



Journal of Science Innovations and Nature of Earth

Journal homepage : <https://jsiane.com/index.php/files/index>

International, Double-Blind, Quarterly, Peer-Reviewed, Refereed Journal, Edited and Open Access Research Journal

A Review on Sleep cycle effect on human body

Manya Arora¹, Neelam^{*1}, Anil Kumar¹, Hridayesh Arya¹

¹Department of Zoology, N.R.E.C. College, Khurja, Bulandshahr, Affiliated to Chaudhary Charan Singh University, Meerut, Uttar Pradesh, India

*Corresponding Author E-mail: neelamtyg@gmail.com

DOI: <https://doi.org/10.59436/jsiane.424.2583-2093>

Abstract

Insufficient or poor sleep can cause a host of physical and mental health issues; this review looks at the science behind the human sleep cycle and how it works. Sleep is regulated by a dynamic interaction between circadian rhythms and sleep homeostasis. Melatonin, a hormone secreted by the pineal gland, plays a crucial role in controlling when we sleep and when we wake up. A small cluster of hypothalamic neurons known as the suprachiasmatic nucleus (SCN) controls its secretion and acts as the body's primary timekeeper. In response to light signals received by the eyes, the SCN synchronizes internal rhythms with the external day-night cycle. During the night, your body goes through two main phases of sleep: rapid eye movement (REM) and non-rapid eye movement (NREM). The brainstem and forebrain's neural networks orchestrate the changes between these phases. Cry1, Cry2, Per1, and Per2 are important clock genes whose expression regulates molecular circadian rhythms. Extended periods of waking raise sleep pressure, which impairs cognition and increases energy expenditure. Sleep homeostasis can be upset by aging and irregular sleep habits, which can lead to structural changes in sleep patterns and decreased sleep efficiency. Shift workers are most affected by these interruptions because their internal clocks frequently don't match their work schedules. Circadian rhythm sleep-wake disorders (CRSWDs), which have a detrimental impact on health and quality of life, are exacerbated by this misalignment. Addressing sleep-related health issues in contemporary culture requires an understanding of these mechanisms.

Keywords: Circadian rhythm, work-rest patterns, sleep behaviour, sleep disorders, sleep homeostasis, wakefulness.

Received 28.03.2025

Revised 22.05.2025

Accepted 19.06.2025

Online Available 20.06.2025

Introduction

According to behavioral definitions, sleep is a reversible condition marked by a lack of responsiveness and perceptual disengagement from the outside world. But it would be more realistic to characterize sleep as a complicated interplay between behavioral and physiological processes (Carskadon & Dement, 2011). Physical symptoms of sleep include lying down, decreased movement, closed eyes, and general behavioral passivity, although these features are not universally required. In some instances, active behaviours such as sleepwalking, sleep talking, and teeth grinding can occur during sleep. Furthermore, anomalies involving sleep may also involve elements of sleep intruding into wakefulness, including episodes of dream imagery, muscle weakness, or sudden sleep episodes (Carskadon & Dement, 2011). Your body goes through two distinct phases when you sleep: rapid eye movement (REM) and non-REM (NREM). Almost every animal and bird studied exhibits these states, which are as different from one another as they are from being awake (Carskadon & Dement, 2011). Typically, the characteristics of the electroencephalogram (EEG) divide non-REM sleep, so into four distinct stages. When a person is not actively dreaming, their electroencephalogram (EEG) will exhibit synchronized activity characterized by features like sleep spindles, high-voltage slow waves, and K-complexes (Carskadon & Dement, 2011). With the lowest arousal thresholds in stage 1 and the highest in stage 4, the four phases of NREM sleep (stages 1, 2, 3, and 4) correspond to a continuum of increasing sleep depth. During NREM sleep, there is typically little to no mental activity. NREM sleep, to put it briefly, is a state in which the brain is largely dormant yet nevertheless controls physical processes in a mobile body (Carskadon & Dement, 2011).

Human Sleep Biology

A healthy sleep schedule is essential for daily functioning and ideal health, whereas inadequate sleep results in worse health problems (Goel *et al.*, 2009). These problems can be obesity, stress, anxiety, and depression. Various methods can be employed to achieve sufficient sleep. Research into historical patterns indicates that before the introduction of artificial light, humans may have experienced multiple sleep periods during the night, particularly in seasons with brief photoperiods (Ekirch, 2001). Research using actigraphy on populations in pre-industrial societies, where significant seasonal variations in night duration are absent, reveals that sleep remains concentrated during nighttime hours, even when darkness persists for 11-12 hours (Yetish *et al.*, 2015).

In regions with warmer climates, agricultural workers adjusted their schedules to cope with the heat. They extended their workday into the late evening hours and began their tasks early in the morning. This practice resulted in reduced nighttime sleep, which they balanced by taking a longer midday rest, known as a siesta (Jacklitsch, *et al.*, 2023).

The "circadian rhythm" is the brain's 24-hour cycle of wakefulness and sleepiness that changes in response to changes in environmental light

(Reddy, Reddy, & Sharma, 2021). Light prevents the pineal gland from producing melatonin, the hormone that is mostly produced at night. According to Nishimon, Nishino, and Nishino (2021), it helps control the body's sleep-wake cycle and circadian rhythms. Problems with metabolism can arise from circadian rhythm changes, which are common in the elderly and include things like inflammation and sleep disruptions (Cardinali *et al.*, 2021). Consequently, certain pathophysiological changes that speed up aging are brought about by sleep cycle abnormalities (Ramirez *et al.*, 2021). Several animals' circadian clocks developed to coordinate internal biological processes with environmental variations (Pitsillou, Liang, Hung, & Karagiannis, 2021). The clock gives the host pinpoint accuracy in timekeeping and remarkable environmental adaptability. The risk of developing cancer, metabolic disorders, and cardiovascular disease increases when drowsiness disrupts or alters circadian rhythms, which in turn increases the risk of rotational changes and other lifestyle factors (Gyorik *et al.*, 2021). Even while everyone knows that messing with people's circadian rhythms is bad for them, there isn't enough information on how to fix it.

