COMMENTARY

Chronobiology and Its Psychiatric Relevance

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Abstract

Chronobiology, stemming from the Greek roots "chrónos" and "biology," delves into the intricate temporal dimensions of life. The circadian rhythm is at the heart of this inquiry, a meticulously studied biological cycle persisting over approximately 24 hours. Governed by the circadian axis, with the suprachiasmatic nucleus (SCN) as its pivot, this complex system integrates sensory input from retinal photoreceptors to coordinate essential rhythmic outputs crucial for circadian regulation. Melatonin, a prominent circadian-regulated hormone, possesses the remarkable ability to synchronize biological rhythms.

Disruptions to this finely tuned mechanism, induced by sudden shifts in routine or seasonal changes, negatively affect circadian integrity. These disturbances can trigger affective disorders, including minor depressive episodes and Winter Blues, underscoring the close relationship between circadian rhythms and mental well-being. Furthermore, individuals with mood disorders often experience a myriad of irregularities in their sleep–wake cycles, highlighting the intricate interplay between biological rhythms and psychological equilibrium.

By unraveling the complexities of these rhythms and elucidating the environmental factors influencing them, novel avenues emerge for developing therapeutic interventions aimed at correcting or even preventing disruptions in biological rhythms. This multifaceted approach holds promise for enhancing our understanding of circadian biology and fostering innovative strategies to promote holistic health and well-being.

Keywords: Chronobiology, Circadian rhythms, Melatonin, Seasonality, Suprachiasmatic nucleus.

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Introduction

Chronobiology, rooted in the Greek words "chrónos" for time and "biology," embodies the scholarly pursuit of unravelling the intricacies of biological time and rhythmic phenomena within organisms.[1] This multidisciplinary field delves into the mechanisms by which living entities synchronize with the cyclical rhythms dictated by celestial bodies such as the sun and moon.

The circadian clock—which comes from the Latin words "circa" and "dies," meaning "about a day"—is essential to this investigation.[2] These intrinsic timekeeping mechanisms, or biological clocks, enable organisms to forecast and adjust to environmental shifts autonomously, irrespective of external light-dark cues linked to day and night. Considering the pervasive presence of circadian rhythmicity across myriad human functions, encompassing both physiological and psychological realms, it is logical to infer that disturbances in the internal mechanisms orchestrating circadian oscillations could incite physical and mental manifestations, potentially culminating in pathological states.[3]

The influence of circadian rhythms extends across a spectrum of bodily activities, encompassing sleep–wake cycles, temperature regulation, hormonal fluctuations, and cognitive functions including attention and mood.[3] As a regulatory force, the circadian cycle exerts significant control over various physiological processes, earning it the epithet of "pacemaker."[3] To maintain synchronization with an individual's environment and preferred daily routine, these circadian rhythms depend on both internal mechanisms and external cues, termed zeitgebers, which provide temporal signals to the body.[4]

Traditionally, the primary markers used to assess human circadian rhythms have been core body temperature and melatonin levels in saliva or plasma. Nevertheless, there is a compelling case to consider behavioral rhythms associated with sleep patterns, meal timings, work schedules, and social commitments as equally vital circadian indicators. Moreover, these behavioral patterns carry profound significance for individuals, shaping their daily routines and interpersonal interactions.[5]

The circadian rhythm, with its duration spanning around 24 hours, emerges as one of the most extensively studied and understood biological rhythms. It orchestrates fundamental physiological processes including sleep–wake patterns, dietary behaviors, fluctuations in core body temperature, neural activity, hormonal release, and cellular rejuvenation.[6]

Circadian rhythms, characterized by diurnal, nocturnal, and crepuscular patterns, intricately govern the temporal dynamics of life. Diurnal rhythms harmonize with the ebb and flow of the day–night cycle, while nocturnal rhythms unfold under the veil of darkness, and crepuscular rhythms mark the transition between dawn and dusk. In contrast, ultradian rhythms, pulsating with shorter intervals and higher frequencies, dictate phenomena like

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feeding cycles in the animal kingdom, while infradian rhythms extend their sway beyond the confines of a single day, exemplified by the human menstrual cycle.[7]

