Circadian Control

Subjects: Pathology

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The disruption of circadian rhythms by environmental conditions can induce alterations in body homeostasis, from behavior to metabolism. The light:dark cycle is the most reliable environmental agent, which entrains circadian rhythms, although its credibility has decreased because of the extensive use of artificial light at night. Light pollution can compromise performance and health, but underlying mechanisms are not fully understood. Metabolism is under strong circadian control and its disruption can lead to various pathologies. Here, we address differences between physiological responses to constant light and dim light at night.

Keywords: circadian ; rhythms ; dim light at night ; chronodisruption ; locomotor activity ; behavior ; hormones ; metabolism

1. Circadian System

Physiological and behavioral processes exert circadian rhythms, which have evolved to adapt organisms to daily environmental changes, such as the light:dark (LD) cycle. Circadian rhythms are generated endogenously, and as the term circadian (latin, circa – approximately, dien – day) suggests, their period is approximately 24 h in the absence of external cues.

The main molecular machinery generating circadian rhythms is the transcriptional–translational feedback loop consisting of positive (brain and muscle ARNT-like 1- *bmal*1 and circadian locomotor output cycled kaput - *clock*) and negative (period - *per1, per2, per3* and cryptochrome - *cry1, cry2*) elements in mammals [1][2]; these components represent the core of the molecular clocks. The proteins CLOCK and BMAL1 promote the transcription of per and cry genes and are expressed during the light phase in the central oscillator. In the cytoplasm, PER and CRY proteins are degraded by casein kinase 1ε [3] and AMP-activated protein kinase [4]. When both these enzymes are saturated, PER and CRY proteins form heterodimers that are translocated into the nucleus, interact with the CLOCK–BMAL1 complex and inhibit their own transcription [5]. The cycle, from the promotion to inhibition of clock genes transcription, lasts approximately 24 h. The molecular clock also contains accessory feedback loops, such as the one containing nuclear receptors, nuclear receptor subfamily 1 group D member 1 (REV-ERB) and retinoic acid-related orphan receptors (ROR) competing to inhibit or activate the bmal1 transcription, respectively [6][7].

Since the endogenous circadian rhythms do not exactly match the 24 h solar cycle, they must be synchronized (entrained) to the environmental cycles by external cues every day. The most potent synchronizing agent, also known as zeitgeber or entraining cue, is the LD cycle that is perceived by intrinsically photosensitive retinal ganglion cells containing photopigment melanopsin [8][9]. Consequently, the retinal signals are transmitted via the retinohypothalamic tract into the central oscillator located in the suprachiasmatic nuclei (SCN) of the hypothalamus [10]. The circadian system is hierarchically organized; the central pacemaker exerts its effects on peripheral oscillators via behavioral, neuronal and hormonal signals. Peripheral organs can also be entrained by other zeitgebers, such as food intake synchronizing the liver and pancreas, and these entraining cues can be more efficient than signals from the central oscillator [11][12][13].

Light mediates its non-visual effects via the SCN but can also directly affect different brain structures, which regulate certain physiological functions. Melanopsin-expressing intrinsically photosensitive retinal ganglion cells transmit information on lighting conditions directly to different brain areas, such as intergeniculate leaflet, the lateral geniculate nucleus of the thalamus [9][14][15], habenular nucleus, nucleus accumbens [9][15][16], medial amygdala, lateral hypothalamus and ventral preoptic area [9][15]. These structures can modulate sleep, mood and cognitive functions, heart rate and glucocorticoid levels [17].

Probably the most known circadian hormonal outputs are melatonin and corticosterone (CORT), which display distinct circadian rhythmicity. Melatonin is synthesized in the pineal gland from an amino acid tryptophan, reaching its maximum during the dark phase. Therefore, melatonin is called “the hormone of darkness” [18]. The synthesis of melatonin is

controlled by the multisynaptic pathway from the SCN [19] and is highly sensitive to nocturnal light exposure [20][21]. As an internal zeitgeber, melatonin provides information about the length of the night through melatonin receptors, MT1 and MT2, which are widely distributed across the body [22]. For example, in pancreatic islets, MT1 receptors are highly expressed in the α-cells, while MT2 receptors predominate in the β-cells [23]. Pleiotropic effects of melatonin have been documented in a number of studies [22][24]. However, there are many controversial effects on metabolism, such as the improvement or worsening of glucose metabolism [25]. Melatonin receptors are also localized in the SCN [[26][27] and melatonin has been proven to feedback to this master oscillator, adjusting its phase [27][28][29]. Corticosterone is a dominant glucocorticoid in rats, and its rhythmical release is under the control of the SCN [30], peaking before the onset of the active phase to prepare the organism for the upcoming stress events throughout the day [18]. One of the very important properties of CORT is its ability to set the phase of peripheral oscillators in many tissues [31][32]. This function is supported by the presence of glucocorticoid receptors in many tissues except for the SCN [31][33].