SCN – Super Chiasmatic Nucleus

In response to periodic changes in their environment, organisms are able to anticipate and coordinate their physiology and behavior using circadian oscillators. According to Moore and Eichler (1972) and Yoo *et al.* (2004), the hypothalamic suprachiasmatic nucleus (SCN) in mammals acts as a master circadian pacemaker by coordinating tissue-autonomous oscillators to produce overt cycles. Circadian rhythms are generated at the molecular level via a feedback loop involving transcription and translation. Protein products of the genes encoding Cryptochrome 1 (Cry1), Cry2, Period 1 (Per1), and Per2 block the transcriptional activity of the transcriptional activators CLOCK and BMAL1 in this circuit (Panda, Hogenesch, & Kay, 2002). When the oscillator's phase changes, so do the mRNA and protein levels of these repressors, especially Per2 (Lee *et al.*, 2001).

Using humoral and synaptic channels, the SCN pacemaker transmits phase information to peripheral oscillators, and it is synchronized by light. Intrinsically photosensitive retinal ganglion cells (ipRGCs) with melanopsin send synaptic input directly to the SCN's retinorecipient cells. In reaction to light, ipRGCs secrete neurotransmitters that bind to their specific receptors and trigger the phosphorylation of the calcium/cAMP response element-binding protein (CREB). Initiating transcription and modifying the phase of the molecular oscillator, activated phospho-CREB (pCREB) binds to the CRE sites on the Per1 and Per2 promoters (Meijer & Schwartz, 2003; Nayak, Jegla, & Panda, 2007; Travnickova-Bendova, Cermakian, Reppert, & Sassone-Corsi, 2002).

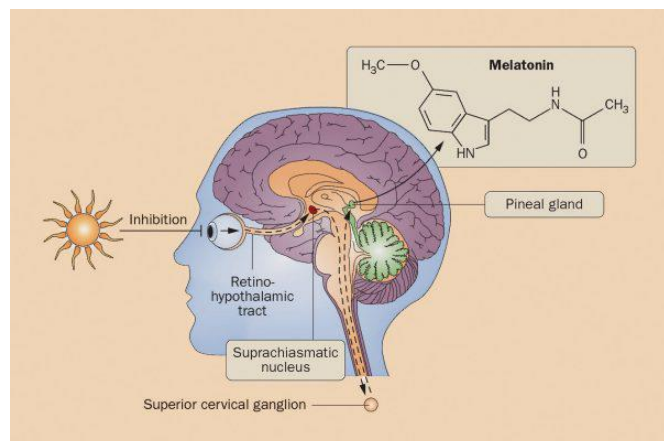


Figure 1 the pineal gland is free to create melatonin, which makes us feel sleepy, when the suprachiasmatic nucleus, a region of the brain, is unable to detect light Adapted from (Konturek *et al.*, 2007).

(Source: <https://www.acs.org/education/chemmatters/past-issues/archive-2014-2015/the-science-of-sleep.html>)

Sleep's Neurophysiology

Pace-Schott and Hobson (2002) identified two distinct stages of sleep: rapid eye movement (REM) and non-rapid eye movement (NREM). Essential for inducing sleep are the neurotransmitters galanin and gamma-aminobutyric acid (GABA) located in the ventrolateral preoptic nucleus. This is set in motion by circadian impulses sent out by the anterior hypothalamus and by internal chemical signals that regulate sleep and wakefulness, such as adenosine, which builds up in relation to the duration of time one is awake (Pace-Schott & Hobson). As a person goes to sleep, their electroencephalogram (EEG) shifts from the rapid, low-voltage waves seen when awake to the slower, higher-voltage waves seen during non-rapid eye movement (NREM) sleep. Subsequently, REM sleep, defined by reduced voltage and higher frequency activity, replaces NREM sleep (Pace-Schott & Hobson). Diencephalic structures that integrate homeostatic and circadian cues initiate sleep (Pace-Schott & Hobson). At the beginning of each sleep cycle, an ultradian oscillator located in the mesopontine junction regulates the regularity with which NREM and REM sleep phases transition (Pace-Schott & Hobson).

The parasympathetic nervous system becomes more active and the sympathetic nervous system becomes less active during non-REM sleep (Pace-Schott & Hobson). In rapid eye movement (REM) sleep, parasympathetic and sympathetic nervous system activity are both increased (Schwartz & Roth, 2008). Three distinct stages make up non-REM sleep. The first stage of NREM sleep, which lasts less than ten minutes on average, is a light sleep period marked by muscle relaxation, slow breathing, and a lowered heart rate (McCarley, 2007). The second stage of NREM sleep is defined as a light sleep phase that precedes the deeper levels. Muscles relax, brain activity decreases, and respiration and heart rate decrease during this phase. This stage lasts between thirty and sixty minutes (McCarley). Deep sleep, with a marked drop in heart rate and respiration, is a hallmark of stage third. At this point, brain waves slow down even more and muscles relax. This stage lasts between twenty and forty minutes (McCarley).

The last phase before a new sleep cycle begins is known as REM sleep. Breathing and heart rate rise during this period, and REM sleep is when most dreams take place (Colten & Altevogt, 2006). As compared to rapid eye movement (REM) sleep, non-REM sleep is associated with much lower metabolic rate and blood flow; these parameters are comparable to those during waking (Colten & Altevogt). Growth hormone is typically secreted in the initial hours after falling asleep, while thyroid hormone secretion rises later sleep (Colten & Altevogt).