Leading this timing is the circadian axis, which is controlled by the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. The SCN, acting as the primary pacemaker, coordinates a wide range of rhythmic outputs, weaving them into the fabric of the circadian pacemaker. Each of its neurons, imbued with intrinsic rhythmicity and imbued with gamma-aminobutyric acid (GABA), reaches its crescendo during the subjective day.[8]

Melatonin, a pivotal hormone intricately intertwined with the circadian rhythm, emerges as a master conductor in the synchronization of biological rhythms. Its genesis unfolds along a complex multisynaptic pathway, stemming from the SCN's command center and extending its reach to the pineal gland. Yet, this symphony is not without its nuances—exposure to light acts as a conductor's baton, suppressing melatonin synthesis and nudging its circadian phase, while diminished SCN activity prompts a surge in melatonin production. As night descends and sleep embraces us, melatonin's crescendo reaches its zenith, only to wane with the first light of dawn, marking the dawn of a new day.[9,10]

Regulation of Circadian Rhythms

Orchestrates a sophisticated dance of biological mechanisms. At the forefront of this intricate system are specialized photosensitive ganglion cells within the retina, housing the photopigment melanopsin.

These cells function as vigilant guardians, detecting light stimuli and sending them to the SCN, which is located inside the hypothalamus and serves as the main conductor of our circadian rhythm, via the retinohypothalamic tract. Neural channels spiral down from this hub, interacting with the spinal cord and superior cervical ganglia. Subsequent post-ganglionic neurons embark on a homeward journey, traversing back to the pineal gland—a vital node where melatonin, the cornerstone hormone in circadian governance, is meticulously crafted and dispatched. Melatonin, in its profound wisdom, acts as a nuanced feedback mechanism, sculpting the rhythmic tapestry of the SCN and harmonizing an array of physiological processes.

This intricate network of pathways ensures the synchronization of circadian rhythms with environmental cues, ultimately regulating biological functions across the body.[11,12]

Circadian Rhythm Biological Indicators

- Physiological and biochemical characteristics are the main phase indicators that are used to measure the circadian rhythm's timing:
- Melatonin secretion in essence, for evaluating the circadian pacemaker's performance, the dim light melatonin onset (DLMO) is an excellent indicator. It assists with diagnosing entrainment to the 24-hour light/dark cycle, assessing mood and sleep issues, and figuring out the best times to administer therapeutic interventions like melatonin therapy or bright light exposure.[13]
- Core body temperature: The nadir of rectal temperature in an average adult typically occurs around 5 a.m., representing the lowest point in the daily temperature cycle.
- Plasma cortisol levels: The concentration of cortisol in the bloodstream serves as another marker of circadian rhythm timing.
- Physiological changes: Parameters such as heart rate, blood pressure, and brain wave activity also exhibit rhythmic variations over a day.
- Cellular processes: Circadian regulation extends to a plethora of cellular activities, encompassing oxidative stress, cell metabolism, immune and inflammatory responses, and the orchestration of the stem cell microenvironment. This intricate interplay sheds light on the temporal dynamics inherent in the circadian rhythm.[14]

Sleep

It is an integrated product of two oscillatory processes: first, sleep homeostasis is a captivating phenomenon characterized by oscillations arising from the buildup and release of sleep debt, intricately modulated by the neurotransmitter adenosine, and second, the circadian clock governs the daily cycle of sleep propensity or arousal. It influences the frequency and intensity of hormonal secretory pulses, notably impacting the secretion of renin and growth hormone. While melatonin and cortisol levels remain relatively unaffected, changes in posture, behavior, and exposure to light during sleep also play a role in circadian rhythm regulation.[15]

A noteworthy correlation has been observed between the function of the circadian pacemaker and individuals' morningness and eveningness tendencies. Referred to colloquially as "morning people" and "evening people," these distinct groups exhibit contrasting patterns in their waking and sleeping routines. Morning individuals typically awaken between 5 and 7 a.m. and retire for the night between 9 and 11 p.m.

