How Does the Circadian Rhythm Function in Blind People Who Have No Light Perception?

Işık Algısı Olmayan Körlerde Sirkadiyen Ritim Nasıl Çalışır?

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Abstract

Circadian rhythms in the body affect physiological functions and behaviors and therefore have important roles on health. These rhythms mainly regulate important physiological processes such as the sleep-wake cycle, autonomic activity, endocrine function and immune system. Regarding biological rhythm, the master structure is the suprachiasmatic nucleus (SCN) in the hypothalamus. Furthermore, many circadian oscillators are present in the central nervous system and peripheral body tissues. These oscillators exhibit their function under the coordination of SCN for the functional integrity of the circadian rhythms. Daily retinal light-dependent stimuli are essential for the rhythm of day and night and the synchronization of circadian clocks. In this synchronization, melatonin hormone has a major role as an endocrine factor. The expression of melatonin is regulated by light signals reaching to the SCN. In many blind people without light perception, circadian rhythm synchronization is impaired due to the inability of the SCN to receive light information. In such cases, serious sleep disorders can be seen. This condition is called non-24-Sleep-Wake Rhythm Disorder. This disorder can be treated with behavioral therapy and medial therapy. Moreover, melatonin or its agonists are used in medical treatment.

Keywords Circadian rhythm, Blind, Light, Melatonin, Biological clocks

Özet

Vücutta, fizyolojik fonksiyonlar ve davranışlara etki eden ve dolayısıyla sağlık üzerinde önemli etkileri olan 24 saatlik sirkadiyen ritimler bulunmaktadır. Bu ritimler başlıca uyku-uyanıklık döngüsü, otonomik aktivite, endokrin fonksiyon ve immün sistem gibi önemli fizyolojik fonksiyonları düzenlemektedir. Biyolojik ritimle ilgili olarak primer yapı hipotalamustaki suprakiyazmatik nükleustur (SCN). Bununla birlikte merkezi sinir sisteminde ve periferal vücut dokularında birçok sirkadiyen osilatörler mevcuttur. Bu osilatörler sirkadiyen ritmin fonksiyonel bütünlüğü için SCN'nin koordinatörlüğünde çalışmaktadır. Günlük retinal ışığa bağlı uyarılar, gece ve gündüz ritmi ve sirkadiyen saatlerin senkronizasyonu için gereklidir. Bu senkranizasyonda endokrin faktör olarak melatonin hormonu önemli bir role sahiptir. Melatoninin salgılanması SCN'ye ulaşan ışık sinyalleri tarafından düzenlenmektedir. Işık algısı olmayan birçok kör bireyde, SCN'nin ışık bilgisini alamamasına bağlı olarak sirkadiyen ritim senkronizasyonu bozulmaktadır. Bu gibi durumlarda ciddi düzeyde uyku bozuklukları görülebilmektedir. Bu durum non-24 Uyku-Uyanma Ritim Bozukluğu olarak adlandırılmaktadır. Bu bozukluğun tedavisi davranışsal terapi ve medikal tedavi ile yapılabilmektedir. Medikal tedavide melatonin veya onun agonistleri kullanılmaktadır.

Anahtar Kelimeler Sirkadiyen ritim, Körlük, Işık, Melatonin, Biyolojik saat

INTRODUCTION

Time-dependent cyclical changes can be observed in organisms ranging from single-celled organisms to mammals. These cyclical events are called as biological rhythms. Considering the cycle times, these biological rhythms are divided into different groups such as ultradian (less than 24 hours, more than one cycle per day), circadian (daily), infradian (a rhythm longer than 24 hours, lasting days, weeks or months) and circannual (annual) rhythms. The word 'circadian' is derived from the Latin words 'circa' (about), 'diem' (day). In 1729, De Mairan pointed out the existence of an endogenous clock in living things based on the movement of the leaves of the Mimosa pudica plant in a 24-hour time period, however, the term circadian was coined in the 1950s (1).

