REVIEW ARTICLE

Light and Life at Night as Circadian Rhythm Disruptors

Eunil Lee[1,2,3] and Mari Kim[1,4]

[1]Department of Preventive Medicine, College of Medicine, Korea University, Seoul, Korea
[2]Department of Environmental and Global Health, Graduate School of Public Health, Korea University, Seoul, Korea
[3]Program in Public Health, Graduate School, Korea University, Seoul, Korea
[4]Institute of Environmental Health, Korea University, Seoul, Korea

Light is an important entraining agent for endogenous circadian rhythms. Artificial light at night (ALAN) negatively influences the circadian system, inducing acute effects on sleep and cognition, as well as chronic endocrine-disrupting effects resulting in obesity, cardiovascular disease, diabetes, and cancer. Although shift workers may be exposed to extreme ALAN, its impact on their health is obscured by factors such as daylight exposure, meal and sleep scheduling, and physical and social behavior. Studies have revealed a significant increase in breast cancer in high ALAN-polluted areas, although the correlation with outdoor or indoor lighting conditions is controversial. Increasing use of electronic devices makes it difficult to assess ALAN exposure in the general population. The development of surrogate markers and critical parameters is crucial for health study by ALAN exposure, and such markers should include risk factors related to ALAN exposure. The present review considers articles investigating the risk of ALAN for shift workers, the general population, and users of electronic devices, and addresses susceptibility factors, including age, sex, and chronotype. Shift workers may be regarded as an extreme ALAN-exposure group, but the growing use of electronic devices and lifestyle changes in the general population make difficult to differentiate ALAN risks to health.

Key Words: Circadian rhythm; Sleep disruption; Cognition; Melatonin; Shift work

INTRODUCTION

The axial rotation of the Earth, together with the light of the sun, generates 24-hour cycles of day and night, and this light-dark cycle is the basis of 24-hour circadian rhythms. Living organisms have their own endogenous circadian rhythms, also with a duration of approximately 24 hours, driven by environmental factors, especially light and darkness [1]. And it is widely known that circadian rhythms of mammals are regulated by an internal biological clock located in the suprachiasmatic nuclei (SCN) situated directly above the optic chiasm [2]. Maintaining the biological clock is crucial for coordinated function throughout the human body because this near-24-hour oscillations are found in essentially every physiological process in the human brain and body [3,4].

The period, phase and amplitude of circadian rhythms can be affected by circadian gene variants, light exposure, social cues, meal times and work schedules [5-8]. Light is the most effective entraining agent for endogenous circadian rhythms and the circadian system is vulnerable to artificial light at night (ALAN). Because of industrialization, urbanization and increase use of electric devices, bright levels of ALAN are expected occasionally and low levels of ALAN are fairly ubiquitous. About 40 lux (lx) of light exposure is common to human and five or more lux is a common exposure level for humans [9]. Satellite images of Earth at night have revealed that ALAN covers 80% of the planet [10].

Throughout the body, tissue functions are influenced by light, and circadian rhythms are aligned by photoentrainment. Abnormal lighting conditions induce many negative consequences on these rhythms, including both an acute impact on alertness and cognition, and an indirect effect through dysregulation of the circadian system [11]. Exposure to dim light during sleep lead to problems with sleep and cognition [12,13]. Exposure to ALAN can also induce broad endocrine effects through direct altering endocrine signal by circadian dyregulation or disrupted melatonin pro-

duction. Most studies have reported the effects of ALAN on disruption of metabolic processes, resulting in obesity or diabetes and cancer incidence [9]. An increase in cancer has been proposed to be the result of the simultaneous, complex effects of three major mechanisms related to circadian disruption by ALAN: inhibition of melatonin secretion, sleep deprivation and chronodisruption [14]. Furthermore, it has been suggested that ALAN is also associated with a higher risk of cardiovascular disease [15,16] and psychiatric disorders such as depression [17-19].

