 2). The spatial data were analyzed and presented using the ArcGIS Version. 10.2.1 (Esri Inc.) platform. Spatial interpolation of the data in the horizontal direction was conducted using the standard inverse distance weighting (IDW) method[61] within the GIS program. We note that the specifications of the PRR-800 are such that noise equivalent irradiance is defined to be 1×10^{-6} μW cm^{-2} nm^{-1} or ~1×10^{-6} μW cm^{-2} nm^{-1} in a given wavelength channel. This irradiance measurement threshold limited our ability to measure accurate values at greater depths than we present here. Likewise, we found that even at the more highly illuminated stations, for longer wavelength light, we reached the measurement threshold within 1–2 meters below the water surface. Therefore, the red part of the spectrum is not analyzed in the current study despite its potential biological significance. Note that to the best of our knowledge, conducting measurements of light with such a low irradiance remains a technological challenge. We are unaware of any published study in which light in the red part of the spectrum with such low values of irradiance has been successfully recorded.

Results and Discussion

The downwelling irradiance (*Ed*) measurements in the Gulf of Aqaba are shown in Figs 3–5. In Fig. 3, the horizontal variation in downwelling irradiance is shown at three depths in the water column (1 m, 5 m, and 10 m,

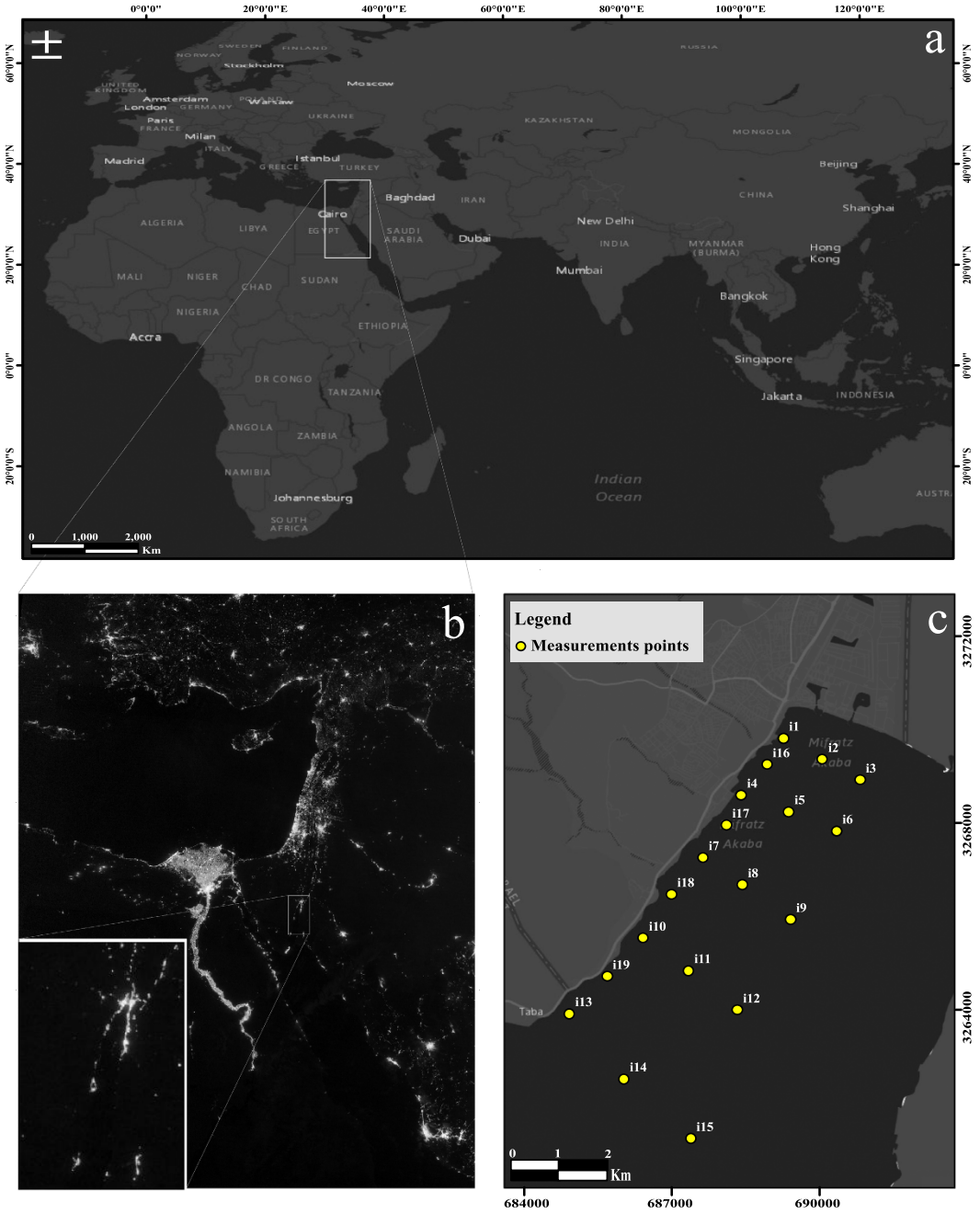

Figure 2. (**a**) World map. (**b**) Night-lights satellite photo of the Middle East and the Gulf of Aqaba close up (Credit: NASA Earth Observatory/Suomi NPP) (**c**) The study area. (**a** and **c** maps were created by using ArcGIS Version. 10.2.1 (Esri Inc.) platform. Sources: Esri, DeLorme, HERE, USGS, Intermap, iPC, NRCAN, Esri Japan, METI, Esri China (Hong Kong), Esri (Thailand), MapmyIndia, TomTom. Esri, DeLorme, HERE, MapmyIndia).