Rotation of the earth around the sun, which takes approximately 24 hours, is the most important factor affecting the lives of organisms in the biosphere. A full rotation completed in 24 hours causes changes called circadian rhythm and during the night and day periods; it shapes the physiological and behavioral functions of organisms (2). In constant environmental conditions, the rhythm can regulate its own function. It has been stated that the rhythm repeats itself every 23.5 hours in mice, which is applied constant darkness for 24 hours and isolated from other stimuli, and every 24.8 hours in humans. A full cycle of rhythmic activities within this time frame is defined as a period. However, the periods may vary according to the species. The cycle of starting and ending time of the rhythm at certain times is carried out by biological clocks called 'circadian timers' (3).

Daily retinal light-dependent stimuli are required for the synchronization of the circadian clocks and the rhythm of day and night period. As a neuroendocrine factor, melatonin is important in this synchronization. Melatonin secretion is regulated by light signals reaching to the suprachiasmatic nucleus (SCN). In many blind people with no light perception, the circadian rhythm synchronization is disrupted due to the SCN's inability to receive light information. In such cases, serious sleep disorders can be observed. The severity of sleep disturbance and other accompanying complaints may vary depending on whether individuals are congenitally blind or blind after a certain age. The same phenomenon is true if blindness occurs in childhood or adulthood. Moreover, in cases where blindness occurs due to diseases such as diabetes, hypertension or retinitis pigmentosa, other symptoms associated with these diseases can be observed frequently, in addition to sleep disorders. In our review, changes in circadian rhythm physiology in individuals with no light perception are presented. Moreover, behavioral and medical therapies that can be applied in such situations are discussed as well.

THE FUNCTIONATING PRINCIPLES OF BIOLOGICAL CLOCKS

All organisms, from the simplest to the most complex, have their own unique internal clocks with an excellent function. The clock, which is unique to mammals, is actually a system that can work on itself and can regulate its own activity. However, just like the winding of the mainspring in a mechanical watch, it must be stimulated by environmental effects. The factors that establish the clock in the organism are defined as "zeitgeber", that is, "time-givers or synchronizer" (4). Light is the most important zeitgeber. Light stimuli activate the melanopsin photopigments in the retina and this stimulation performs the time setting of the internal clock (5). Similar to a mechanical clock, winding the mainspring starts the spinning of the wheels. Thus, the clock spring, which will activate the other component, is compressed. The spring begins to relax cyclically and the interlocking gears continue to rotate precisely and the spring continues to discharge at the same rate. In mammals, the main wheel begins to turn with the light stimuli reaching to the SCN. The turning of the main circuit provides the expression of clock-related transcription factors BMAL1 and CLOCK and moves the central wheel connected to this circuitry. This wheel is the promoter region of the clock-related Per and Cry genes. With the activation of the promoter, the second, minute and hour circuits connected to the same vertical axis begin to spin.

These rings belong to the clock genes. In mammals, there are many clock-related genes distributed throughout the body. One full turn of the seconds wheel turns a single cog of the minute wheel. One full revolution of the minute hand gear rotates a single gear of the clock wheel. One full rotation of the scorpion gear on the watch dial equals a 12-hour time period, so two complete revolutions give a 24-hour period. As with a mechanical clock, the biological clock stops when the spring is fully discharged. The biological clock can keep its rhythm even when it is close to stopping (6,7).

PHYSIOLOGICAL SIGNIFICANCE OF SCN

The SCN, a double structure located in the upper part of the optic chiasm in the hypothalamus, is also called the master clock. It is the primary circadian pacemaker in mammals (8). The structure of the SCN consists of neurons and glial cells. It is thought that glial cells have the quality to give this structure an executive feature. Not all of these cells show rhythmic features. However, it is suggested that the periods of cells with rhythmic features may be different. The SCN is specialized for stimulus transmission and coordination with a layering of core and cortex. While the core part is responsible for the formation of rhythm, the cortex part is responsible for sending rhythm-related stimuli to other oscillators and thus ensuring coordination. Preservation of the structural and functional integrity of the core area of the SCN is important for body temperature, heart rate, melatonin and cortisol levels, and the rhythm of locomotor activity (9).

