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Review article

Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption

Yvan Touitou [a,*], Alain Reinberg [a], David Touitou [b]

[a] Fondation Ophtalmologique A. de Rothschild, Unité de Chronobiologie, 25 rue Manin, 75019 Paris, France
[b] UHSA - Groupe Hospitalier Paul Guiraud, 54, avenue de la République, 94806 Villejuif, France

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ABSTRACT

Exposure to Artificial Light At Night (ALAN) results in a disruption of the circadian system, which is deleterious to health. In industrialized countries, 75% of the total workforce is estimated to have been involved in shift work and night work. Epidemiologic studies, mainly of nurses, have revealed an association between sustained night work and a 50–100% higher incidence of breast cancer. The potential and multifactorial mechanisms of the effects include the suppression of melatonin secretion by ALAN, sleep deprivation, and circadian disruption.

Shift and/or night work generally decreases the time spent sleeping, and it disrupts the circadian time structure. In the long run, this desynchronization is detrimental to health, as underscored by a large number of epidemiological studies that have uncovered elevated rates of several diseases, including cancer, diabetes, cardiovascular risks, obesity, mood disorders and age-related macular degeneration. It amounts to a public health issue in the light of the very substantial number of individuals involved. The IARC has classified shift work in group 2A of "probable carcinogens to humans" since "they involve a circadian disorganization". Countermeasures to the effects of ALAN, such as melatonin, bright light, or psychotropic drugs, have been proposed as a means to combat circadian clock disruption and improve adaptation to shift and night work. We review the evidence for the ALAN impacts on health. Furthermore, we highlight the importance of an in-depth mechanistic understanding to combat the detrimental properties of exposure to ALAN and develop strategies of prevention.

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* Corresponding author.
E-mail address: yvan.touitou@chronobiology.fr (Y. Touitou).

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1. Introduction: The internal clock and the circadian system

Circadian rhythms are endogenous rhythms with a periodicity of approximately 24 h (24 ± 4 h). They are widespread and regulate most, if not all, of the major physiological systems in mammals. Circadian rhythms are unquestionably the most studied in the literature though other periods exist that range from milliseconds (i.e. ultradian rhythms, for which the period extends from milliseconds to 20 h) to a year (i.e. infradian rhythms, for which the period extends from 28 h to a year) [1]. Circadian rhythms are dependent on an internal clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. Each of the paired suprachiasmatic nuclei is composed of a heterogeneous group of about 10,000 interconnected neurons that give rise to circadian rhythms through specific neuronal gene expression patterns and by the rate at which they fire action potentials.

In addition to this, peripheral clocks have been identified in numerous tissues such as cerebral cortices [2,3], liver, kidney, heart, skin, and the retina, and these are capable of acting in an autonomous manner [4,5]. The SCN subsequently synchronizes peripheral clocks with each other and thus aligns the entire circadian system to the external light-dark cycle. The possible interrelationships between the main clock located in the SCN and the peripheral clocks in other tissues are actively being investigated [6]. The SCN serves in part as a clock, synchronizing other clocks in peripheral tissues, and in part directly orchestrates circadian physiology [7].

The SCN generates circadian rhythms by means of a transcriptional-translational feedback loop. In short, the mechanism is formed by the basic helix-loop-helix (bHLH) Per-Arnt-Sim (PAS) domain containing transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1), which activate the expression of three *Period* (*Per 1–3*) and two *Cryptochrome* (*Cry 1–2*) genes by binding to their E-box (5′-CACGTG-3′) promoter elements. The PERIOD (PER 1–3) and CRYPTOCHROME (CRY1–2) proteins rhythmically accumulate, heterodimerize, and translocate to the nucleus to suppress their own transcription by interaction with the CLOCK:BMAL1 complex. CLOCK/BMAL1 also rhythmically control the expression of nuclear receptors, such as REV-ERBα/β (reverse transcript of erythroblastosis gene) and RORα/β/γ (retinoic acid related (RAR) orphan receptor), which in turn repress and activate *Bmal1* expression, respectively, conferring amplitude and robustness to the oscillations in the molecular clockwork. From a molecular point of view, light activates the expression of several genes in SCN with different expression patterns [8].

We critically review the evidence from a large number of epidemiological studies for an association between long-term exposure to light at night (ALAN) and detrimental effects on health, such as cancer, diabetes, overweight and obesity, mood disorders, and age-related macular degeneration. Furthermore, we underline the importance of an in-depth mechanistic understanding to limit and combat the detrimental properties of exposure to light at night and develop strategies to prevent deleterious effects on health.

2. Light control of melatonin secretion

The circadian system in human beings is a complex entity that starts in the eye and that terminates in the pineal gland, which produces melatonin (5-methoxy-*N*-acetyltryptamine), a neurohormone essential for functioning of the clock. In humans, melatonin is secreted during the dark phase of the light–dark cycle. Daytime melatonin levels are hence comparatively very low. Light is considered to be the most potent circadian synchronizer for humans, although non-photic time cues, such as meal times, physical activity and social interaction, also play a part in synchronization of the circadian system. Since the period of the internal clock in humans is not exactly 24 h but close to 24.2 h [10,11] daily exposure to light allows maintain the 24 h cycle of the internal clock.

The synchronizing effect of light on the clock begins at the fetal stage in mammals through secretion of maternal melatonin [12]. While light is a key factor that controls the secretion of melatonin, it differentially