Disruption of the molecular clockwork by environmental conditions can induce alterations in the body homeostasis, from behavior to metabolism. From the environmental cues, the LD cycle is of primary importance, since it has been very stable as life has evolved under LD conditions. However, over the last few decades, this environmental signal has lost its reliability because of the extensive use of artificial light at night [34][35]. The consequences of this new challenge on the performance and health of animals and humans are not fully understood and can be extremely important. Therefore, extensive research is needed to evaluate possible mechanisms and consequences of artificial light at night and predict the possible negative impacts on health and behavior.

During a long history, people have been used to being exposed to high-intensity sunlight (~100,000 lx) during the day [36] and low-intensity moonlight (0.1–0.3 lx) during the full moon phase on a clear night [37]. In contrast, in recent years, people have experienced much lower intensity (400–600 lx) of lighting during the day and a higher illumination of 100–300 lx in the evening due to the lighting in offices and households [38]. Moreover, light-emitting devices (e.g., tablets, smartphones, computers) providing 30–50 lx of light are used at night [39]. The negative consequences of exposure to light at inappropriate times of the day can especially be observed in long-term shift-workers, who may suffer from metabolic diseases [40][41], cardiovascular diseases [42][43] and cancer [44][45]. The detrimental effects of artificial light at night are not observed only in humans but also in other ecosystems [46][47][48]. Moreover, recently, the rate of light pollution has been increasing rapidly due to urbanization and the introduction of efficient and cost-effective light-emitting diodes that accelerate the process of light pollution. The night-time illuminance in urban areas reaches 20 lx [49][50], and even 150 lx in some places [50].

2. Differences in Responses to Constant Light and Dim Light at Night

Constant light (LL) disrupts endogenously generated circadian rhythms in physiology and behavior. Behavioral consequences of LL have usually been evaluated as rhythms in locomotor activity and consist of arrhythmia, changes in the free-running period and even “splitting the rhythm”, as shown convincingly in mice [51]. Alterations of these overt rhythms probably result from disrupted synchrony among cellular circadian oscillators localized in neurons of the SCN. Dim light at night (dLAN) disturbs a daily variability to a lesser extent than LL, and a phase-advanced or even dual rhythms were recorded in mice and rats, respectively [52][53]. Thus, it seems that dLAN does not affect the coupling of individual clocks localized in the SCN to the extent as constant light. The decoupling can relate to the intensity of dLAN and dose-dependent studies in this area are needed.

The attenuated or decoupled oscillations in SCN, due to dLAN can affect rhythmic feeding activity, which is usually limited to the active phase of the day (the night-time in nocturnal rodents). Food intake is a strong zeitgeber for peripheral tissues, especially the liver, and deregulated feeding cycles can misalign peripheral oscillators among each other and with the central oscillator [54]. After dLAN or LL exposure, the circadian timing system is not fully effective, and organisms lose their timing integrity, because physiological and behavioral rhythms are not in an appropriate phase or even eliminated. These conditions can have serious negative consequences for the brain and other body functions; it is expected to participate in the development and progress of many “diseases of civilization”, such as obesity, type 2 diabetes, cardiovascular and neural diseases and cancer. Therefore, consequences of dLAN should also be analyzed in relation to these pathologies, either in human studies or in animal models.

Changes in metabolism seem to be more profound after exposure to LL in comparison with dLAN. Both conditions can deteriorate health status and be related to the level of light contamination, but a threshold which initiates these processes has not been established yet and should be determined. It is possible that there is no single value, but a continuum, which reflects huge interindividual and interspecies differences, nocturnality/diurnality and probably also a photoperiodic history of individuals. As indicated, different levels of irradiance have been applied in experiments and these differences, together with the quality of light sources, can contribute to the high variability of obtained results. From the included studies, it is

obvious that different rhythms lose their circadian “properties” at different levels of irradiance. This may reflect a different power of how the lighting conditions induce desynchronization among SCN neurons, as well as stabilizing rhythmic inputs from peripheral organs (behavioral and physiological rhythms). Generalization on the basis of one rhythm (locomotor activity) can be oversimplifying and therefore it is necessary to evaluate additional behavioral (drinking, feeding, response to aversive stimuli) and physiological (body temperature, cardiovascular rhythms, hormonal, metabolic and immune) parameters which can feedback to the SCN and stabilize its intrinsic property and circadian output rhythms. Moreover, there is a lack of studies exploring parameters of circadian rhythm such as mesor, acrophase or amplitude after dLAN exposure, because the usually employed two time-point studies cannot reveal complex changes in rhythmicity.

Clearly, more studies are needed to understand the effects of circadian disruption and links which result in the acceleration of pathophysiological processes. This understanding is important to elucidate the role of chronodisruption induced by artificial light as an influenceable factor in the development of diseases of civilization in humans.

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