MOLECULAR PHYSIOLOGY OF THE CIRCADIAN RHYTHM

The mammalian circadian clock is a complex structure formed by the combination of feedback and feedforward mechanisms. It is thought that a significant portion of the genes associated with the biological clock have been identified, however the full mechanism is not clear yet. These genes structurally have a helix-loop-helix structure. Defined members of transcription factors consist of Clock, Bmal1 (brain and muscle Arnt-like protein 1), three Period genes (Per1, Per2 and Per3), two Cryptochrome genes (Cry1 and Cry2), three orphan nuclear receptors Nr1d1 (nuclear receptor family subclass group 1), from RevErb α and Ror-α (8,10,11). The transcriptional/translational feedback loops (TTFL) that generate spontaneous oscillations of gene and protein expression with a circadian period are the basis of the SCN's circadian timekeeping system. When the Per and Cry genes are expressed, the transcription factors CLOCK and BMAL1 operate on the E-box regulatory regions to start this cycle. Subsequently, during the daylight period of the circadian rhythm, the PER and CRY proteins build up and travel into the nucleus as sizable multimeric complexes, where they eventually reach a level where they repress their own transcription as well as the transcription of other CLOCK/BMAL1-activated genes. Following this, existing inhibitory complexes gradually degrade during the circadian rhythm's nocturnal period, and eventually Per and Cry transcription regenerates about 24 hours after it was first started. In order to modulate Bmal1 expression and improve stability, amplitude, and precision, other TTFL components, such as the E-box-driven transcriptional regulators ROR and REV-ERB (retinoic acid-associated orphan nuclear receptors), feed into the core oscillation via RRE elements (D-box and Rev-ErbA/ROR response elements) (12).

Besides the Per and Cry genes, CLOCK/BMAL1 also activates the transcription of the retinoic acid-associated orphan nuclear receptors RevErb-α and Ror-α. While this activation is suppressed by RevErb-α, it is activated by Ror-α (13). Other genes controlled by the circadian clock can also be regulated by the molecular clock, as they contain an E box in their promoter region (14). Regulation of clock genes with nuclear receptors such as RevErb-α, Ror-α, PPAR-α (Peroxisome proliferator-activated receptor-alpha), especially melatonin and other hormones, nutritional signals (fatty acids and derivatives), cellular redox status (NADH/NAD ratio, oxidized and reduced forms of nicotinamide adenine dinucleotide) provides rhythmic activity (15).

THE ROLE OF THE LIGHT IN REGULATING THE CIRCADIAN RHYTHM

Light is the most important factor that effects the circadian rhythm (Figure 1). Depending on the day/night cycle, the light level that affects the rhythm is independent of the endogenous clock. Since the light stimulus masks the endogenous rhythm, this interaction is defined as the masking effect of light. Although the SCN is only excited by light, peripheral oscillators are not entirely light dependent. Peripheral clocks are coordinated by light information from the SCN (1). Since the rhythm of light information from the retina can affect the SCN, the retina is considered as an oscillator (16). Photic signals from the retina reach the SCN directly via a neuronal pathway called the "retino-hipothalamic tract" (RHT) (5). A study in mice suggested that photic signals could reach the SCN even when rod and cone photoreceptors in the retina were eliminated. In the stated study, it was also determined that low levels of melanopsin photopigment were secreted from retinal cells. These pigments mediate the stimulation of the SCN by the light stimulus (17). It is suggested that melanopsin is not equally sensitive to light, further it is more sensitive to blue light (18). The primary neurotransmitter in RHT is glutamate. This mediator binds to the N-methyl-D-aspartate (NMDA) receptor in the SCN, increasing the intracellular Ca2+ levels, thereby activating mitogen-activated protein kinase (MAPK). With the activation of this kinase, the cyclic AMP-response element binding protein (CREB) is phosphorylated and activated. The promoter regions of circadian genes contain binding sites for CREB. In response to light, CREB and MAPK activity are regulated by the SCN. This master oscillator also delivers the light signals to the surrounding light-excited oscillators (19).

