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Circadian Health and Light: A Report on the National Heart, Lung, and Blood Institute's Workshop

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Abstract

Despite the omnipresence of artificial and natural light exposure, there exists little guidance in the United States and elsewhere on light exposure in terms of timing, intensity, spectrum, and other light characteristics known to affect human health, performance, and well-being; in parallel, there is little information regarding the quantity and characteristics of light exposure that people receive. To address this, the National Center on Sleep Disorders Research, in the Division of Lung Diseases, National Heart, Lung, and Blood Institute, held a workshop in August 2016 on circadian health and light. Workshop participants discussed scientific research advances on the effects of light on human physiology, identified remaining knowledge gaps in these research areas, and

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CONFLICT OF INTEREST STATEMENT

PCZ reports the following conflicts of interests: consultant for Philips, Merck, Jazz. KPW reports the following conflicts of interests: board member of the Sleep Disorders Research Advisory Board—National Heart Lung and Blood Institute, Board of Directors of the Sleep Research Society, and Scientific Advisory Board of CurAegis Technologies; consultant for CurAegis Technologies and Circadian Therapeutics; research support from CurAegis Technologies, Philips Inc., Somalogics, NIH, Office of Naval Research, and the PAC-12; stock options from CurAegis Technologies; speaker for the Department of Energy and the Illuminating Engineering Society. ICM, MB, MGF, BPH, SH, SMH, RJN, WAB, MKB, ADL, KMS, and MJT declare that they have no conflict of interests.

articulated opportunities to use appropriate lighting to protect and improve circadian-dependent health. Based on this workshop, participants put forth the following strategic intent, objectives, and strategies to guide discovery, measurement, education, and implementation of the appropriate use of light to achieve, promote, and maintain circadian health in modern society.

Keywords

light exposure; built environment; public health; circadian rhythms; sleep

Light and dark exposure entrains the master circa-dian clock in the hypothalamic suprachiasmatic nuclei, which regulate the 24-h rhythms in physiology and behavior. Light exposure during the day and during the night can also elicit direct effects on the brain and body. Approximately 10% to 20% of gene expression cycles over the 24-h day and abnormalities in circadian rhythms contribute to an array of metabolic, immunological, and basic behavioral pathology. Potential health risks associated with disturbed circadian rhythms encompass medical conditions and threats to public health and safety. With this in mind, the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) and National Center on Sleep Disorders Research (NCSDR) convened a workshop on circadian health and light in August 2016 to assess knowledge gaps and identify opportunities to use light exposure to improve circadian-dependent health. Specifically, the workshop panel was charged with addressing the following:

1. Translate advances in sleep and circadian science into opportunities and strategies to improve the health of the nation
2. Assess knowledge gaps and opportunities to use appropriate lighting in the built environment to improve circadian-dependent health
3. Identify opportunities to leverage existing study activities including population-based cohorts to quantify the impact of improved circadian-appropriate lighting on heart, lung, and blood physiology and related disorders as well as on critical societal outcomes affecting public health and safety

The modern environment, with its widespread use of electric lighting and 24/7 lifestyle, is accompanied by patterns of light and dark exposure that differ from the natural light and dark cycle (Ekirch, 2005; Wright et al., 2013) and are thought to play a role in circadian health (de la Iglesia et al., 2015; Stevens and Zhu, 2015). Less than 2 decades ago, researchers discovered the intrinsically photoreceptive retinal ganglion cells (ipRGCs) that contain the photoreceptor pigment melanopsin, thereby elucidating a direct pathway by which light influences circadian rhythms (Berson et al., 2002; Hattar et al., 2002). This pathway's myriad connections with various brain areas further expands the non-image-forming roles of light exposure (Hattar et al., 2006; Bannaroch, 2011). The classical rod and cone photoreceptors also stimulate the ipRGCs and therefore contribute to the non-image-forming effects of light (Lucas et al., 2012; Hattar et al., 2003). Increasing evidence from human and nonhuman animal studies indicate that the timing, intensity, wavelength, and duration of light exposure as well as other light characteristics may affect health.