Contrastingly, individuals with evening chronotypes often rise later, typically awakening between 9 and 11 a.m., and people fall later, typically spanning from 11 p.m. to 3 a.m. The majority of individuals fall along a spectrum between these two extremes. Morning types tend to adhere more strictly to their circadian rhythms, while evening types demonstrate a greater capacity for adapting to fluctuating schedules. One conjecture posits that evening types exhibit reduced reliance on external light cues for circadian entrainment, suggesting heightened internal regulation over their biological clocks. Notably, the pineal gland remains inactive during daylight hours but becomes active in darkness, inducing diminished alertness while escalating drowsiness.[16]

Sleep and core body temperature: At around 5 a.m., rectal temperature reaches its nadir, approximately 2 hours before the usual wake time. For morning types, for morning individuals, this aligns with the midpoint of their typical 8-hour sleep duration, whereas for evening types, it occurs closer to their waking hours. Melatonin phase markers demonstrate a more robust association with sleep timing when contrasted with the minimum core temperature. The diminishing trend in melatonin levels proves to be more consistent and dependable than the cessation of melatonin synthesis.[17]

Seasonality

The fluctuation in day length stands as the reliable marker for seasonal shifts. Longer nights during winter prompt extended periods of heightened melatonin secretion, contrasting with shorter nights in summer, which lead to abbreviated melatonin elevation. In seasonally breeding creatures, the melatonin profile is influenced by day length, interpreted by the reproductive axis via melatonin receptors within the pituitary glands pars tuberalis. Notably, birth rates exhibit seasonal fluctuations, with minor peaks observed during spring and summer. Throughout the year, the duration of elevated melatonin remains constant, underscoring humans' ability to register changes in day length. Nevertheless, this innate capacity is often obscured by artificial lighting schedules and unwanted noise disturbances pervasive in contemporary society.[18]

Aging

As individuals age, their circadian system undergoes significant changes, including a shortened circadian period and an advanced circadian phase. This results in earlier waking and sleeping times, with reduced amplitudes of circadian rhythms. Aging also leads to decreased tolerance to phase shifts, such as those from jet lag, and alterations in sleep patterns characterized by diminished slow-wave sleep and disrupted circadian regulation of cortisol levels.[19]

Disorders of Circadian Rhythm

Disorders of circadian rhythm involve disruptions from routine changes, seasonal shifts, and genetic factors, affecting the body's internal clock. These disturbances impact various biological rhythms, including sleep–wake cycles, appetite regulation, and social rhythms. Often accompanying mood disorders like major depression and bipolar disorder, lead to physiological imbalances such as temperature fluctuations, cortisol levels, and melatonin secretion. Additionally, genetic sleep disorders like mood disorders interact with both delayed sleep–wake phase syndrome (DSPS) and familial advanced sleep–wake phase disorder (FASPS), highlighting the intricate connection between circadian rhythm abnormalities and mental health. Circadian rhythm sleep disorders encompass both contextual variants such as jet lag and shift work sleep problems, as well as built-in types such as DSPS, advanced sleep–wake phase disorder, irregular sleep–wake rhythm disorder, and nonsynchronized sleep–wake moreover to pre-existing varieties including nonsynchronized sleep–wake disorder, advanced sleep–wake phase disorder, irregular sleep–wake rhythm disorder, and DSPS.[19–21]

Delayed Sleep–Wake Phase Disorder (DSPS)

When there is a discernible lag between the internal circadian rhythm and the external light-dark cycle, it is referred to as DSPS. This incongruity precipitates challenges in initiating sleep during customary bedtime hours, alongside a proclivity for sleep onset and awakening times that deviate toward later intervals compared with the traditional schedule.