MELATONIN SYNTHESIS

Another input signal that tells the body time is the melatonin hormone. Since melatonin production is affected by the SCN, this also acts as the output signals. Melatonin secretion has a nocturnal rhythm. The extensions of the neurons in the SCN link directly down to the brain stem and reach the upper part of the thoracic cord without making synaptic connections with any cells. After synapses with cells in this area, these neuronal extensions reach the pineal gland through a series of chain pathways and terminate in the pinealocytes which are responsible for melatonin production. Neuronal signals originating from the SCN in the dark stimulate the secretion of noradrenaline from the axonal terminals around the pinealocytes. This mediator activates the β-adrenergic receptor in pinealocytes and melatonin synthesis begins (20,21).

The blood melatonin concentration is approximately 3-10 times higher in the night period than during the daytime. Melatonin secretion begins at 21:00-22:00 in the evening, reaches its maximum level at 02:00-03:00 am and ends at 07:00-09:00 pm in the morning (22,23). Light stimulation at night tenders false information to the SCN as if the daytime period is extended. According to this information, melatonin synthesis in pinealocytes is stopped by the SCN. The untimely decrease in circulating levels causes disruption in the melatonin cycle (24). Different light stimuli such as lighting, which cause changes in the natural light signal, cause dysregulation in the rhythm of melatonin. As a result of this situation, false circadian information is transmitted to many body cells that interact with melatonin.

The mammalian retina contains cones, rods, and retinal ganglion cells that express the photopigment melanopsin (mRGCs), which plays an important role in circadian photo-continuity. The mRGC projections extend along the dorsolateral geniculate nucleus to the pretectal nucleus of the midbrain and contribute to the formation of the pupillomotor light reflex. The photoreceptors provide circadian photocontinuity at different light intensities (25). The mRGCs can survive with complete loss of rods and cones in people with severe retinal degeneration and may contribute to the assessment of brightness and support of visual function (26).