Wakefulness's Neurophysiology

Wakefulness is defined as an alert mental state characterized by responsiveness to environmental cues and self-awareness (Miller & O'Callaghan, 2006). On the other hand, according to Miller and O'Callaghan, your sensitivity to environmental cues reduces as you sleep. As the brain is actively engaged during wakefulness, the frequency of coordinated neuronal firing in the cerebral cortex increases. However, sleep duration has a negative effect on neuronal firing synchronization and speed (Vyazovskiy *et al.*, 2009). The energy-supplying glycogen in astrocytes is drained while we're awake and replenished while we sleep (Benington & Heller, 1995). To maintain alertness, a cascade of neurotransmitters begins in the brainstem and ascends to the midbrain, hypothalamus, thalamus, and basal forebrain. According to Brown *et al.* (2012), the posterior hypothalamus plays a crucial role in initiating wakefulness-inducing cortical activity. Neuronal connections regulate the transition from awake to asleep, and the posterior hypothalamus plays a role in this process. Wakefulness is characterized by alertness, the capacity to react to environmental stimuli, and

conscious awareness of one's immediate environment. It differs from sleep, in which one is less responsive to environmental cues (Miller & O'Callaghan). The energy-supplying glycogen in astrocytes is drained while we're awake and replenished while we sleep (Benington & Heller, 1995).

A variety of neurotransmitters that originate in the brainstem and ascend to the midbrain, hypothalamus, thalamus, and basal forebrain facilitate communication that improves alertness (Brown *et al.*, 2012). The posterior hypothalamus plays a crucial role in the stimulation of the cortex that initiates wakefulness (Brown *et al.*, 2012). According to Takahashi, Lin, and Sakai (2006), histamine neurons in the nearby posterior hypothalamus and tuberomammillary nucleus regulate wake-selective brain networks. Neurons that carry orexin are associated with arousal and extend widely throughout the brain, close to histamine neurons (Hirano *et al.*, 2018). Chemelli *et al.* (1999) found a correlation between orexin deficiency and nocturnal sleepiness and unexpected sleep episodes. Cortical activity regulates wakefulness, while orexin and histamine neurons work together to influence orexin. (Anaclet *et al.*, 2009).

Sleep homeostatic regulation

Sleep equilibrium occurs after you've been awake for a while. To compensate for the buildup of drowsiness and sleep pressure, sufficient volume and duration of sleep are intended when sleep is permitted (Huang, Zhang, & Qu, 2014). According to Huang, Zhang, and Qu (2014) and Peng *et al.* (2020), adenosine in the basal forebrain is a key physiological regulator of sleep homeostasis. Upon metabolism of adenosine triphosphate, neurons and glial cells generate the endogenous chemical adenosine (Landolt, 2008). It accumulates outside of cells and has the potential to influence the circadian rhythm circuits (Landolt, 2008). To make you more aware, it works by blocking the adenosine A2A receptor. This receptor is crucial for controlling the amount of oxygen that the heart needs, the blood flow to the coronaries, and the neurotransmitters in your brain (Per Landolt 2008). A neuromodulator called nitric oxide is produced by an inducible nitric oxide synthase in the basal forebrain during extended periods of awakeness (Kalinchuk *et al.*, 2006). There is a link between the activation of the immune response and prolonged periods of wakefulness, and this enzyme is produced during inflammation. According to Kalinchuk *et al.* (2006b). The cortical-stimulating neurotransmitter histamine improves wakefulness and decreases sleepiness upon entry into the basal forebrain (Kárpáti *et al.*, 2019). Extended wakefulness prolongs neuronal activity cycles in various brain regions, leading to increased energy consumption. When energy is depleted, adenosine levels rise (Wigren *et al.*, 2007). Long-term neural activity during prolonged wakefulness may be linked to energy depletion and sleep homeostasis (Wigren *et al.*, 2007).

Sleep deprivation impairs the recovery sleep of older animals. Reduced increases in adenosine, nitric oxide, and lactate levels in older individuals can be observed in studies on sleep homeostasis and homeostatic sleep responses (Rytönen *et al.*, 2010; Wigren *et al.*, 2009).

The circadian clock regulates wakefulness and sleepiness throughout the day through the suprachiasmatic nucleus (SCN) (Ono & Yamanaka, 2017). When clock genes are expressed, the SCN links transcription-translation negative feedback loops to generate circadian rhythms. The activity of neurons in the SCN varies throughout the day (containing genes spanning around a 24-hour period, such as *Per*, *Cry*, and *Bmal1*) (Belle & Diekmann, 2018; Tamanini *et al.*, 2005). Daytime electrical activity in the SCN is higher than nighttime electrical activity (Fuller, Gooley, & Saper, 2006). The circadian rhythm in the SCN is controlled by neurotransmitters and hormones. For example, the SCN coordinates light/dark cycles with the natural rhythm of melatonin secretion, a hormone that is created and released by the pineal gland at night under darkness. In particular, blue light (460–480 nm) can prevent the generation of melatonin at night (Claustrat & Leston, 2015). Nonetheless, a melatonin's main physiological role is to inform the body of the daily cycle of light and dark, which helps to coordinate physiological processes that react to variations in light exposure. (Claustrat & Leston, 2015). Regulatory of wakefulness and slumber is another critical function of these neurons (Welsh, Takahashi, & Kay, 2010). The mesolimbic dopamine system is one of several brain systems that are involved in the various stages of awareness that occur during the sleep-wake cycle (Oishi & Lazarus, 2017). By sending signals to the nucleus accumbens and lateral hypothalamus, neurons that contain glutamatergic nitric oxide synthase 1 enhance alertness, while damage to glutamate cells postpones its start (Oishi & Lazarus, 2017). In contrast, turning on Yu *et al.* (2019) found that injury to GABAergic neurons in the ventral tegmental area leads to an increase in alertness together with the induction of prolonged non-REM-like sleep that resembles sedation. Using a two-process paradigm, the regulation of wakefulness and slumber has been elucidated. These processes, which are called S and C, are driven by the circadian clock and homeostatic systems, respectively. The circadian clock regulates process C, which is reliant on the body's natural rhythms, and process S represents the pressure to sleep, which increases as one is up for longer periods of time (Borbély, Daan, Wirz-Justice, & Deboer, 2016).