respectively) and in two wavelength channels [589 nm (yellow light) and 443 nm (blue light), respectively]. In Fig. 4, a vertical cross sectional map (depth versus distance from the shore) of downwelling irradiance in the same two wavelength channels is shown, encompassing measurements from stations i1, i5, i8, i12, and i15 (refer to Fig. 2 for station locations). From Figs 3 and 4, one can see that artificial light from the city of Eilat was detected from the nearest adjacent waters (e.g., station i1 in Fig. 2; 500 m from the city) out to distant points in the center of the gulf (e.g., station i15 in Fig. 2; 9.5 km from the city). In addition to light from the city of Eilat, Eilat's main port, located less than 300 m from station i4 in Fig. 2, the oil jetty terminal's offshore pier, which is also located close to station i4, and light sources from the city of Aqaba also contribute to the field of unnatural light in the gulf.

From Fig. 3 and 4, there is a clear horizontal gradient of irradiance, with horizontal differences of more than 1.5 orders of magnitude in the yellow channel and 0.8 orders of magnitude in the blue channel down to 10-m depth. For example, at station i4 at a depth of 1 m under the water's surface, the measured irradiance in the 589-nm wavelength channel is 4.6×10^{-4} μW cm^{-2} nm^{-1} (the maximum value that was measured), while at the