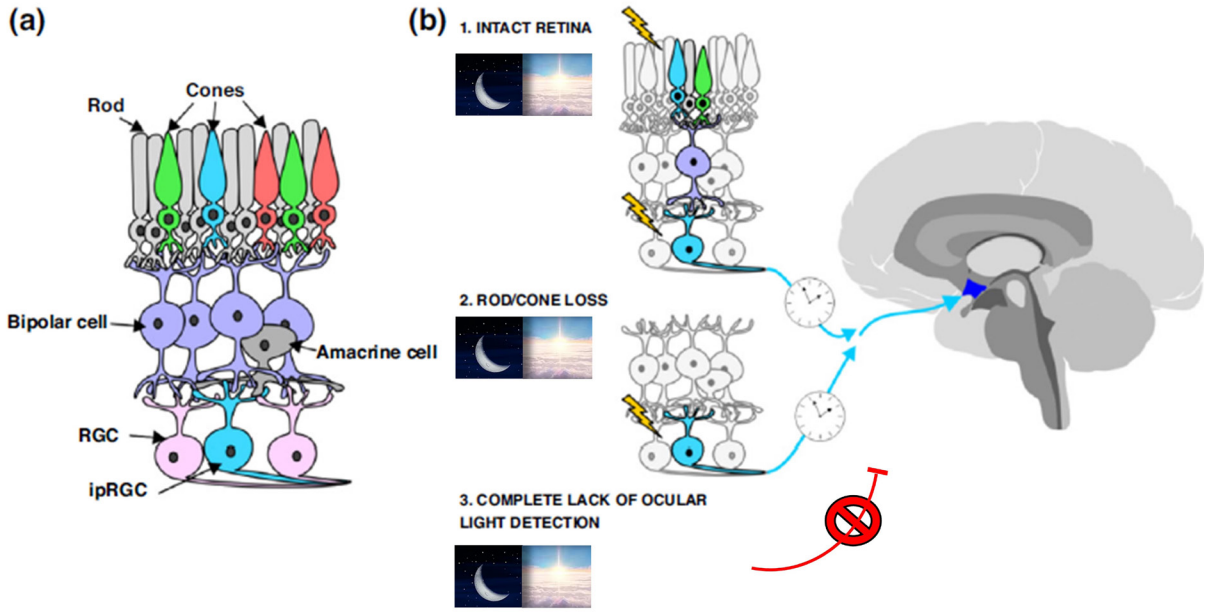

Figure 1. A schematic of photoreceptors contributing to photoentrainment in mammals.
(a) Human retinal photoreceptors include retinal rod and cone photoreceptors and inner retinal photosensitive retinal ganglion cells (ipRGCs). IpRGCs are directly photosensitive thanks to their melanopsin expression. However, bipolar and amacrine cells also receive synoptically directed rod/cone inputs through retinal interneurons. (b) Day-night changes in light intensity are encoded in the activity of ipRGCs. In an intact visual system (panel 1), rods and cone responses are transmitted to ipRGCs via retinal interneurons. Melanopsin-driven responses also contribute to ipRGC light-evoked activity. In the absence of rods/cones (such as retinal degeneration, panel 2), melanopsin can still maintain light-evoked activity in ipRGCs. IpRGC axons (shown by blue arrows) dominate the input of the master circadian clock within the suprachiasmatic nucleus of the hypothalamus (marked in dark blue in the human brain in the figure), driving its activity with external day-night cycles in radiation. When there is a complete lack of ocular light perception (panel 3), no visual information is transmitted to the suprachiasmatic nucleus (Modified from ref. 4).

CIRCADIAN RHYTHM STATUS IN THE BLIND PEOPLE WITH NO LIGHT PERCEPTION

The SCN, which receives light information, also receives data from different parts of the brain that do not contain light information through neuropeptide Y, including intergeniculate leaflet and serotonergic projections (14,27). Circadian clocks in the body are synchronized by the autonomic nervous system, accompanied by body secretory and neuronal pathways. Melatonin, adrenocorticotropic hormone (ACTH), and glucocorticoids together contribute to the synchronization of physiological functions by working within the nervous system through a feedback mechanism. Mealtime and various systemic cues, which do not contain light information, also strengthen the internal connections to adjust the clocks in the periphery of the body. The organization of the circadian rhythm is an alternative mechanism. Due to the inability of blind individuals and some occupational groups such as Astronauts and Submarines to synchronize their SCN with light information, their biological clock rhythms are disrupted. Even in individuals with a normal regular circadian rhythm, temporary circadian drift (jet-lag) occurs after long air travels (28).

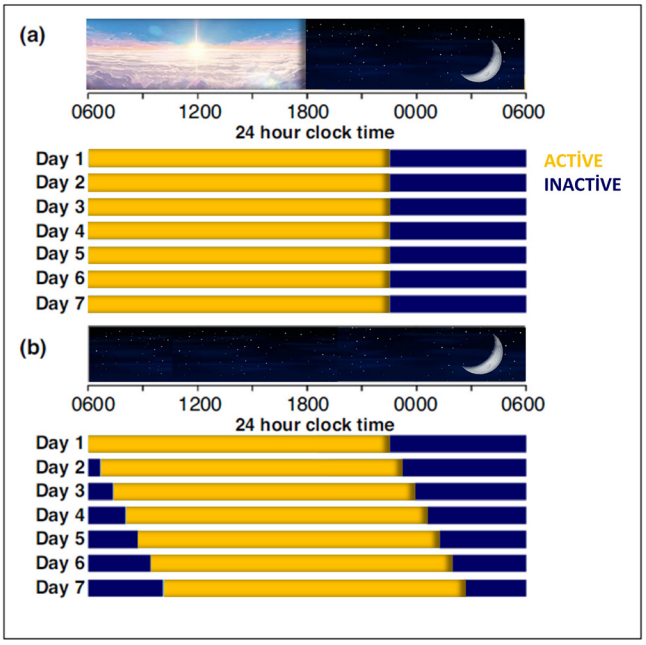

Figure 2. Behavioral rhythms in the natural light/dark cycle and without photic input.
(a) A weekly chart of daily patterns in a person's sleep-wake behavior on a daily basis. It shows a chart of the periods of activity (yellow) and inactivity (dark blue) that would be predicted for an individual drifting normally for seven days. (b) A weekly chart of sleep-wake behavior in the absence of photic inputs (in constant darkness or no photoreception). Without photic cues, the free-running period of the human circadian clock describes activity with a period longer than 24 hours. In this case, the activity pattern gradually moves out of phase with external time, with periods of activity/inactivity later each day (Modified from ref. 4).