Many people around the world suffer from sleep disorders without ever receiving a proper diagnosis or treatment (Caylak, 2009). Various elements impact these diseases; these include genetics, psychology, physiology, and behavior (Caylak, 2009). Disruptions to the normal sleep-wake cycle can affect mental health and even be a sign of neurodegenerative disorders in some people (Chong, Xin, Ptáček, & Fu, 2018; Kinoshita, Okamoto, Aoyama, & Nakaki, 2020). Age-related changes in sleep patterns include an increase in the proportion of light non-REM sleep phases and a decrease in the proportion of deep non-REM sleep, total sleep time, and rapid eye movement (REM) sleep (Lloret *et al.*, 2020). But some oscillatory sleep patterns show less spindle density and slower wave activity. Damage to the slow oscillation-sleep spindle connection and the theta-gamma coupling has been associated with Alzheimer's disease biomarkers. Sleep disturbances may be precursors of Alzheimer's disease, since amyloid beta and tau proteins have been associated with them (Lloret *et al.*, 2020). Furthermore, sleep disorders are strongly influenced by hereditary variables (Taheri & Mignot, 2002). Mutations in the *hPer2* gene in humans are one cause of this disease. An autosomal dominant condition characterized by early morning waking and sleeping hours is familial advanced sleep phase syndrome. A connection between this and the period gene, which is responsible for resetting the body clock when exposed to light. Sleep deprivation affects many gene expression regulators, including methylases, acetylases, core clock genes, and ribosomal proteins (Xu *et al.*, 2007). The circadian rhythm system's capacity to control the human transcriptome is impaired by sleep deprivation. Appropriate sleep duration may improve the temporal structure of the human transcriptome (Archer *et al.*, 2014). Circadian dyssynchronization has detrimental effects, as shown in studies with simulated night shifts when participants slept at inconvenient times, which disrupted the natural harmony between their internal biological rhythms and the outside world (Kervezee, Cuesta, Cermakian, & Boivin, 2018). Kervezee *et al.* (2018) found that working evenings can have substantial health implications.

Initial Sleep Cycle-

Stage 1 NREM sleep, which typically lasts only one to seven minutes, is the first sleep cycle that a normal young adult experiences. In this phase, arousal thresholds are low, meaning that minimal stimuli such as a soft call, a light touch, or subtle sounds can easily wake the individual. Besides marking the initial transition from wakefulness throughout the night, stage 1 often manifests as a transitional period to sleep. A notable increase in stage 1 sleep is often a sign of severely fragmented sleep (Rechtschaffen & Kales, 1968). After stage 1, the person moves into stage 2 NREM sleep, which is identified by the electroencephalogram's (EEG) K-complexes and sleep spindles. Stage 2 typically persists for about 10 to 25 minutes and requires a stronger stimulus for arousal compared to stage 1. It's interesting to note that in stage 2, the identical stimulus that produces waking in stage 1 might only cause a K-complex without causing genuine awakening (Rechtschaffen & Kales, 1968). The sleep enters stage 3 NREM sleep when high-voltage, slow-wave EEG activity appears as stage 2 goes on. When slow-wave activity (at least 75 μ V and two cycles per second) takes up more than 20% but less than 50% of the EEG, it is referred to be stage 3. This stage, which usually lasts only a short while during the initial cycle, acts as a bridge to stage 4, where slow-wave activity exceeds 50% of the EEG and persists for 20 to 40 minutes. Arousal becomes increasingly difficult in these deeper stages, requiring stronger external stimuli (Rechtschaffen & Kales, 1968). Short bouts of stage 3 and stage 2 sleeps may occur before the first REM sleep period begins, and a sequence of body movements frequently indicates an ascent to lighter NREM stages. Typically, this first REM episode lasts between one and five minutes. Arousal thresholds during REM sleep are highly variable, possibly because internal cognitive processes or dream incorporation diminish responsiveness to external stimuli (Rechtschaffen & Kales, 1968).

Early research in animals, such as cats, suggested that REM sleep exhibited the highest arousal thresholds, leading it to be referred to as "deep sleep" in animal studies. However, this is not to be mistaken with the human NREM phases 3 and 4, which are also known as deep sleep or slow-wave sleep (SWS). SWS occasionally denotes the full duration of NREM sleep in other animals, highlighting important terminological differences across species (Rechtschaffen & Kales, 1968).

NREM – REM Cycle

Nightly cycles of rapid eye movement (REM) and non-REM (non-rapid eye movement) sleep occur in alternating fashion. As the night progresses, the length of time spent in rapid eye movement (REM) sleep tends to rise. Stage 2 of the non-REM sleep phase increasingly takes over the NREM part of subsequent sleep cycles, with stages 3 and 4 of the non-REM sleep phase gradually decreasing in duration or even going away entirely on occasion. The duration of the first NREM-REM cycle is usually 70 to 100 minutes, whereas the duration of the second and subsequent cycles is approximately 90 to 120 minutes. The typical duration of the NREM-REM cycle while sleeping is 90–110 minutes (Carskadon & Dement, 2011).

In young adults, slow-wave sleep (SWS) primarily dominates the NREM segments early in the night, particularly during the first third of sleep. Conversely, the last portion of the night is when REM sleep episodes are most noticeable. Later in the night, close to the transition into REM sleep, there are frequently brief bursts of consciousness that are rarely remembered when one wakes up. The body temperature rhythm suggests that the preferential concentration of REM sleep toward the end of the night is controlled by a circadian oscillator (Czeisler, Zimmerman, Ronda, & Moore-Ede, 1980; Zulley, 1980). In contrast, the early-night dominance of SWS is believed to be a reflection of homeostatic sleep pressure rather than circadian control, with its prominence diminishing progressively as sleep continues (Weitzman, Czeisler, Zimmerman, & Moore-Ede, 1980).