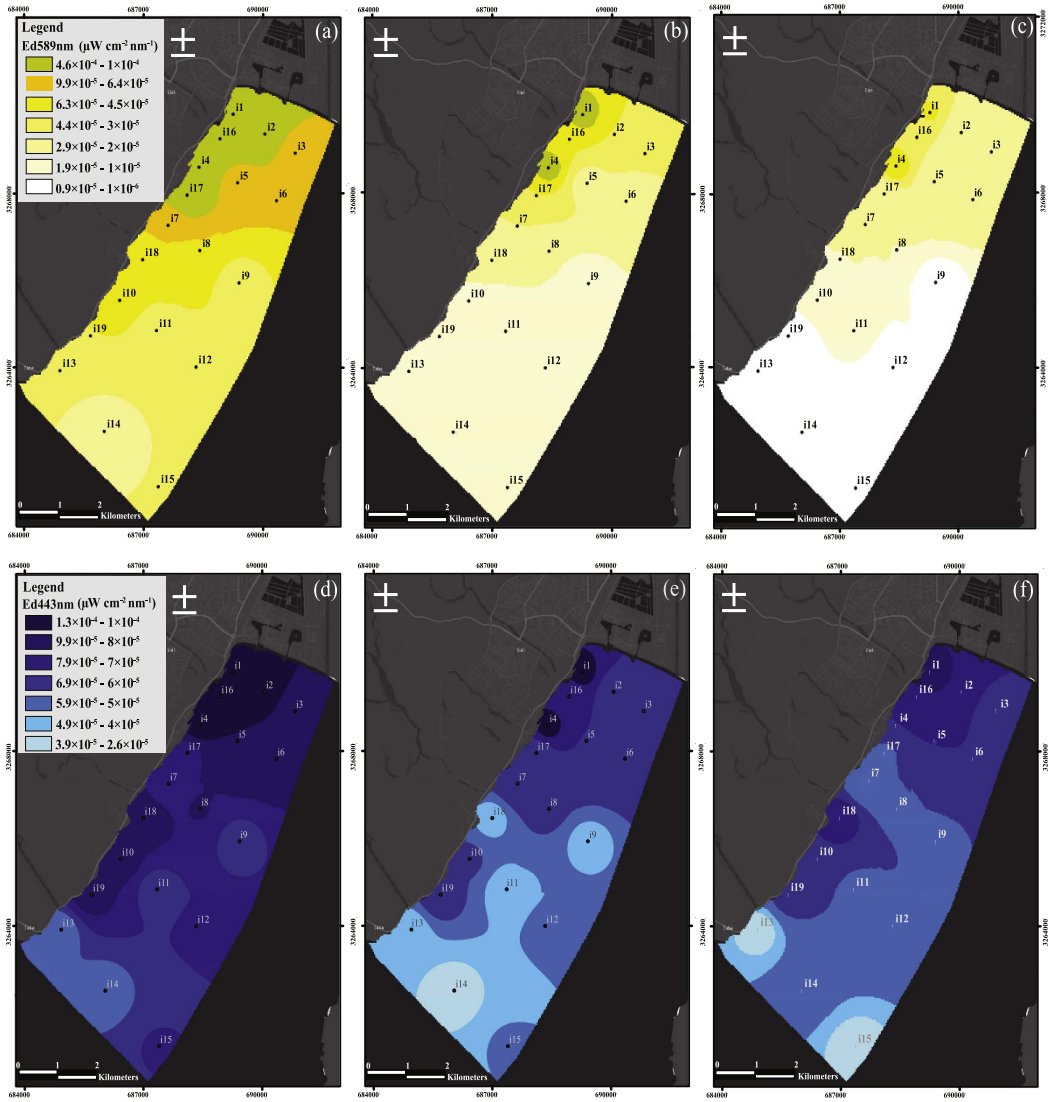

Figure 3. GIS maps of downwelling irradiance, *Ed*, sampled in the Gulf of Aqaba at 1-m, 5-m, and 10-m depth in the wavelength channels of yellow light (589 nm; (**a**–**c**), respectively) and blue light (443 nm; (**d**–**f**), respectively), on the night of August 12th, 2015, at 22:00 local time (GMT + 3). Black/white dots represent sampling locations. The irradiance of yellow light ranged between 1×10^{-6} (bright yellow) and 4.6×10^{-4} (bright green) $\mu W\ cm^{-2}\ nm^{-1}$. The irradiance of blue light ranged between 2.6×10^{-5} (bright blue) and 1.3×10^{-4} (dark blue) $\mu W\ cm^{-2}\ nm^{-1}$. (**a**–**f**) maps were created by using ArcGIS Version. 10.2.1 (Esri Inc.) platform. Sources: Esri, DeLorme, HERE, USGS, Intermap, iPC, NRCAN, Esri Japan, METI, Esri China (Hong Kong), Esri (Thailand), MapmyIndia, TomTom. Esri, DeLorme, HERE, MapmyIndia).

most remote station (station i15; 6.3 km from station i1), at the same depth of 1 m, the measured irradiance in the 589-nm wavelength channel is at the measurement threshold of $1 \times 10^{-6}\ \mu W\ cm^{-2}\ nm^{-1}$. However, due to the multiple light sources contributing to the irradiance at each station, the horizontal gradient is not as steep as would be expected from a one over distance squared dependence from a single localized light source. On the contrary, the irradiance measured at the more remote stations is higher than would be expected from such as simple dependence on distance, thus underscoring the fact that the light pollution is still a significant factor at those relatively large distances. This fact is even more evident from the measured irradiance in the 443-nm wavelength channel, in which the values measured at stations i10 and i19 at a depth of 1 m under the water's surface ($8 \times 10^{-5}\ \mu W\ cm^{-2}\ nm^{-1}$ and $7.6 \times 10^{-5}\ \mu W\ cm^{-2}\ nm^{-1}$, respectively) are almost as high as the value measured at station i1 at the same depth ($1.3 \times 10^{-4}\ \mu W\ cm^{-2}\ nm^{-1}$). In addition to the superposition of multiple light sources, sky glow caused by scattering of the light in the atmosphere, as mentioned in the Introduction, can also distribute light from the coastal light sources out to the middle of the gulf.

In Fig. 5, a vertical profile of downwelling irradiance at station i4 in three wavelength channels [520 nm (green light), 589 nm (yellow light), and 443 nm (blue light)] is shown. From Fig. 5, one can see that the intensity of the lights of the city of Eilat and its industrial sections, especially in the yellow and blue parts of the emitted light spectrum, is high enough for the light to penetrate beyond the first few meters of the water column. A weak signal