Evening and night shift workers have a greater risk for exposure to both ALAN and irregular light-dark patterns, and have been shown to be at increased risk for diseases, especially cancer [20]. In 2007, the International Agency for Research on Cancer (IARC) classified "shift work that involves circadian disruption" as a probable human carcinogen, based on limited evidence of carcinogenicity for breast cancer in human studies and sufficient evidence in experimental animals [19,20]. Further systemic reviews found insufficient evidence to support an association between night shift work and breast cancer risk [21] and recent review study reported no evidence for a dose relationship between night-shift work and breast cancer risk [22]. This limited evidence associating ALAN with cancer may be related to the lack of a quantitative assessment of ALAN and melatonin levels in human studies [23]. However shift work itself is not an exact proxy for ALAN because the health of shift workers is not only affected directly by ALAN but also by altered exposure to daylight, changes in the timing of daily activities including eating, sleeping, physical activities as well as changes in pattern of social behavior [19]. When evaluating ALAN as a risk factor in human disease, the total exposure patterns to hazardous ALAN and to day light should be assessed, not just ALAN itself [24].

A few epidemiological studies reported a significant associations between ALAN and breast cancer among the general populations in Israel, the state of Georgia in the United States and South Korea [25-27]. These studies all used satellite-measured ALAN levels to determine exposure. However, these levels were not correlated with measured bedroom light levels in evening or nighttime [28,29]. And there is only a weak correlation between satellite-measured ALAN and outdoor light levels [28]. These studies suggest that the significant association of ALAN with breast cancer in general population should not be interpreted as a direct ALAN risk in breast cancer. However the satellite-measurements can be a good indication of exposure to ALAN, because it is associated with economic development including the increase use of electricity for working, eating and enjoying leisure time at night [30-32].

The methods of assessment of ALAN exposure were categorized as either outdoor or indoor, based on measuring tools [33]. Outdoor ALAN exposures were typically recorded using satellite data, whereas indoor ALAN exposure was based on individual lighting habits while sleeping and/or indoor illumination levels directly measured by photometer, ActiWatch, HOBO pendant. The measurements of ALAN should be used alongside personal exposure time to evaluate its circadian disrupting effects. In the study of circadian disruption and disease risk, Figueiro [3] described the urgent need to consider the following: 1) characteristics of light stimulus must be specified including quantity, spectrum, timing, duration and distribution, 2) light stimulus must be measured with calibrated instrument, and 3) daytime light exposures must also be taken into account. The circadian disrupting effects by ALAN should be considered with reference to light exposure during the day, as very little daytime light also dampens human circadian rhythm.

The increase in use of electronic devices makes it more difficult to assess ALAN exposure in people. Humans are almost continuously exposed to unintentional artificial light because of an exponential increase in the use of computers, consoles, tablets, TVs and smartphones [34]. It is possible to monitor the light exposure and circadian-disrupting effects, including changes of melatonin secretion or clock genes, in a small group of people. However, in a large population, it is almost impossible to evaluate long-term circadian disruption caused by a lifetime of ALAN exposure from diverse artificial lighting sources, with differing light intensities and spectrums, duration of exposure and time of day or night. It is necessary to develop surrogate markers and critical parameters for the assessment of ALAN exposure based on experimental studies, such as the exposure scenario techniques used in the study of chemical exposure [35]. In the application of exposure scenario techniques for evaluating ALAN exposure, it is important to fill the gap between the experimental and real world data, to understand the complex interaction between chronodisruption, the suppression of melatonin, and sleep problems, especially in susceptible members of the population, such as children and adolescents [36,37]. These markers should include risk behaviors related to ALAN exposure (BALAN). In this review, the important BALAN for shift workers, the general population, and users of electronic devices are addressed, with an emphasis on the need to study how to estimate long-term ALAN exposure based on limited data, by combining BALAN. Circadian disruption resulting from ALAN exposure may be complicated by a change in sleep quality or quantity, variations in meal or exercise time, or genetic factors. However, this review focuses only on ALAN exposure and related behaviors.

METHODS

The circadian disruptors, ALAN and BALAN, can be classified into three categories based on artificial lighting sources [19,38]; the first category is circadian disruption by changing of the day-night cycle, such as in shift work or jet lag. The second category is location of residence, such as urban light pollution, and the third category includes lifestyle choices, such as use of electronic devices at night. By reviewing articles related to ALAN risk for each of these categories, the important behaviors or lifestyle related to exposure to ALAN are considered. In addition, personal susceptibility factors, including age, sex, and chronotype are addressed.