Length of Sleep

There are several elements that affect how long people sleep at night, with voluntary control being particularly significant in humans, making it challenging to define a universal "normal" sleep pattern. On average sleeping is reported by young adults around 7.5 hours on weekdays and extending to approximately 8.5 hours on weekends. However, substantial variability exists both across individuals from night to night. Genetic predispositions also play an important role in determining sleep duration), upon which volitional behaviors such as staying up late or waking with an alarm are superimposed (Karacan & Moore, 1979).

Additionally, the length of prior wakefulness influences sleep need, though not in a strictly proportional manner. Circadian rhythms further modulate sleep length, meaning the timing of sleep onset significantly impacts total sleep duration, because REM sleep is essential for maintaining sleep throughout the peak circadian periods, its percentage rises with the length of sleep (Dijk & Czeisler, 1995).

Circadian Rhythms

The distribution of sleep stages is strongly influenced by the circadian period at which sleep starts. Particularly, REM sleep exhibits a diurnal regularity, peaking in the morning when the body's core temperature is at its lowest. (Czeisler, Zimmerman, Ronda, & Moore-Ede, 1980; Zulley, 1980). Therefore, REM sleep may predominate the sleep episode and even manifest right at sleep initiation if sleep onset is postponed until the peak REM phase, such as the early morning hours (Czeisler *et al.*, 1980).

Such a reversal of the typical sleep architecture is often observed in individuals who undergo acute phase shifts, such as during abrupt work schedule changes or after rapid travel across multiple time zones (Czeisler *et al.*, 1980).

The timing and length of sleep are also strongly related to the circadian phase, according to research done in settings without any external time cues (Zulley, Wever, & Aschoff, 1981).

In these free-running circumstances, sleep start often happens during the body temperature cycle's falling phase, but there is also a noticeable secondary surge in sleep onset that corresponds to afternoon naps (Zulley, Wever, & Aschoff, 1981). On the other hand, sleep termination usually happens when the body temperature rhythm is rising (Strogatz, 1986).

Human Circadian Rhythm Disorders

Various human circadian rhythm disorders are characterized by disruptions in the interplay between the internal body clock and the external day-night cycle (The Journal of Clinical Sleep Medicine, 2005).

The intrinsic circadian rhythm sleep disorders (CRSDs) classification system developed by the American Academy of Sleep Medicine is helpful for understanding how this misalignment impacts the sleep-wake cycle (The Journal of Clinical Sleep Medicine, 2005).

People who suffer from advanced sleep phase disorder or syndrome typically start their main sleep period earlier than their chosen clock time, which means that they go to bed and get up earlier than they would like. However, delayed sleep phase disorder (DSPD) makes it such that sleep and wakefulness start later than the ideal clock time. Regardless of these alterations, the sleep-wake cycles of both DSPD and advanced sleep phase disorder ASPD consistently reflect the 24-hour day-night cycle (The Journal of Clinical Sleep Medicine, 2005).

Contrarily, a pattern of one to two hour delays between wake and sleep phases is a characteristic of free-running disorder (FRD), sometimes called non-24-hour sleep-wake syndrome (American Academy of Sleep Medicine, 2005). People with an irregular sleep-wake rhythm (ISWR) experience unpredictable and spatially fragmented waking and sleeping episodes, as well as brief, random bursts of sleep throughout the day and night (American Academy of Sleep Medicine, 2005).

Other known CRSDs include shift work disorder and jet lag disorder; however, these are extrinsic disorders that arise as a result of a disrupted sleep pattern, whether intentional or not, and do not indicate a malfunction of the circadian clock (Dagan and Eisenstein, 1999).

Circadian rhythm sleep disorders (CRSDs) are characterized by persistent or recurrent disruptions to the normal sleep-wake cycle. According to the American Academy of Sleep Medicine (2005), these disruptions typically occur when the body's circadian clock mechanism doesn't work properly or when the circadian rhythm isn't in sync with the demands of society or the

workplace. Significant impairments in everyday functioning might be observed as a result of these interruptions (American Academy of Sleep Medicine, 2005).

There are two main types of CRSDs, each with its own set of underlying mechanisms. On one hand, there are disorders that affect the endogenous circadian system, such as free-running disorder, irregular sleep-wake rhythm, advanced sleep phase disorder, and delayed sleep phase disorder. On the other hand, disorders like shift work disorder and jet lag disorder are caused by a misalignment between the internal clock and the external environment (The Journal of Clinical Sleep Medicine, 2005).

To diagnose CRSDs, it is essential to collect a comprehensive sleep-wake history that is supported by diagnostic tools such as actigraphy and sleep diaries. There is some useful objective data provided by two physiological markers of circadian phase: melatonin release and core body temperature. In 2005, Benloucif and colleagues produced the following study. Typically worn on the non-dominant wrist for 7 to 14 days, actigraphy measures rest-activity patterns to determine circadian timing. There is a strong correlation between the endogenous circadian phase, melatonin, and the rhythms of body temperature and the sleep-wake cycles. The process by which the pineal gland produces melatonin, called Dim Light Melatonin Onset (DLMO), usually begins in a poorly illuminated environment two to three hours before the usual start of sleep. The lowest point in core body temperature often occurs about two hours before to typical waking time, as reported by Benloucif *et al.* (2005). In 2005, Benloucif and colleagues produced the following study. Because patients with CRSD frequently report symptoms of insomnia and/or excessive daytime sleepiness, clinicians evaluating patients with sleep-wake disturbances should always consider circadian rhythm abnormalities as a potential comorbidity or part of the differential diagnosis. In 2005, the American Academy of Sleep Medicine.