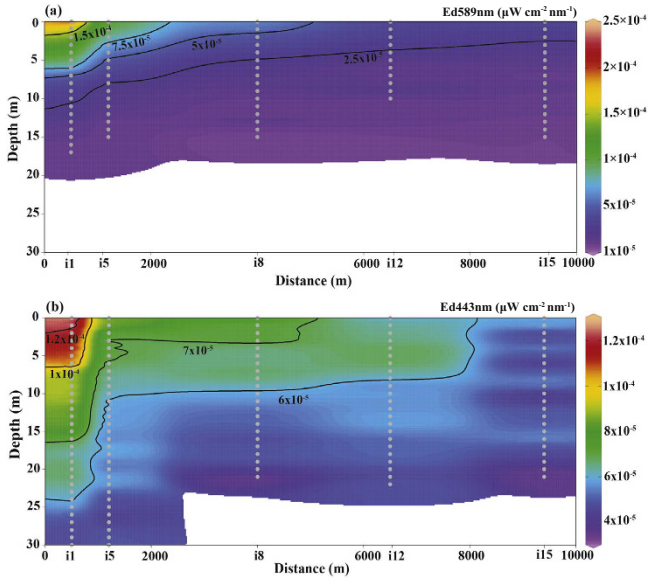

Figure 4. Vertical cross sectional map (depth versus horizontal distance) of downwelling irradiance (*Ed*) in the wavelength channels of (**a**) yellow (589-nm) and (**b**) blue (443-nm) light, sampled on the night of August 12th, 2015 at 22:00 local time, in the Gulf of Aqaba water column. The map encompasses measurements at stations i1, i5, i8, i12, and i15 (refer to Fig. 2 for station locations). The x-axis represents the distance from the city of Eilat. The uncertainty in the values of irradiance is $\pm 1 \times 10^{-6}$ μW cm^{-2} nm^{-1}. From the surface down to 30 m (the lowest depth at which the instrument was deployed), *Ed* ranged from 2.5×10^{-4} to 1×10^{-6} μW cm^{-2} nm^{-1} in the 589-nm (yellow) channel and from 1.2×10^{-4} to 1×10^{-6} μW cm^{-2} nm^{-1} in the 443-nm (blue) channel. Note that the irradiance of the yellow light reached noise level at a depth of 20 m, while the irradiance of blue light reached noise level at a depth of 22–23 m at stations i8, i12, and i15. The white region of the graphs indicates locations at which the measurements were below the measurement threshold. The measurement locations are shown as gray dots.

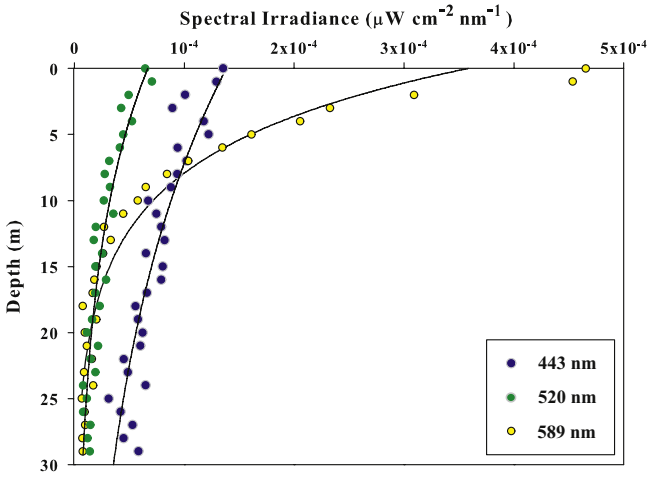

Figure 5. Downwelling irradiance (*Ed*) in the blue (443-nm), green (530-nm), and yellow (589-nm) wavelength channels, respectively, sampled on the night of August 12th, 2015, at 22:00 local time, in the Gulf of Aqaba water column at station i4 (see Fig. 2). *Ed* ranged from 4.6×10^{-4} to 1×10^{-6} μW cm^{-2} nm^{-1} in the 589-nm (yellow) channel, from 7×10^{-5} to 1×10^{-6} μW cm^{-2} nm^{-1} in the 520-nm (green) channel, and from 1.3×10^{-4} to 5.8×10^{-5} μW cm^{-2} nm^{-1} in the 443-nm (blue) channel. The irradiance of green and yellow light reached the instrument limit at depths of 15 and 20-m, respectively. The irradiance of blue light did not reach noise level down to the maximum depth to which the instrument was deployed (30 m).

(close to the measurement threshold) was even detected at a depth of 30 m. However, at the more remote measuring locations, the signal to noise ratio dropped within a few centimeters below the water surface. As is evident in Fig. 5, at station i4, down to a depth of ~7 m, the irradiance of yellow light was higher than that of blue light, but below a depth of ~7 m, the irradiance of blue light became higher than that of yellow light. The higher rate of

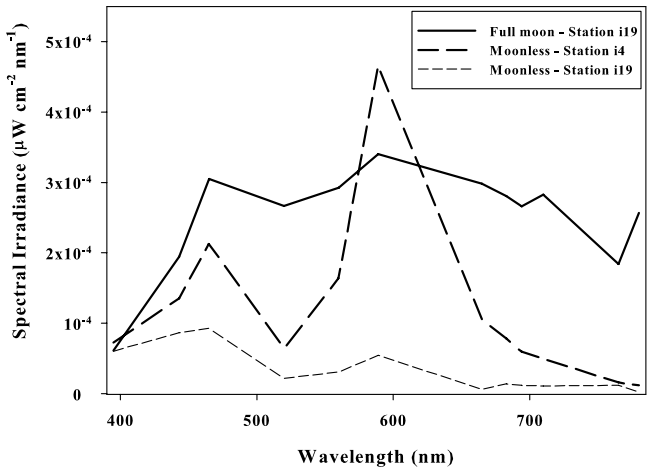

Figure 6. The spectral dependence of measured downwelling irradiance on the water surface on a moonless night (the night of August 12th, 2015) at 22:00 local time at a highly illuminated station (station i4; long dashed line) and at a low illuminated station (station i19; short dashed line), and on a full moon night (the night of September 9th, 2014) at 23:00 local time at the low illuminated station (station i19; solid line). Stations i4 and i19 are located 150 m and 200 m, from the coastline, respectively.