RESULTS AND DISCUSSION

Shift workers and jet lag

Night shift work has become a common occupation: approximately 15% to 18% of all workers in Europe and the United States work with night shift schedules [39], and 15% to 30% in Korea [40]. Exposure levels of ALAN to shift workers at night were estimated to be from 50 lx to 100 lx, and sometimes exceeding to 200 lx [20]. Exposure to ALAN at night leads to melatonin suppression, changes in clock gene expression, and misalignment of sleep [19].

Nocturnal melatonin suppression for different light spectra was plotted based on a mathematical model by Rea et al. [41], who were among the panel members participating in the National Toxicology Program's workshop [19]. The plot showed acute suppression of melatonin following 1 hour exposure of the retina to light, with more efficient suppression induced by daylight than incandescent light [19]. Artificial light inhibits the melatonin levels by about 5% by 30 lx exposure, 15% by 100 lx, 35% by 300 lx, and 55% by 1,000 lx. Maximum suppression was 70%, following exposure to over 10,000 lx.

Night shift nurses showed significantly lower levels of the melatonin metabolite urinary 6-sulfatoxymelatonin (aMT6s) than day-shift nurses when measured at waking time. However, night shift workers did not show peak melatonin levels while sleeping during the day [42]. The peak melatonin levels occurred during the night among nurses working rotating shifts, and melatonin levels were not different between night and day shift nurses when the nurses experienced ALAN levels below 80 lx [43]. A reduction in the suppression of melatonin was found among night shift workers, from 40.6% down to 22.9%, as the number of recent night shifts increased, which suggests a phase shift or adaptation to night work [20,44]. Papantoniou et al. [44] also reported that the peak level of melatonin of night shift workers occurred 3 hours later than day-shift workers, and the greater the number of consecutive nights worked, the greater the reduction in aMT6s concentration. Rotating-shift workers also displayed no differences in melatonin levels between night shift and day/evening shift workers, with a possible partial phase shift in their melatonin rhythms [45]. Better health and sleep pattern index scores were reported by air traffic control specialists who preferred rotating schedules and who did not work night shifts than by shift workers [46].

In today's society, the two most common causes of circadian disruption are jet lag and shift work [38]. The changing of light-dark cycles results in circadian misalignment because the light signal is recognized instantaneously by a master pacemaker, the SCN, but peripheral clocks of major organ systems need time to synchronize to new cycles. Shift workers go through a slow adaptation over the course of the week that results in a low nighttime melatonin amplitude [20]. Similarly, humans flying across different time zones also need re-entrainment to a new light-dark cycle, and may suffer "jet lag." Re-entrainment rates are reported to be around 90 min per day for delayed phase shifts and 60 min per day for advanced phase shifts [47,48]. It takes about 8 days for re-entrainment in the case of a 8 hour advanced phase shift, and 5 days for the same length hours of delayed phase shift, based on a computational model of the mammalian circadian clock [49-51].

These findings show that ALAN exposure in shift workers may be highly variable according to work-rotation schedules. A recent cohort study showed no increase in the risk of breast cancer among shift workers compared to the general population, in spite of a significant trend of increased breast cancer cases with average hours of night-work per week [52]. Further studies are needed to determine whether there is an increase of breast cancer in the general population linked to the increased use of electronic devices or a decrease of breast cancer in shift workers given preventive measures, including the rotation of shift schedules. One other possibility may be a decrease in susceptible workers among the shift-workers, because those who are susceptible do not select shift jobs, or quit early.

About 5% to 10% of shift workers complain of sleep or gastrointestinal disturbance. This is called "shift work disorder" and is similar to the symptoms of jet lag [53]. Only some shift-workers experience "shift work disorder," indicating that some shift-workers may be at a greater risk for adverse outcomes related to shift work [38]. Factors predisposing people to poor adaptation to shift-work include shift schedule, age, gender, chronotype [54-56], physiology [57-59] and genetic differences [60-65]. Increased drowsiness was seen due to sleep deprivation from ALAN which in turn leads to risk of traffic accidents [66]. And sleep deprivation also affects neuroimmune-endocrine axis, which plays an important role in regulating of cell proliferation and immune protection, including the production of cytokines [67-70].