Conclusion

There are two separate physiological states that make up sleep, and this review will focus on the biological bases of both REM and non-REM sleep. The sleep-inducing neurotransmitters galanin and gamma-aminobutyric acid (GABA) are located in the ventrolateral preoptic nucleus of the brain. The circadian clock governs daily sleep and wake cycles. This internal timing system, located in the suprachiasmatic nucleus (SCN), is regulated by various neurotransmitters and hormones. For instance, the SCN synchronizes melatonin production released by the pineal gland during nighttime darkness with environmental light and dark cycles. Numerous factors determine the length of nighttime sleep, with voluntary behaviors playing a significant role in humans. As a result, defining a single “normal” sleep duration is challenging. On average, young people report sleeping around 7.5 hours on weekdays and up to 8.5 hours on weekends. A lack of orexin has been linked to excessive daytime drowsiness and episodes of sudden sleep onset. Circadian rhythm sleep disorders (CRSDs) arise from persistent disruptions in the sleep-wake cycle. These disturbances typically stem from internal circadian system dysfunctions or misalignment between biological rhythms and external social or occupational obligations. Many individuals today struggle with insufficient sleep due to long working hours or neglecting sleep needs contributing to a range of physical illnesses, poor health outcomes, and mental health challenges.

Reference

Anaclet, C., Parmentier, R., Ouk, K., Guidon, G., Buda, C., Sastre, J. P., *et al.* (2009). Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models. *J Neurosci*, 29(46), 14423–14438.

Archer, S. N., Laing, E. E., Möller-Levet, C. S., van der Veen, D. R., Bucca, G., Lazar, A. S., *et al.* (2014). Mistimed sleep disrupts circadian regulation of the human transcriptome. *Proc Natl Acad Sci U S A*, 111(6), E682–E693.

Baburina, Y., Lomovsky, A., & Krestinina, O. (2021). Melatonin as a potential multitherapeutic agent. *J Pers Med*, 11(4), 274.

Belle, M. D. C., & Diekmann, C. O. (2018). Neuronal oscillations on an ultra-slow timescale: daily rhythms in electrical activity and gene expression in the mammalian master circadian clockwork. *Eur J Neurosci*, 48(8), 2696–2717.

Benloucif, S., Guico, M. J., Reid, K. J., Wolfe, L. F., L'Hermite-Baleriaux, M., & Zee, P. C. (2005). Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. *Journal of Biological Rhythms*, 20, 178–188.

Benington, J. H., & Heller, H. C. (1995). Restoration of brain energy metabolism as the function of sleep. *Prog Neurobiol*, 45(4), 347–363.

Borrmann, H., McKeating, J. A., & Zhuang, X. (2021). The circadian clock and viral infections. *J Biol Rhythms*, 36(1), 9–22.

Borbély, A. A., Daan, S., Wirz-Justice, A., & Deboer, T. (2016). The two-process model of sleep regulation: a reappraisal. *J Sleep Res*, 25(2), 131–146.

Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E., & McCarley, R. W. (2012). Control of sleep and wakefulness. *Physiol Rev*, 92(3), 1087–1187.

Cardinali, D. P. (2021). Melatonin and healthy aging. *Vitam Horm*, 115, 67–88.

Carskadon, M. A., & Dement, W. C. (2011). Normal human sleep: An overview. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (5th ed., pp. 16–26). St. Louis, MO: Elsevier Saunders.

Caylak, E. (2009). The genetics of sleep disorders in humans: narcolepsy, restless legs syndrome, and obstructive sleep apnea syndrome. *Am J Med Genet A*, 149A(11), 2612–2626.

Chemelli, R. M., Willie, J. T., Sinton, C. M., Elmquist, J. K., Scammell, T., Lee, C., *et al.* (1999). Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*, 98(4), 437–451.

Chong, S. Y. C., Xin, L., Ptáček, L. J., & Fu, Y. H. (2018). Disorders of sleep and circadian rhythms. In *Handb Clin Neurol* (Vol. 148, pp. 531–538).

Claustrat, B., & Leston, J. (2015). Melatonin: physiological effects in humans. *Neurochirurgie*, 61(23), 77–84.

Colin-Gonzalez, A. L., Aguilera, G., Serratos, I. N., Escibano, B. M., Santamaria, A., & Tunes, I. (2015). On the relationship between the light/dark cycle, melatonin and oxidative stress. *Curr Pharm Des*, 21(24), 3477–3488.

Colten, H. R., Altevogt, B. M., & Institute of Medicine (US) Committee on Sleep Medicine and Research (Eds.). (2006). *Sleep disorders and sleep deprivation: An unmet public health problem*. Washington (DC): National Academies Press (US).

Czeisler, C. A., Weitzman, E. D., Moore-Ede, M. C., *et al.* (1980). Human sleep: Its duration and organization depend on its circadian phase. *Science*, 210, 1264–1267.

Czeisler, C. A., Zimmerman, J. C., Ronda, J. M., *et al.* (1980). Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep*, 2, 329–346.

Dagan, Y., & Eisenstein, M. (1999). Circadian rhythm sleep disorders: toward a more precise definition and diagnosis. *Chronobiol Int*, 16, 213–222.

de la Iglesia, H. O., Fernandez-Duque, E., Golombek, D. A., *et al.* (2015). Access to electric light is associated with shorter sleep duration in a traditionally hunter-gatherer community. *J Biol Rhythms*, 30(4), 342–350.

Dijk, D. J., & Czeisler, C. A. (1995). Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci*, 15(5), 3526–3538.

Ekirch, A. R. (2001). Sleep we have lost: Pre-industrial slumber in the British Isles. *American Historical Review*, 106(2), 343–386.

Fuller, P. M., Gooley, J. J., & Saper, C. B. (2006). Neurobiology of the sleep-wake cycle: Sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms*, 21(6), 482–493.

Goel, N., Rao, H., Durmer, J. S., & Dinges, D. F. (2009). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*.

Gyorik, D., Eszlari, N., Gal, Z., Gal, Z., Torok, D., Baksa, D., *et al.* (2021). Every night and every morn: Effect of variation in CLOCK gene on depression depends on exposure to early and recent stress. *Front Psychiatry*, 12, 687487.

Hirano, A., Hsu, P. K., Zhang, L., Xing, L., McMahon, T., Yamazaki, M., *et al.* (2018). DEC2 modulates orexin expression and regulates sleep. *Proc Natl Acad Sci U S A*, 115(13), 3434–3439.