Research in rodents has shown that light exposure is tied to numerous physiological and behavioral outcomes, including body mass regulation (Fonken et al., 2010), metabolism (Wideman and Murphy, 2009; Coomans et al., 2013), depressive behaviors (Gonzalez and Aston-Jones, 2008; Wideman and Murphy, 2009; Bedrosian et al., 2013), and responsiveness to cancer treatment (Dauchy et al., 2014). Altering the duration of light exposure and the timing of feeding in relation to light exposure impaired glucose metabolism and resulted in weight gain for mice (Fonken et al., 2010; Coomans et al., 2013). Moreover, constant light exposure in rats resulted in greater adiposity, decreased melatonin levels, changes in metabolism (increased feed efficiency and lower food and water intake), altered circadian rhythms (free running with decreased overall activity), and increased irritability compared with rats kept in constant darkness or on regular light-dark cycles (Wideman and Murphy, 2009). On the other hand, constant light deprivation for 6 weeks in rats resulted in neural damage of monoamine brain systems and depressive behavioral phenotypes compared with rats kept in 12:12 light-dark conditions (Gonzalez and Aston-Jones, 2008). The wavelength of light exposure also needs to be taken into account; hamsters exposed to long-wavelength (red) light at night showed less depressive responses and less alteration of neuronal structure than hamsters exposed to shorter-wavelength (blue) light at night (Bedrosian et al., 2013). In addition, dim light exposure during rats' normal dark period increased the growth of breast cancer tumors and conferred resistance to therapy (Dauchy et al., 2014). These animal model findings suggest that timing, duration, and additional components of light exposure are all vital constituents of a healthy environment.

Similarly, human studies, both in the field and in the laboratory, add insights into the far-reaching influences of light exposure, such as on depression (Rosenthal et al., 1985; Wallace-Guy et al., 2002; Lam et al., 2016), metabolic responses (Figueiro et al., 2012; Danilenko et al., 2013; Cheung et al., 2016), body weight (Reid et al., 2014), sleep timing and quality (Wallace-Guy et al., 2002; Cho et al., 2013; Boubekri et al., 2014; Figueiro et al., 2017), sleep and behavior in Alzheimer's disease patients (Ancoli-Israel et al., 2003; Figueiro et al., 2014, 2015), and patient recovery and well-being (Ritchie et al., 2015). Several characteristics of light exposure are critical to the determination of health outcomes. Morning bright light has a well-established antidepressant effect for those suffering from seasonal affective disorder (Rosenthal et al., 1985) as well as those suffering from nonseasonal depression (Lam et al., 2016). Manipulating light exposure also resulted in alterations in metabolic function, appetite, and body fat; morning light exposure of 1300 lux for at least 45 min between 0600 h and 0900 h for 3 weeks in obese women resulted in reduced body fat and appetite (Danilenko et al., 2013). However, other findings indicate that daytime exposure to bright light and blue-enriched bright light have little influence on 24-h energy metabolism or on glucose and insulin levels after a test meal when compared with typical room light (Melanson et al., 2018); these discrepant findings highlight a need for further research on this topic. On the other hand, timing of light exposure has been associated with body mass index, with more light exposure earlier in the day correlating with lower body mass index (Reid et al., 2014). These associations may be related to hormonal changes. With sleep restriction of 5 h of time in bed followed by 2 h of light exposure to different wavelengths (633 nm, 532 nm, 475 nm) in the morning immediately upon waking, attenuations were noted in the alterations of the levels of the appetite-

regulating hormones leptin and ghrelin due to sleep deprivation (Figueiro et al., 2012). Furthermore, both morning and evening blue-enriched light exposure increased insulin total area and β -cell function and insulin resistance, whereas only evening exposure resulted in higher glucose peak values compared with dim light in healthy, young adults (Cheung et al., 2016). Evening use of blue-enriched light-emitting devices has also been associated with negative impacts on sleep (e.g., longer time to fall asleep, reduced evening sleepiness), reduced melatonin secretion, later timing of the circadian clock, and reduced alertness the next morning (Chang et al., 2015; Chinoy et al., 2018). In addition, sleep quality is affected by multiple environments, such as light exposure in the workplace (Boubekri et al., 2014; Figueiro et al., 2017) and in the overnight sleep environment (Cho et al., 2013), thereby providing multiple venues in which light could be manipulated to improve health. Indeed, there has been much discussion as of late on the possible health consequences of the recent implementation of light-emitting diode lights, which can emit a higher content of short-wavelength light, for community street lighting. In line with these concerns, a recent satellite radiometer study (Kyba et al., 2017) has shown that Earth's electrically lit outdoor surface is growing by radiance and area each year. There is emerging evidence that human-made light at night exposure may have negative consequences on human well-being (e.g., Obayashi et al., 2018), and this is an area that warrants further investigation (Lunn et al., 2017). Altogether, these compelling findings and recent developments give urgency to further explore the role of light in health and implement existing knowledge.

