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Review

Light at night as an environmental endocrine disruptor

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ABSTRACT

Environmental endocrine disruptors (EEDs) are often consequences of human activity; however, the effects of EEDs are not limited to humans. A primary focus over the past ~30 years has been on chemical EEDs, but the repercussions of non-chemical EEDs, such as artificial light at night (LAN), are of increasing interest. The sensitivity of the circadian system to light and the influence of circadian organization on overall physiology and behavior make the system a target for disruption with widespread effects. Indeed, there is increasing evidence for a role of LAN in human health, including disruption of circadian regulation and melatonin signaling, metabolic dysregulation, cancer risk, and disruption of other hormonally-driven systems. These effects are not limited to humans; domesticated animals as well as wildlife are also exposed to LAN, and at risk for disrupted circadian rhythms. Here, we review data that support the role of LAN as an endocrine disruptor in humans to be considered in treatments and lifestyle suggestions. We also present the effects of LAN in other animals, and discuss the potential for ecosystem-wide effects of artificial LAN. This can inform decisions in agricultural practices and urban lighting decisions to avoid unintended outcomes.

1. Introduction

Industrialization and urbanization have been beneficial for the prosperity and health of people, but have also introduced novel threats to wildlife and humans. Environmental endocrine disruptors (EEDs), which alter hormone homeostasis often to the detriment of organisms, are one consequence of human activity. EEDs are a growing concern over the past ~30 years. Although primary focus has been directed to the effects of chemicals found in plasticizers, pharmaceuticals, and pesticides, non-chemical sources such as light at night (LAN) can also interfere with the endocrine system. Low levels of LAN are nearly ubiquitous in the modern world [1,2]. Because evolution of life has occurred under dark nights over millions of years, and animals have only been exposed to artificial LAN for about 100 years, it is not surprising to discover that LAN likely perturbs circadian organization.

The daily light-dark cycles produced by the earth's rotation are a central influence over organismal behavior. The most salient cyclic behavior is sleep, but many other behavioral and physiological processes follow a daily cyclic pattern as well. Daylight is essential for regulating daily activity patterns in many animals; some animals are active at night, while it is beneficial to be active during the day for others. In addition, core body temperature also follows a daily rhythm in endotherms [3]. Virtually all life has internalized the environmental light-dark cycles in the form of circadian rhythms. Circadian rhythms are endogenous biological rhythms with periods of about 24 h. Circadian rhythms persist in the absence of environmental cues [4]; however, organisms use environmental cues, such as light, to entrain their circadian rhythms precisely to the 24-hour solar day [5].

Entraining circadian rhythms to the solar day allows individuals to synchronize with environmental conditions and display appropriate behaviors and physiological responses. Endogenous circadian rhythms are present in virtually all living organisms, including bacteria, plants, invertebrates, and vertebrates. Again, light is the most effective entraining agent, or *zeitgeber*. In many vertebrates, light stimulates intrinsically photosensitive retinal ganglion cells, which depolarize and synapse directly onto neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus. The master biological clock is located within the SCN where approximately 20,000 neurons maintain a transcriptional autoregulatory feedback loop. The molecular mechanism of the circadian clock has been reviewed in detail elsewhere [6]. This autoregulatory loop is the primary mechanism driving circadian rhythms; however, there is increasing evidence of additional processes, including posttranslational modifications [7] and cAMP signaling [8], that are also essential for maintenance. Time-of-day information, based on light intensity, is then relayed from the SCN to other brain regions, as well as to peripheral tissues, stimulating appropriate responses.

In vertebrates, in addition to the molecular clock, circadian rhythmicity is also influenced by the nightly secretion of melatonin from the pineal gland. Light stimulates clock gene transcription in the SCN, which sends GABAergic inhibitory signals through the paraventricular

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nucleus (PVN) of the hypothalamus. These PVN neurons then send projections through the intermediolateral cell column (IML), which stimulates norepinephrine release from the superior cervical ganglion (SCG). Norepinephrine then activates melatonin synthesis and secretion from the pineal gland [9]. In this way, light has an inhibitory effect on melatonin secretion, and the onset of dark triggers melatonin secretion. Melatonin has a negative feedback effect on clock gene transcription in the SCN, and is important for circadian rhythmicity [10,11].

The circadian clock directly induces a cyclic hormonal rhythm in endocrine tissues. Human serum cortisol concentrations, and corticosterone in many other vertebrates, fluctuate daily, with the highest concentrations in the early morning, within 30–45 min of waking in diurnal species [12,13]. Serum thyroid-stimulating hormone (TSH) follows a 24-hour profile, with a maximum between 0200 and 0400 h and a nadir between 1600 and 2000 h [14,15]. Furthermore, melatonin influences several endocrine pathways, including the stress and reproductive axes [16], and also signals to adipose tissue and influences body weight [17]. Many endocrine tissues are also innately cyclic via endogenous expression of clock genes. Therefore, disrupted circadian rhythms can have broad physiological outcomes through several pathways.