Hirshkowitz, M., Whiton, K., Albert, S. M., *et al.* (2015). National Sleep Foundation's sleep time duration recommendations: Methodology and results summary. *Sleep Health*, 1(1), 40–43.

Huang, Z. L., Zhang, Z., & Qu, W. M. (2014). Roles of adenosine and its receptors in sleep-wake regulation. *Int Rev Neurobiol*, 119, 349–371.

Jin, Y., Choi, Y. J., Heo, K., & Park, S. J. (2021). Melatonin as an oncostatic molecule based on its anti-aromatase role in breast cancer. *Int J Mol Sci*, 22(1), 438.

Kalinchuk, A. V., Lu, Y., Stenberg, D., Rosenberg, P. A., & Porkka-Heiskanen, T. (2006). Nitric oxide production in the basal forebrain is required for recovery sleep. *J Neurochem*, 99(2), 483–493.

Kalinchuk, A. V., Stenberg, D., Rosenberg, P. A., & Porkka-Heiskanen, T. (2006). Inducible and neuronal nitric oxide synthases (NOS) have complementary roles in recovery sleep induction. *Eur J Neurosci*, 24(5), 1443–1456.

Karacan, I., & Moore, C. A. (1979). Genetics and human sleep. *Psychiatr Ann*, 9, 11–23.

Kelly, R. M., Healy, U., Sreenan, S., McDermott, J. H., & Coogan, A. N. (2018). Clocks in the clinic: Circadian rhythms in health and disease. *Postgrad Med J*, 94(1117), 653–658.

Kervezee, L., Cuesta, M., Cermakian, N., & Boivin, D. B. (2014). Simulated nightshift work induces circadian misalignment of the human peripheral.

Kinoshita, C., Okamoto, Y., Aoyama, K., & Nakaki, T. (2020). MicroRNA: A key player for the interplay of circadian rhythm abnormalities, sleep disorders and neurodegenerative diseases. *Clocks Sleep*, 2(3), 282–307.

Kurhaluk, N. (2021). Alcohol and melatonin. *Chronobiol Int*, 38(6), 785–800.

Landolt, H. P. (2008). Sleep homeostasis: A role for adenosine in humans? *Biochem Pharmacol*, 75(11), 2070–2079.

Lee, C., Etchegaray, J. P., Cagampang, F. R., Loudon, A. S., & Reppert, S. M. (2001). Posttranslational mechanisms regulate the mammalian circadian clock. *Cell*, 107(7), 855–867.

Lee, E. E., Amritwar, A., Hong, L. E., Mohyuddin, I., Brown, T., & Postolache, T. T. (2020). Daily and seasonal variation in light exposure among the old order Amish. *Int J Environ Res Public Health*, 17(12), 4460–4476.

Lloret, M. A., Cervera-Ferri, A., Nepomuceno, M., Monlór, P., Esteve, D., & Lloret, A. (2020). Is sleep disruption a cause or consequence of Alzheimer's disease? Reviewing its possible role as a biomarker. *Int J Mol Sci*, 21(3), 1168.

Lockley, S. W., Barger, L. K., Ayas, N. T., Rothschild, J. M., Czeisler, C. A., & Landrigan, C. P. (2007). Effects of health care provider work hours and sleep deprivation on safety and performance. *Joint Commission J Qual Patient Saf*, 33(11), 7–18.

McCarley, R. W. (2007). Neurobiology of REM and NREM sleep. *Sleep Med*, 8(4), 302–330.

Medic, G., Wille, M., & Hemels, M. E. (2017). Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep*, 9, 151.

Meijer, J. H., & Schwartz, W. J. (2003). In search of the pathways for light-induced pacemaker resetting in the suprachiasmatic nucleus. *J Biol Rhythms*, 18(3), 235–249.

Miller, D. B., & O'Callaghan, J. P. (2006). The pharmacology of wakefulness. *Metabolism*, 55(10 Suppl 2), S13–S19.

Möller-Levet, C. S., *et al.* (2014). Mistimed sleep disrupts circadian regulation of the human transcriptome. *PNAS*, 111(6), E682–E691.

Moloudizargari, M., Moradkhani, F., Hekmatirad, S., Fallah, M., Asghari, M. H., & Reiter, R. J. (2021). Therapeutic targets of cancer drugs: Modulation by melatonin. *Life Sci*, 267, 118934.

Moore, R. Y., & Eichler, V. B. (1972). Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Res*, 42(1), 201–206.

Nayak, S. K., Jegla, T., & Panda, S. (2007). Role of a novel photopigment, melanopsin, in behavioral adaptation to light. *Cellular and Molecular Life Sciences*, 64(2), 144–154.

Nishimon, S., Nishino, N., & Nishino, S. (2021). Advances in the pharmacological management of non-24-h sleep-wake disorder. *Expert Opin Pharmacother*, 22(8), 1039–1049.

Oishi, A., Gbahou, F., & Jockers, R. (2021). Melatonin receptors, brain functions, and therapies. *Handb Clin Neurol*, 179, 345–356.

Oishi, Y., & Lazarus, M. (2017). The control of sleep and wakefulness by mesolimbic dopamine systems. *Neurosci Res*, 118, 66–73.

Ohdo, S. (2010). Chronotherapeutic strategy: Rhythm monitoring, manipulation and disruption. *Adv Drug Deliv Rev*, 62(9–10), 859–875.

Ono, D., & Yamanaka, A. (2017). Hypothalamic regulation of the sleep/wake cycle. *Neurosci Res*, 118, 74–81.

Panda, S., Hogenesch, J. B., & Kay, S. A. (2002). Circadian rhythms from flies to human. *Nature*, 417(6886), 329–335.

Pandi-Perumal, S. R., BaHammam, A. S., Brown, G. M., Spence, D. W., Bharti, V. K., Kaur, C., *et al.* (2013). Melatonin antioxidative defense: Therapeutic implications for aging and neurodegenerative processes. *Neurotox Res*, 23(3), 267–300.