pernycthemeral, free running, or non-24-hour sleep-wake rhythm disorder (non-24-SWRD). Although many environmental signals or "zeitgeber" can affect circadian rhythms, the most important signal is the light information. The importance of light in the synchronization of rhythms is precisely determined by the change in 24-hour rhythm in blind people. The same situation has been demonstrated experimentally in people with normal vision, by changing the 24-hour circadian rhythm with constant dim light application (29). In completely blind people, the circadian processes lose synchronization due to the lack of light entry into the circadian clock. This leads to an abnormal phase angle between the circadian clock and sleep-wake behavior, and as a result, it turns into a disorder that negatively affects social, academic and professional life (4).

The first definition of non-24-SWRD has been observed in 1977 from a 28-year-old man who was congenitally blind with no conscious light perception and was complaining of insomnia and hypersomnolence (30). More than half of the blind people who do not have a conscious perception of light cannot synchronize with 24 hours of a day (31). Despite a clear social urge to maintain a 24-hour schedule, eat, work and social contact during the day, and sleep at night, the circadian rhythm of non-entrained individuals will work freely, thus moving in and out of phase. This is diagnosed as non-24-SWRD. In some cases, blind individuals may entrain, but this usually coincides with the wrong time of the phase (classified as delayed or advanced sleep-wake phase disorder) (31,32). Circadian misalignments can have significant adverse effects on physiology, with these individuals exhibiting shifting circadian behaviors for up to 8 hours, both forward and delayed. A disruption and absence of circadian photoentrainment has profound impacts on both health and life quality. The most common reported disorder or consequence is a disruption of sleep/wake cycles (31–33).

First-line management in the treatment of completely blind patients suffering from non-24-SWRD consists of non-drug therapies aimed to enhance alternative zeitgebers (synchronizers of circadian rhythms). Patients are encouraged to establish regular bedtime, wake-up, and meal schedules to engage in physical activity in the morning. If some light perception persists, exposure to daylight or bright light in the morning is recommended. Stimulating the wake systems in the morning with intellectual activities, cold showers or intense physical exercise might be helpful

(29). It is controversial whether drug-free treatment alone is sufficient. However, it is certain that adding drug therapy to the drug-free treatment protocol will be much more beneficial in regulating the circadian rhythms of the blind people who have no light perception. Drug based medications are immediate-release melatonin (available over-the-counter in many countries), melatonin extended-release, and melatonin agonists.

CONCLUSIONS

The SCN, the body's master biological clock, has an important role in regulating circadian rhythms. The natural period of the circadian rhythm is slightly longer than 24 hours and requires an exposure from day light and daily synchronization with the solar cycle. Melatonin is an important endocrine factor in the regulation of circadian rhythms. The production of this hormone is regulated by light and is suppressed during the bright period of the day. Thus, this hormone supports circadian synchronization with a feedback loop. In completely blind people, the absence of light disrupts the circadian synchrony, leading to a gradual shift of circadian rhythms in the majority of blind people. Associated with this gradual desynchrony is non-24-SWRD, a condition characterized by cyclical episodes of severe insomnia and excessive daytime sleepiness. This disorder is common in the blind with no light perception. Behavioral and medical approaches are used in treatment to entrain and maintain circadian rhythms. The benefit of behavioral therapy alone is limited. Medical treatment can be applied alone or combined with behavioral therapy. When behavioral therapy and medical therapy are combined together, the effect of treatment might increase. The major medications of this kind of treatment are melatonin or melatonin agonists.

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