decrease of the irradiance of yellow light with depth is due to the correspondingly higher attenuation coefficient of yellow light in such waters[62] (case I waters; refer to the Introduction) (e.g., K_d at 443 nm = 0.035 m^{-1}; K_d at 589 nm = 0.14 m^{-1} [56]), as well as due to the geometrical configuration of the measurements. (At the air-water interface, yellow light is refracted into a direction farther from vertical than blue light, and therefore the yellow light propagates along a longer path from measurement depth to measurement depth under the water. The fact that the sources of light are localized/pseudo-point sources, and that fact that at each station we measured irradiance through a localized area parallel to the water's surface, also adds a factor of a decrease with distance squared to the cosine of the local zenith angle, which only accentuates this same effect. For example, from a rough estimation of the attenuation coefficient based on a combination of our daytime and nighttime irradiance measurements (not shown here), the attenuation coefficient of yellow light is ~0.05 m^{-1} higher at depths of ~5–20 m under the water due to geometrical effects than it would be for a plane parallel light source, while the attenuation coefficient of green light is only ~0.03 m^{-1} higher than it would be for a plane parallel light source and only at depths of ~5–10 m under the water, and the attenuation coefficient of blue light is at most 0.01 m^{-1} higher than it would be for a plane parallel light source and only over a range of a few meters depth).

In Fig. 6, the spectrum of downwelling irradiance on the water surface on the night of August 12th, 2015 at 22:00 local time is shown for two locations, a more illuminated station (station i1 in Fig. 2; black curve) and a less illuminated station (station i19 in Fig. 2; gray curve). From Fig. 6, one can see that not only does the absolute value of irradiance differ at the two stations but also the spectral dependence. The peak in the 589-nm wavelength channel due to sodium lighting is especially prominent at station i4, close to the city and the port. In contrast, at the less illuminated station, the blue (443 nm and 465 nm) parts of the spectrum exhibit higher peaks, due to the different types of artificial lighting used in proximity to station i19. Such spectral information at different sites in the gulf is important for assessing the extent and type of impact of the light pollution on the local environment.

Also shown in Fig. 6 are spectral measurements of moonlight on the night of a full moon (the night of September 9th, 2014) at 23:00 local time. From Fig. 6, one can see that at station i4 (again near the city and port) on a moonless night, the measured irradiance in the 443-nm and 465-nm wavelength channels are of comparable values to the measured irradiance on the night of the full moon. Furthermore, the irradiance measured in the 589-nm wavelength channel at station i4 on the moonless night is higher than the irradiance measured in the 589-nm channel at station i19 on the night of a full moon. Therefore, artificial nighttime illumination in the Gulf of Aqaba is indeed comparable to and may even exceed the illumination of moonlight. Note that since the intrinsic attenuation coefficient of the water would be the same for both artificial nighttime light and moonlight, and since, as we see from Fig. 6, the irradiance of artificial nighttime light is similar to or larger than the irradiance of moonlight at the surface of the water, the same would be true deeper in the water column where the corals are located.

Our measurements show a clear gradient of unnatural illumination originating from the cities of Eilat and Aqaba and their surroundings into the waters of the Gulf of Aqaba. We have found that in certain wavelength channels, there is almost a two orders of magnitude difference in the irradiance of nighttime light pollution in the Gulf of Aqaba between reef areas next to Eilat and sections of the gulf that are more distant, both at the surface and under water. The fact that the irradiance of artificial light is not uniform over the water body indicates that the effect on water biota may not be uniform. We note that while in terms of vision, a gradient of two orders of magnitude is not extreme (marine animals that navigate vertically through the water column during the day experience similar or larger gradients of light), it is a gradient of light that exists when no light should exist.

The light pollution we have measured in the current study is a potentially harmful factor due to the unique proximity of the coral reefs to the shore and to the urban light sources. The unique geographic setting has to be considered in relation to the manifold different aspects of the influence of light on the structure and functions of coral reefs[33,63–65]. This underscores the importance of mapping the spatial and spectral distribution of artificial light in area as Gulf of Aqaba and determining the gradients of light pollution along the gulf. Such mapping provides an experimental framework for the rigorous study of the manifold effects of light pollution on marine life, enabling a comparison of exposed reef sectors to more distant reef sectors as controls. Furthermore, determining the spectral characteristics and sensitivity thresholds of light induced damages and perturbations will provide city planners and municipal lighting designers with critical information necessary to prevent further damage to the gulf's most important natural treasures and the main socioeconomic resources of the region's residents.