Evaluating the effects of ALAN on circadian disruption in shift-workers requires careful and complex light exposure assessment, including the intensity and spectrum of the lights, as well as the duration of exposure during both day and night, with a rotating shift schedule. More important considerations in this type of study regard the selection of control subjects, who are already exposed to ALAN in daily life. Personal susceptibility and modifying factors should be included for evaluating the risk of ALAN for shift-workers. However, this information can only be obtained from small-subject studies. Studying a large number of subjects, would need the development of surrogate markers based on light exposure and related behaviors at day and night, for both shift workers and the general population.

ALAN exposure in the general population

Exposure to ALAN in the home is significantly associated with both subjective and objective sleep problems in the elderly population [71], while outdoor ALAN is associated with altered sleep behavior in both the general [72] and in elderly [73] population. It has also been shown to be a risk factor for weight gain and the development of obesity in women [74] and general population [75]. Exposure to light at night during sleep, including dim light, may be associated with these sleep and obesity problems, because

dim light exposure increases the frequency of arousal, and the amount of shallow and REM sleep [12], by disturbing cerebral hemodynamics via the endothelial and autonomic systems, without cortical involvement [76]. A decrease of brain activation while working is also reported after sleeping under 10 lx light [13]. ALAN also affects learning and memory impairment [77] with increase of neurodegenerataion in Alzheimer's drosophila model [78].

Bright light exposure before bedtime can cause a circadian rhythm shift of cortisol and induces bipolar disorder associated genes [79]. And increase in oxidative stress was found by bright light exposure before bedtime [80] with impaired response inhibition following morning, when evaluated by near-infrared spectroscopy [81]. Evening bright light induces robust melatonin suppression in preschool-age children [36,82]. Room light exposure before bedtime also suppresses melatonin onset and shortens melatonin duration in healthy volunteers [83].

Indoor and outdoor ALAN should be measured together with space-time information to evaluate ALAN exposure in the general population, especially in children. However, it is not possible to gather individual information on space-time ALAN exposure, both indoors and outdoors, for a community based cancer study. Kloog et al. [25,84,85] used satellite photometry or self-reports of bedroom brightness for a breast cancer study. Several subsequent studies found a significant association between breast cancer and satellite ALAN levels [26,27,86]. However, critical studies have shown that satellite photometry is not correlated with measured bedroom light levels in the evening or night [28,29] and has only a weak correlation with outdoor light levels [28]. Satellite photometry did not provide enough variability to evaluate the association between melatonin and outdoor ALAN levels [87]. Another problem for satellite-measured LAN being used as proxy for ALAN exposure in the general population is the difference of peak wavelength. In satellite data, the peak wavelength is close to 555 nm for visual acuity, rather than the 460 nm spectral sensitivity of the circadian system [88].

Although satellite photometry is not a good surrogate for ALAN exposure in the general population, it may offer an effective representation for the circadian-disrupting effects of urban life. Most people in modern societies live in a built-up environment, which induces circadian disruption because of the absence of suitable light during the day and the presence of light at night, in other words, "dim, extended, aperiodic light exposure" [20]. For this reason, satellite-measured ALAN may be associated with the integrated conditions of urban life, affecting circadian rhythms by low light exposure in the day and high light exposure at night, including room lighting, outdoor lighting and the use of electronic devices. This study may support this hypothesis, because breast cancer risk is associated with satellite photometry, rather than indoor, questionnaire-based ALAN data [89].

Circadian disruption from electronic devices

Human ALAN exposure has been extended from room and outdoor lighting to the light-emitting screens of many electronic devices. Light from electronic devices can suppress melatonin secretion [90-92], and affect sleep physiology and sleepiness [90,93,94], cognitive performance [95], and mood [96].

A study involving young volunteers demonstrated that exposure to computer screens for 2 hours in the evening significantly disrupted sleep, biological rhythms, and cognitive performance, irrespective of light intensity [34]. Exposure to light-emitting diodes (LED) computer screens has a larger impact than non-LED screen [95]. The peak emission of LEDs is in the blue light range, and they emit twice as much blue light as non-LED display screens. Therefore, exposure to LED screens has a larger effect on the biological clock than white incandescent and compact fluorescent bulbs [37] and may cause photoreceptor damage [97].

Comparing the evening use of smartphones with either blue light-suppression devices or conventional LED displays, use of blue light LED smartphones may negatively influence sleep without significant changes in serum melatonin and cortisol levels [98]. Wearing goggles that block blue light when using a tablet for two hours has been shown to result in higher melatonin levels [92].