Despite increased interest in the aforementioned links between light exposure and health, most research has been conducted on wavelength and timing of light exposure with little attention afforded to the influence of prior history of light exposure. Given that prior exposure to light can dampen subsequent melatonin suppression by light by 10% to 15% (Hébert et al., 2002; Smith et al., 2004) and influence phase-shifting responses to a light stimulus (Chang et al., 2011), the role of prior light exposure is likely important in effects seen on health outcomes. In particular, there may be great value in investigating whether duration, intensity, wavelength, or other characteristics of light exposure during the day may mitigate some of the adverse effects of light exposure at night. For instance, a week-long or weekend exposure to outdoor light throughout the wake period resulted in an earlier dim-light melatonin onset compared with the modern environment that has greater indoor and less outdoor light exposure (Wright et al., 2013; Stothard et al., 2017). In addition to the implications of light exposure's effects on alertness, metabolism, depression, and other health outcomes, there are also implications of results from laboratory studies that used controlled lighting, such as dim lighting or uniform indoor lighting across the wake period. There is a need for laboratory studies to incorporate measurement of prior light exposure and account for light exposure throughout the study to determine how the history of light exposure affects subsequent responsiveness to light exposure and health outcomes. The potential contribution of light exposure history not only shows the complexity of the relationship between light exposure and health outcomes but also highlights many additional avenues to explore how light exposure may be used to improve health.

Although there have certainly been numerous advances in this area, many knowledge gaps remain, including the need to elucidate further the role of light in health and ways to implement light exposure as a modifiable risk factor to create a healthy lighting

environment. Opportunities abound to aid this effort; for example, the field needs to better understand and elucidate 1) the need for light in brain function, 2) the influence of light on peripheral tissue function, 3) the function of light on circadian entrainment, 4) optimal light exposure characteristics (or “photoceuticals”) for promoting robust circadian rhythms and circa-dian health, 5) the effects of light exposure history on light adaptation in the retina, 6) mechanisms by which light exposure affects risk and treatment of disease, and 7) optimal lighting parameters for improvements in mood and cognition.

The potential for light to be used as a health promotion tool will be enhanced by developing tools to measure the “dose” of the relevant light spectrum across 24-h periods in conjunction with systemic, molecular, and cellular markers of physiological function. Studies are needed to better understand the association between “dose” characteristics such as light exposure, duration, intensity, and spectrum and the risk of neurological, metabolic, and mental health pathobiology. Similar to pharmaceuticals, light properties may have “photoceutical” importance for therapeutic purposes. The prevalence of altered light exposure patterns in postindustrial communities presents immediate opportunities for current knowledge to be implemented in real-world applications while simultaneously moving forward with scientific inquiries and advances. Implementation research will be needed to translate the scientific advances in lighting and biology into effective health messages for the public, while resources will also be needed to guide policy makers who are considering how to create healthier environments.

Following discussion of the current state of the science, the effects of light on health, and identification of a variety of knowledge gaps, workshop participants set forth an overarching long-term goal for lighting research (strategic intent) and enumerated immediate objectives, goals, and strategies for real-world translation.

STRATEGIC INTENT

The strategic intent is to leverage advances in the effects of light on human physiology and incorporate appropriate use of light for promoting health, safety, performance, and well-being to optimize adaptation to modern society.