With respect to the effect of artificial nighttime light on phototroph photosynthesis, Raven and Cockell[26] measured PAR close to a city and estimated that the combination of full moon light and sky glow (including the contributions of scattering by water vapor and reflection by clouds) could in some cases reach the lower limit required for photosynthesis (0.1 μmol photons $m^{-2} s^{-1}$ [66]). At the water surface in the most illuminated locations, we measured a value of total PAR that is slightly above 0.1 μmol photons $m^{-2} s^{-1}$, namely ~0.5 μmol photons $m^{-2} s^{-1}$. Nevertheless, according to our estimation, this total PAR is likely to have a negligible effect on net carbon fixation. [Compare these values to the typical PAR of ~100–2,000 μmol photons $m^{-2} s^{-1}$ that we measured under daylight conditions between the hours of 11:00 and 13:00 local time on a monthly basis from August 2014 to December 2015 using the same methods (results not shown here)]. Under the water surface and at less illuminated locations, where the total PAR measured is even lower, photosynthesis should be completely negligible.

Though the effect of the total PAR on net carbon fixation and photosynthesis is likely to be negligible, the light pollution at the levels reported in the current study may still affect more sensitive physiological and behavioral patterns and processes. These might include synchronization of biological clocks, navigation, migration, reproduction, phototaxis and bioluminescence, and may thereby lead to the impairment of regional marine organisms, as suggested elsewhere (e.g., refs 16 and 67). For example, as we mentioned in the Introduction, several species of corals have been found to be extremely sensitive to the blue region of the light spectrum[10,21,24]. Moreover, the fact that the irradiance of artificial light at certain stations and in certain wavelengths is similar to or even higher than the irradiance of moonlight on full moon nights (Fig. 6) reinforces the potential disruptive influence of light pollution on the marine ecosystems in the gulf. Therefore, we suggest that future studies of the effect of blue light and of light pollution in general on the specific biological functions of marine organisms and of their ecosystem-level consequences in the Gulf of Aqaba should be given high priority.

Conclusions

From our *in situ* measurements, we have found that nighttime illumination in the Gulf of Aqaba is dominated by the spectral characteristics of low pressure sodium vapor lights. However, we found that the 589-nm sodium vapor light signature at the surface becomes secondary to the irradiance of blue (443 nm) light from a depth of ~7 m; we found that this 443-nm wavelength light is the most penetrating wavelength in the waters of the gulf. Therefore, the ongoing change in the type of lighting used (the tendency to use more LED lighting, with a stronger blue component) will likely result in a considerable increase in the amount of light that will reach deeper into the water column and to the sea floor, thus exposing more areas of the reef to nighttime light.

We have found that in some locations, the irradiance of near shore artificial light is equal to or exceeds the irradiance of the light of the full moon. Hence, we expect that nighttime light pollution in those locations will interfere significantly with the activities of marine organisms that are synchronized with the phases of the moon. There is a particular danger of upsetting diurnal light/dark vision based behavioral feeding and feeding avoidance patterns of reef dwelling and pelagic organisms, which would destabilize the ecosystem structure and its functions.

Researchers currently face the challenge of disentangling the cumulative effects of all of the facets of human disturbance on coastal ecosystems with which artificial night lighting is often correlated, such as urban development, noise, exotic invading species, animal harvesting, and resource extraction. Even assessing the separate and combined impacts of direct artificial light and sky glow is not trivial.

By providing researchers and decision makers with hitherto unavailable information about the spatial dispersion of disturbed and relatively pristine reef sections of the Gulf of Aqaba, the data presented in the current study should serve as an important contribution towards further research on light pollution and coral reefs and towards future legislation. We expect that this study will prompt follow-up studies on the effects of light pollution on diverse coastal, shallow water ecosystems, helping to predict future shifts in their structure, assemblages, and function. We also expect that our results will promote future efforts to combine an assessment of the influences of light pollution on the specific physiology and behavior of coral reefs and their denizens with an assessment of the bathymetric and geographic boundaries of such effects. Locally, we expect that this study will serve scientists, governmental and local authorities, and interested NGOs in their efforts to ensure the health of the Gulf of Aqaba's unique coral reefs. The study will have immediate effects on the design of municipal lighting systems and related legislation. We suggest that as coastal cities such as Aqaba and Eilat continue to develop, measurements of light pollution should be included routinely as part of environmental monitoring protocols on both sides of the gulf, and we hope that this study will provide an impetus for collaboration between scientists in Jordan and Israel on this important topic. We also hope that the unique data presented here will raise general public awareness of the issue of coastal light pollution both locally and globally.

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Acknowledgements

We would like to thank the Interuniversity Institute for Marine Sciences for making their facilities available to us. This research was supported by the Ministry of Science, Technology, and Space, Israel (grant number is 3-11110).

Author Contributions

R.T. conducted the light measurements, analyzed the data, generated all the GIS maps and figures and performed the different forms of data presentation, under the guidance of D.I. and Z.D. All authors contributed equally to the writing process of the paper. All authors discussed the results and implications and commented on the manuscript at all stages.