Pace-Schott, E. F., & Hobson, J. A. (2002). The neurobiology of sleep: Genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci*, 3(8), 591–605.

Peng, W., Wu, Z., Song, K., Zhang, S., Li, Y., & Xu, M. (2020). Regulation of sleep homeostasis mediator adenosine by basal forebrain glutamatergic neurons. *Science*, 369(6508), eabb0556.

Pitsillou, E., Liang, J., Hung, A., & Karagiannis, T. C. (2021). The circadian machinery links metabolic disorders and depression: A review of pathways, proteins and potential pharmacological interventions. *Life Sci*, 265, 118809.

Ramirez, A. V. G., Filho, D. R., & de Sá, L. B. P. C. (2021). Melatonin and its relationships with diabetes and obesity: A literature review. *Curr Diabetes Rev*, 17(7), e072620184137.

Rechtschaffen, A., & Kales, A. (Eds.). (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute.

- Reddy, S., Reddy, V., & Sharma, S. (2021). Physiology, circadian rhythm. In StatPearls. Treasure Island (FL): StatPearls Publishing.
- Ruan, W., Yuan, X., & Eltzschig, H. K. (2021). Circadian rhythm as a therapeutic target. *Nat Rev Drug Discov*, 20(4), 287–307.
- Rytkönen, K. M., Wigren, H. K., Kostin, A., Porkka-Heiskanen, T., & Kalinchuk, A. V. (2010). Nitric oxide mediated recovery sleep is attenuated with aging. *Neurobiol Aging*, 31(11), 2011–2019.
- Schwartz, J. R., & Roth, T. (2008). Neurophysiology of sleep and wakefulness: Basic science and clinical implications. *Curr Neuropsychopharmacol*, 6(4), 367–378.
- Spiegel, K., Sheridan, J. F., & Van Cauter, E. (2002). Effect of sleep deprivation on response to immunization. *JAMA*, 288(12), 1471–1472.
- Strogatz, S. H. (1986). The mathematical structure of the human sleep-wake cycle. New York: Springer-Verlag.
- Taheri, S., & Mignot, E. (2002). The genetics of sleep disorders. *Lancet Neurol*, 1(4), 242–251.
- Takahashi, K., Lin, J. S., & Sakai, K. (2006). Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. *J Neurosci*, 26(40), 10292–10298.
- Tamaru, T., & Takamatsu, K. (2018). Circadian modification network of a core clock driver BMAL1 to harmonize physiology from brain to peripheral tissues. *Neurochem Int*, 119, 11–16.
- Tamanini, F., Yagita, K., Okamura, H., & van der Horst, G. T. (2005). Nucleocytoplasmic shuttling of clock proteins. *Methods Enzymol*, 393, 418–435.
- The International Classification of Sleep Disorders: Diagnostic and Coding Manual. (2005). 2nd ed. Westchester, IL: American Academy of Sleep Medicine.
- Travnickova-Bendova, Z., Cermakian, N., Reppert, S. M., & Sassone-Corsi, P. (2002). Bimodal regulation of mPer1 gene expression by CREB and CLOCK/BMAL1: A basis for circadian transcription. *PNAS*, 99(11), 7728–7733.
- Vyazovskiy, V. V., Olcese, U., Lazimy, Y. M., Faraguna, U., Esser, S. K., Williams, J. C., *et al.* (2009). Cortical firing and sleep homeostasis. *Neuron*, 63(6), 865–878.
- Webb, W. B., & Dinges, D. F. (1989). Cultural perspectives on napping and the siesta. In *Sleep Alertness* (pp. 247–265).
- Weitzman, E. D., Czeisler, C. A., Zimmerman, J. C., *et al.* (1980). Timing of REM and stages 3 + 4 sleep during temporal isolation in man. *Sleep*, 2, 391–407.
- Welsh, D. K., Takahashi, J. S., & Kay, S. A. (2010). Suprachiasmatic nucleus: Cell autonomy and network properties. *Annu Rev Physiol*, 72, 551–577.
- Wigren, H. K., Rytkönen, K. M., & Porkka-Heiskanen, T. (2009). Basal forebrain lactate release and promotion of cortical arousal during prolonged waking is attenuated in aging. *J Neurosci*, 29(37), 11698–11707.
- Wigren, H. K., Schepens, M., Matto, V., Stenberg, D., & Porkka-Heiskanen, T. (2007). Glutamatergic stimulation of the basal forebrain elevates extracellular adenosine and increases the subsequent sleep. *Neuroscience*, 147(3), 811–823.
- Xu, Y., Toh, K. L., Jones, C. R., Shin, J. Y., Fu, Y. H., & Ptáček, L. J. (2007). Modeling of a human circadian mutation yields insights into clock regulation by PER2. *Cell*, 128(1), 59–70.
- Yetish, G., Kaplan, H., Gurven, M., *et al.* (2015). Natural sleep and its seasonal variations in three pre-industrial societies. *Curr Biol*, 25(21), 2862–2868.
- Yoo, S. H., Yamazaki, S., Lowrey, P. L., Shimomura, K., Ko, C. H., Buhr, E. D., *et al.* (2004). PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *PNAS*, 101(15), 5339–5346.
- Yu, X., Li, W., Ma, Y., Tossell, K., Harris, J. J., Harding, E. C., *et al.* (2019). GABA and glutamate neurons in the VTA regulate sleep and wakefulness. *Nat Neurosci*, 22(1), 106–119.
- Zant, J. C., Rozov, S., Wigren, H. K., Panula, P., & Porkka-Heiskanen, T. (2012). Histamine release in the basal forebrain mediates cortical activation through cholinergic neurons. *J Neurosci*, 32(38), 13244–13254.
- Zulley, J. (1980). Distribution of REM sleep in entrained 24-hour and free-running sleep-wake cycles. *Sleep*, 2, 377–389.
- Zulley, J., Wever, R., & Aschoff, J. (1981). The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflugers Arch*, 391, 314–318.