OBJECTIVES AND GOALS

1. Discovery: Elucidate the mechanisms by which light properties (such as timing, spectrum, intensity, dynamic quality, and duration) affect brain and peripheral tissue function, with particular emphasis on the following:
 - a. the influence of light beyond sleep and circadian regulation such as alertness and mood,
 - b. stimulus parameters and measures of response to light stimuli, and
 - c. the contribution of light exposure history to the effects of subsequent light exposure on various functions related to health, in particular as to how optimal daytime light exposure may mitigate adverse effects of nighttime light exposure.

2. Measurement: Develop consensus on measurement of light and appropriate devices (e.g., sensors, biomarkers) as well as analytical and computational methodologies.
3. Implementation: Develop and implement best practices for healthy lighting.
 - a. Target vulnerable populations including older adults, children, adolescents, those with dementia, and those for whom lighting exposure or lack thereof may contribute to the risk of health disparities (such as night-shift workers).
 - b. Develop protocols to enhance outcomes in intensive care, neonatal, and other clinical populations at risk of inappropriate lighting exposures.
 - c. Implement circadian-appropriate lighting as a primary prevention strategy in building healthier environments across the life span.
 - d. Measure light exposure in population studies and its association with the risk of disease.
4. Education: Develop educational strategies to communicate an integrated understanding of how light, sleep, and circadian timing contribute to health.
5. Develop the evidence base and lighting resources required to inform the development of public policies and healthy environments.

STRATEGIES

1. Education
 - a. Foster and encourage new teams of researchers including scientists, developers, architects, industry, schools, and educators working with the wide array of federal agencies and other stakeholders in need of guidance on light and circa-dian health such as the National Institute for Occupational Safety and Health total worker health, Department of Energy solid-state lighting, National Aeronautics and Space Administration, Defense Advanced Research Projects Agency, Department of Housing and Urban Development, Department of Defense, Department of Education, National Highway Traffic Safety Administration, Occupational Safety and Health, Green Building Council, the American Institute of Architects, and the Illuminating Engineering Society.
 - b. Develop educational resources for dissemination in schools and to the public.
 - c. Incorporate light and circadian and sleep health in professional training of physicians, health care providers, architects, urban designers/planners, social workers, and other relevant vocations.
2. Discovery

- a. Elucidate the neurobiological mechanisms linking light to brain function and the pathways synchronizing central and peripheral physiological functions.
 - b. Determine neurobiological mediators of light effects on behavioral outcomes.
 - c. Develop mathematical models of circa-dian-appropriate light doses and light exposure across the day required to protect brain function.
 - d. Determine sex differences, ethnic-racial differences, and differences across the life span in response to light for circadian rhythms, mood, cognition, metabolism, and other physiological functions.
 - e. Investigate seasonal effects/responses to light exposure and their potential consequences for humans.
 - f. Compare light exposure requirements and neurobiological differences in diurnal and nocturnal mammals to better understand the role of light in human disease.
 - g. Investigate how light exposure history modifies retinal sensitivity and influences the response to artificial light, especially at night.
3. Implementation
- a. Determine if light exposure or photo-ceutical “dosing” influences the efficacy of neuropsychiatric, metabolic, pharmacotherapies, and/or linked therapies through neurobiology or alteration of circadian timing and, if so, how these influences can be optimized.
 - b. Develop primary intervention strategies leveraging the light environment to reduce risks to health in clinical populations.
 - c. Elucidate the role of light exposure and circadian function as social determinants of health in population-based studies.
 - d. Develop tools and resources to guide the development of policy and public health.
4. Measurement
- a. Biomarkers of circadian, sleep, metabolic, and immune responses to light are needed to diagnose and stratify risks to health and to measure the efficacy of lighting-based interventions.
 - b. Develop technologies facilitating objective measurement of light exposure and responses (phase-response curves, sensitivity, acute versus chronic, seasonal) in various populations (e.g., children, adolescents, older adults).

In this workshop, participants articulated opportunities to leverage lighting technology to protect and enhance health. The wide-reaching implications of the lighting environment involve an interdisciplinary approach, and subsequently, the strategic intent, objectives, and

strategies put forward by the workshop panel aspire to incorporate diverse expertise. Cooperation among these areas of expertise is needed to simultaneously implement existing knowledge into current lighting paradigms while pursuing further knowledge on the potential use of light to achieve and maintain circadian health.

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