Additional Information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Tamir, R. *et al.* The spectral and spatial distribution of light pollution in the waters of the northern Gulf of Aqaba (Eilat). *Sci. Rep.* **7**, 42329; doi: 10.1038/srep42329 (2017).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

MARIO MOTTA, MD – AMA TRUSTEE

Street Lighting

Outdoor Street Lighting, Glare, and Circadian Rhythm Disturbance

I have been a light pollution advocate for many years. Certainly 30 years ago I was most interested in the sky glow that affects our view of the starry night, and though that remains a major concern, there are now many medical, safety, and environmental concerns that are paramount. On an energy committee in my town, I was able to show that poorly lit intersections with severe glare by unshielded lighting had the highest accident rate. Further review of published studies has shown that as the eye ages, it becomes much more sensitive to disability glare, impairing safe driving. That led to my 2009 resolution, which suggested that all streetlights be properly shielded to prevent such glare, making both the streets and the elderly driving in the evening safer. This resolution is still cited by lighting companies.

In 2012, knowing the research activities of many scientists from around world on the effects of nighttime lighting on human physiology, I invited four prominent researchers to help me write a Council on Science and Public Health (CSAPH) report, “Light Pollution: Adverse Health Effects of Nighttime Lighting.” This 27-page report with 134 peer-reviewed references highlighted the adverse health effects of circadian rhythm disturbance. Suppressing melatonin production through excessive night lighting, especially blue light, leads to myriad deleterious health effects. The most stunning is an increase in certain endocrine-related carcinomas. It is now well known that circadian disturbance causes a 20–30% increase in breast cancer rates, and a similar increase in prostate cancers. Indeed, this past year (2017) the Nobel Prize in medicine was awarded to Young, Rosbach, and Hall, because they elucidated the biochemical pathways that lead to increased cancer by melatonin suppression. In addition, obesity, diabetes, metabolism issues, and immune system are all affected by melatonin suppression. The World Health Organization has even listed shift workers, who have repeated melatonin suppression as a “known Carcinogen, level 2.”

After the 2012 report came out, there was some pushback from the lighting industry. However, in 2014 General Electric wrote its own white paper on this subject, and agreed not only with the AMA report, but also liberally quoted from our report. The GE report stated that corporate policy would change to take note of melatonin production in its lighting policies and products. Shortly after that, Apple developed a blue reduction in its phones and computers for late night. Many other companies have since adopted this practice. Again, with the Nobel Prize, and over 1,000 peer-reviewed papers, this is now settled science! The last section of the 2012 report also raised the alarm that excessive

outdoor blue light was also causing environmental harm, as all living creatures have a circadian rhythm — even a one-celled life!

NEW 2022: UN report on light pollution completed and submitted.

The United Nations Office for Outer Space Affairs and Spain, jointly with the International Astronomical Union (IAU) are organizing an online Workshop on the topic of "Dark and Quiet Skies for Science and Society". The face to face Conference is postponed to 19-23 April 2021 and will be hosted by the Instituto de Astrofísica de Canarias (IAC) at Santa Cruz de La Palma, Canary Islands, Spain. In lieu of the on site meeting, the first week of October 5-9, 2020 there was a virtual meeting. Mario Motta has been asked to be a participant, and will deliver a talk on human effects of light pollution on tuesday Oct 6. He also is an author of the Light pollution health effects part of the report of this meeting that deals with many aspects of astronomy from light pollution to satellite proliferation issues. This is a worldwide event, and the final publication will be sent to the UN General Assembly for ratification. *I am hopeful that this document, if ratified, will have a worldwide impact on light pollution issues, similar to the 2016 AMA report on the same issue.* See link below for full details.
http://research.iac.es/congreso/quietdarksky2020/pages/home.php
final UN submission document 2022, I am very happy to have been part of this for the past 2 years, and also that it mirrors AMA policy on human effects of light pollution, we did it first!

https://zenodo.org/record/5874725#.YhgMzujMIpc

NEW! PBS Nova article on light pollution, I was consulted on and quoted:

https://www.pbs.org/wgbh/nova/article/light-pollution-led-nantucket-solutions/

LED Lighting

In the ensuing years the lighting industry has developed LED lighting and plans to replace all outdoor lighting with LEDs over the next 10 years. Given my 2012 paper, and many reports of environmental damage by excessive blue, I was able to convince the CSAPH to let me lead on one more report, "Human and Environmental Effects of Light Emitting Diode (LED) Community Lighting," which was adopted at the 2016 AMA annual meeting by the HOD. This particular report hit a nerve with the lighting industry. However, the report actually says that we should replace outdoor lighting with LED lights to save energy, and we should shield all streetlights to prevent glare — that was widely accepted. The last resolve stating that blue light should be limited in outdoor

lighting and streetlights should use 3000K or lower color temperature led to severe consternation in the lighting industry. The issue was that many companies were trying to sell 4000K lighting, as those were the first type of LEDs manufactured. They had inventory already made. LED lights use a blue LED and coat it to absorb the blue and re-emit at lower "warmer" color temperature (e.g., 3000K). However, 4000K lighting is 30–34% blue light. The 2012 paper and thousands of studies have already shown this is bad for humans and the environment in general. The AMA report suggested no higher than 3000K; nowadays, there is good 2700K lighting, even 2400K lighting, and the trend is lower. There is evidence that high blue leads to severe insect, bird, and mammalian effects in nature. It has even been shown to effect salmon runs and plankton!