The evaluation of ALAN exposure from electronic devices should consider light intensity, including blue light, time of day, and duration of usage. However, it is also important to note that there are a wide range of electronic devices, including televisions, consoles, computers and cell phones. Adolescent exposure to ALAN through the use of electronic devices is not easily distinguishable from other health-risk behaviors, such as media overuse and internet addiction [37]. Late-night cell phone use by adolescents has been associated with a reduction in sleep quality [99]. In the United States, about 74% of adolescents have internet access at home [100] and excessive mobile phone/internet usage may also lead to sleep disturbances to adolescents [101-104] and adults [105]. Overuse of electronic media is also associated with sedentary behavior at home [106], which presents a cardio-metabolic risk [107]. It is necessary to develop an average mixed-ALAN exposure index, by use of each type electronic device, to estimate the ALAN exposure based on the questionnaire study.

Personal susceptibility

Acute melatonin suppression by ALAN is influenced by light exposure during the day, inter-individual sensitivity, chronotype, age, and photic history [108-110]. Individual differences in the response of light may be related to individual differences in prior light exposure and/or genetic differences [111]. There is a large inter-individual variation in response to light intensity with highly sensitive individuals even responding to 30 lux exposure [112].

Chronotype has an independent effect to melatonin rhythms affected by rotating-shift work [113]. Associations between chronotype and obesity showed mixed results [114]. Of the 5 articles exploring this link, 3 found a positive association between evening chronotype shift workers and obesity, while 2 studies did not support this relationship. A recent review only addressed a limited number of studies into chronotype and nutrition, and further research is needed [115].

The sensitivity of adolescents to ALAN may lead to sleep misalignment with poor sleep quality, and this should be considered a matter of public health [116]. Melatonin levels under standard room lighting conditions (120−140 lx) was suppressed to a higher degree in children than in adults (51% vs. 26% inhibition, respectively [117]. Increased sensitivity to evening light was found among pre/mid puberty adolescents compared to their late/postpubertal counterparts [118]. Circadian rhythms undergo a gradual loss of amplitude with ageing, and older people generally suffer from less sleep and poorer sleep efficiency [119,120]. However, young adults appeared more vulnerable to chronic sleep deficiency than older adults [121]. This result suggest that exposure to ALAN for young adults should be a cause of concern.

Men show a strong response to blue light in the late evening, even at very low light levels, compared to women [122]. However, female health is known to be susceptible to the impact of desynchronizing work schedules [123] and nighttime impairment in cognitive performance is greater in women than in men [124]. Sex differences in SCN electrical activity suggests that female might be able to phase shift more readily than males, thus resetting to environmental cues [125]. Disruption of circadian rhythms and increase of oxidative stress were more commonly found in female volunteers than in males in the study of bright exposure before bedtime [80].

Selecting or classifying susceptible populations is very important for identifying health risks from any hazard, because the susceptible population may have a different risk to the same exposure compared to the general population. Age and sex are very important modifying variables in relation to ALAN exposure, and are easy to measure by questionnaire. Chronotype can also can be determined by questionnaire, however the high sensitivity to evening light exposure would require further studies for proper evaluation.

CONCLUSION

To improve the assessment of ALAN exposure as a circadian disruptor, it is necessary to use wearable monitoring devices that measure light intensity in conjunction with the time of day and eating and sleeping behavior. The development of a questionnaire to assess light exposure, including social life and activities during the day and night, is also required [19]. For the evaluation of the health risks caused by ALAN exposure in a large group of subjects, it is necessary to develop surrogate markers to represent ALAN exposure and related behaviors, including shift work, room lighting, outdoor lighting, and the use of electronic devices during the day and night. To develop parameters of risk assessment based on exposure scenario methodology, we need to perform more experimental studies, including animal and human intervention studies as well as small cohort studies, for detailed monitoring of ALAN exposure from various lighting sources, including the use of personal electronic devices.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Eunil Lee: participated in the conceptualization and design of the study and paper collection, and drafted the paper. Mari Kim: participated in design of the study, review and editing drafts of the paper with writing some of the paper.

ORCID iD

Eunil Lee
https://orcid.org/0000-0003-1524-5046

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