The circadian system is vulnerable to aberrant lighting outside the solar day due to its high sensitivity to light. Exposure to constant bright light can greatly disrupt or completely abolish circadian rhythms [18], but brief durations of bright light, or reduced light levels, are also disruptive. Just a brief pulse of light can transiently induce expression of *Period 1* (*Per1*), a core clock gene, and phase shift the molecular clock [19]. In Siberian hamsters, just one 30 min pulse of light during the dark phase was sufficient to activate the neurons of the SCN [20]. Furthermore, very low levels of LAN are also capable of disrupting the clock. The rhythmic expression of three essential clock genes, *Per1*, *Per2*, and *cryptochrome 2* (*Cry2*) were attenuated by exposure to just 5 lx of light [21], a level ubiquitous in urban/suburban areas. In addition, light differentially affects secretion of melatonin as a function of the time of day. In humans, peak melatonin secretion occurs between midnight and 0400 h, and exposure to light at night during this time inhibits melatonin secretion for the entire night [22,23]. Light at night, therefore, can be disruptive at multiple levels of circadian circuitry.

Whereas bright levels of light at night are experienced occasionally, low levels of light at night are fairly ubiquitous. Forty lux of light is the approximate level of light commonly emitted from electronic devices including cellular phones held approximately 30 cm from the face, and therefore is a common exposure level for humans. Five lux of light is approximately 5 times brighter than moonlight and is comparable to levels of light pollution around urban centers [2]; thus, 5 or more lux is a common level of exposure for humans and many other animals (Fig. 1). Light can directly alter endocrine signaling from circadian dysregulation or disrupted or dampened melatonin production, or indirectly through inflammatory responses or elevated circulating stress hormones. We will discuss these mechanisms in relation to the consequences of LAN exposure below.

This review will describe many epidemiological and basic science studies investigating the role of LAN in circadian disruption and physiological outcomes. Epidemiological and clinical results refer to diurnal humans, whereas most basic science research is conducted in nocturnal rodents. Diurnal (day-active) and nocturnal (night-active) species' locomotor activity profiles are opposite from one another,

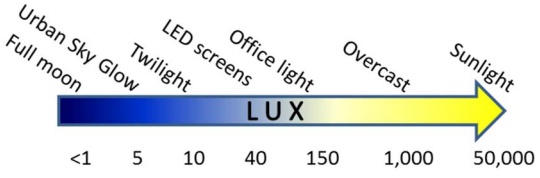

Fig. 1. Approximate levels of light emission from common sources.

however, the underlying mechanisms of the molecular clock are highly conserved between diurnal and nocturnal species. The structural and molecular components of the SCN are similar; however, some downstream components of the system can vary between nocturnal and diurnal animals [24]. Importantly, the effects of light on entraining circadian rhythms, as well as the photic inhibition of melatonin, are highly similar between nocturnal and diurnal animals. In addition, many of the behavioral effects of circadian dysregulation are similar between diurnal and nocturnal rodents [25,26]. LAN often disrupts sleep in diurnal animals, and thus the resulting effects cannot be attributed to circadian dysregulation independently from sleep disturbances. Therefore, using nocturnal animals in studies of LAN allows the isolation of the effects of circadian dysregulation in the absence of alterations in sleep.

2. Effects of light at night on human health

The broad endocrine effects that result from LAN exposure can have many physiological outcomes to human health. Most studies investigate the effects of LAN on disruption of metabolic processes, resulting in obesity or diabetes, and cancer incidence. Additionally, altered hormonal signaling from LAN can result in elevated stress and reproductive abnormalities. In this section we will discuss each of these physiological outcomes in relation to human health.

2.1. Obesity and metabolic disorders

Obesity has become an epidemic in our modern world, with global obesity rates in adults nearly double what they were in 1980. More than 2 in 3 adults and 1 in 6 children and adolescents are considered obese in the United States [27]. Obesity is a leading risk factor for type 2 diabetes, heart disease, high blood pressure, stroke, fatty liver disease, osteoarthritis, and some types of cancers. An estimate of the economic cost of obesity in the U.S. in 2008 was approximately $147 billion/year [28]. Thus, obesity is a major detriment to both human health and the economy.

A notable trend in night shift workers is an overall higher incidence of obesity [29] and metabolic syndrome compared with individuals who do not participate in night shift work. In a simulated study of night shift work in humans, more than one night of shift work reduced the total daily energy expenditure by ~3%, indicating metabolic dysregulation [30]. Furthermore, Danish nurses who work night shifts have a higher risk of diabetes compared with those working day shifts [31]. Activity during typical sleeping hours, and conversely sleeping during waking hours, presents an assortment of behavioral alterations that could lead to weight gain, including the time of day food is consumed, the type of food consumed, and changes in overall activity level. However, an additional factor of growing interest is the aberrant exposure to light during natural sleeping hours. A recent population-level study correlates global levels of LAN with obesity rates. In this model, LAN explains 70% of the variation in prevalence rates of overweight and obese individuals, while controlling for other lifestyle characteristics, such as food consumption [32]. In addition, a study investigating type 2 diabetes risk in night shift workers that separates early and late chronotypes, reported that individuals with a late chronotype had the highest diabetes risk when working daytime schedules, and conversely, individuals with an early chronotype had the highest risk when working night shifts [33]. These data support a role for circadian disruption in the metabolic dysregulation associated with shift work.

Animal models of shift work also support the idea that circadian misalignment contributes to metabolic dysregulation. Several rodent studies have been conducted to elaborate on LAN as a contributing factor in metabolic dysregulation. Mice exposed to lighting regimes mimicking shift work had impaired glucose tolerance [34]. Rats exposed to LAN also had impaired glucose tolerance, and the effect was time- intensity- and wavelength-dependent [35]. A number of studies