When the AMA report came out, it was hailed by researchers, and many cities paused their efforts to study it closely. They came to the same conclusion, and demanded warmer 3000K — or even 2700K — lighting. Many companies changed their products and are now thriving, while others are still fighting. To date, most large cities have now adopted the AMA recommendation and use "AMA Compliant Lighting"! New York, Chicago, Tucson, Phoenix, Los Angeles, San Francisco, San Diego, Georgia, Toronto, Montreal, and many others have changed their lighting plans and demand 3000K or lower. This is helped by the fact that wherever 4000K lighting was installed, citizens immediately complained about the harsh glare of bluish light. Some cities, such as Monterey and Davis in California, even sued their cities and demanded a switch to 3000K or lower.

I consider this a huge win, and it shows the power and influence the AMA can exert when we use science and recommendations for the common good. The 2016 report has in the words of many lighting engineers "revolutionized" the lighting industry. This would not have occurred without the AMA publishing this report and cities looking at it and demanding "AMA Compliant Lighting."

NEW: The IES (illuminating Society of engineers) who make the guidelines many cities use to guide street lighting, has revised their recommendations. They now parrot the 2016 CSPH report. This is the group that was ***'demanding"*** that the AMA delete its recommendations on street lighting after our CSPH 2016 report, objecting to the recommendation that cities use no higher than 3000K lighting and lashed out at the AMA for daring to tell them their lighting recommendations were wrong. Based on our scientific data the AMA stood by its position

Then last year I was invited to speak to their roads comm in Quebec, and debated their chair at a lighting meeting in California. They stated they would take my recommendations and talk under advisement.. It appears that without admitting they were wrong they have quietly changed their tune…. Street lighting will now hopefully follow AMA guidance everywhere.

See below:

The Illuminating Engineering Society has published its new comprehensive lighting recommendation (RP-8-18). Their recommendations are historically widely used as the lighting bible for cities. RP-8-18 recently won an award at LIGHTFAIR International for its new thinking on lighting in the age of LED. It is a must have for Public Works and area developers. **There are now many recommendations and discussions included that highlight the concerns of the American Medical Association and the International Dark-Sky Association.** Their concerns are seen as being in line with lighting that also provides the best visibility.

Here are highlights:

1. Do not exceed the recommended light levels. Excessive light can create glare that can reduce visibility to the point where the visibility is worse than using no lighting at all plus headlights. (This is almost verbatim from the AMA 2016 report concerning visibility under higher glare LED street lights.)

2. For decorative lighting, use only shielded versions due to glare and light trespass problems with unshielded models.

3. Design for the impact of lighting on human health, animals, and the night sky. To minimize skyglow, choose longer wavelength LED color that scatters less in the atmosphere (lower blue and warmer white or amber in color), and avoid over lighting to minimize the amount of light reflected from the surface below. Bluer LEDs also disrupt circadian function by suppressing melatonin which in turn disrupts sleep and allows some hormone based cancers to grow faster at night.

4. Shorter wavelength light does allow better color rendition and peripheral acuity, but warm white provides very good visibility on major streets while reducing perceived glare and lower traffic areas do not need maximum brightness as headlights combined with less bright street lights work at slower speed limits.

5. Luminance (reflected light off the street) rather than illuminance (how much light is hitting the street) is the recommended calculation method for most roadway lighting and the new standard includes a calculation for veiling luminance. RP-8-14 for roadway lighting was incorporated into RP-8-18.

REFERENCE:

2012 paper describing human health and environmental effects of poor lighting

AMA Health Effects Light at Night

CSPH report advising municipalities to limit all LED lighting to below 3000K

CSAPH Report 02-A-16 (PDF)

American Journal of Preventive Medicine, 2013 article on LED lighting health effects

AJPM13

GE paper agreeing with AMA position

GE Lighting And Sleep Whitepaper (PDF)

Article form myself and Richard Stevens on human health harm

American Journal of Preventive Medicine (PDF)

Article on breast cancer risk from melatonin suppression

Cancer 2013 (PDF)

Great article from National Geographic on environmental damage of bad lighting

https://www.nationalgeographic.com/science/2019/04/nights-are-getting-brighter-earth-paying-the-price-light-pollution-dark-skies/

US skyscrapers kill 600 million — yes, million — birds every year
https://www.cnn.com/2019/04/08/americas/bird-building-collisions-scli-intl-scn/index.html

Impressive article from Nature Magazine Jan 2018 of environmental damage

https://www.nature.com/articles/d41586-018-00665-7

LED lights damage eyes and disturb sleep, European health authority warns
A French health authority warned of the dangers of blue light, stating this wavelength can damage the eye's retina while also disturbing our biological and sleep rhythms.

Read in CNN: https://apple.news/AJgTaLQGpSNSGy5kbXooy9Q

NOVA PBS:
https://www.pbs.org/wgbh/nova/article/light-pollution-led-nantucket-solutions/

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