Despite resembling insomnia, individuals with DSPS typically exhibit no difficulties when permitted to adhere to their innate sleep schedule. However, the persistent sleep deprivation associated with DSPS can detrimentally affect productivity and elevate the risk of depression and other stress-related ailments. The disorder is associated with genetic variations in the hPER3 gene and presents in two distinct forms: adolescent/temporary onset, affecting a substantial portion of teenagers, and lifelong DSPS, impacting a smaller percentage of adults. Light therapy, melatonin supplements, or adhering to the patient's normal sleep–wake cycle are possibilities for treatment approaches.[22–24]

Advanced Sleep–Wake Phase Disorder

The condition known as advanced sleep–wake phase disorder describes a state in which sleep quality is maintained but sleep onset and wake hours are earlier than traditional social expectations. Despite its lower prevalence compared to Delayed Sleep Phase Syndrome (DSPS), ASPD often evades detection due to the affected individual's ability to conform to conventional work schedules seamlessly. In cases of autosomal-dominant FASPS, people usually experience an advancement of about 4 hours in their sleep–wake cycle each day. This phenomenon stems from a single nucleotide polymorphism within the hPER2 gene, culminating in compromised functionality of the molecular mechanisms governing the circadian rhythm.[25]

Nonsynchronized Sleep–Wake Disorder

Within this disorder, individuals experience a delay in the onset of sleep each day. Typically, it extends by approximately 1–2 hours, reflecting a circadian cycle ranging between 25 and 26 hours. Nonetheless, certain individuals may manifest significantly lengthened delays in their sleep onset. This disorder presents a significant challenge to individuals, particularly those who are blind but also impacts sighted individuals, marked by a daily postponement in the initiation of sleep, individuals experience a cyclical disruption of their sleep patterns, alternating between periods of wakefulness and sleep during conventional day and night hours or residing in darkness during alternate periods. This inconsistency not only hampers daily activities like employment and social engagements but also fosters feelings of isolation, compromises physical health, and can precipitate depressive symptoms. The disorder exacerbates existing health concerns due to disrupted circadian rhythms.

Optimal management approaches, encompassing the regulation of sleep schedules, cultivation of robust social support networks, and comprehensive addressing of mental health concerns, are imperative in ameliorating the detrimental repercussions of nonsynchronized sleep–wake disorder, thereby enhancing persons' overall quality of life and holistic well-being. Conversely, the disorder known as disrupted sleep–wake cycle syndrome is characterized by at least three episodes of irregular sleep. Transpiring within a 24-hour period, predominantly afflicts elderly individuals grappling with dementia. However, this disorder also manifests in cohorts with developmental disorders like autism spectrum disorder and those grappling with traumatic brain injury or brain tumors.[26,27]

Shift Work Sleep Disorders

The excerpt discusses two interrelated phenomena: sleepiness in individuals whose work hours overlap with typical sleep periods, and sleep deprivation resulting from sudden transitions in sleep schedules. In both cases, manifestations include a propensity for napping, diminished cognitive acuity, heightened irritability, decreased productivity, and increased susceptibility to accidents. External disruptions such as noise and social commitments often hinder attempts to rest during unconventional hours, exacerbating the misalignment with the body's circadian rhythm, furthermore, nighttime light exposure can cause sleep deprivation by the suppression of melatonin production. Nevertheless, sleep deprivation symptoms frequently gradually improve when a regular sleep–wake routine is followed. These observations underscore the significance of maintaining regular sleep patterns as a pivotal strategy in mitigating the adverse consequences of sleep disturbances on both overall well-being and cognitive performance.[28,29]

Jet Lag

Due to the timing of day and night shifts in the new time zone, transmeridian travel causes a disruption in the biological clock and the sleep–wake cycle. This discrepancy often consequent in pronounced fatigue and a general sense of malaise. However, as the body gradually adapts to the altered schedule, its internal clocks undergo an adjustment period, ultimately ameliorating these symptoms.[29]

Treatment for Sleep–Wake Cycle Disturbance

Behavioral therapy or sleep hygiene intervention entails instructing the patient to refrain from daytime napping and the consumption of caffeine and other stimulants prior to bedtime. Additionally, patients are advised to reserve their bed solely for sleep and sexual activities.[30]

Bright light therapy, utilized to synchronize sleep patterns by either advancing or delaying the circadian rhythm, entails subjecting individuals to intense light exposure from sources such as natural sunlight for roughly 30–60 minutes every day, either a light box emitting up to 10,000 lux or a wearable light therapy device emitting up to 500 lux. The timing of the therapy session is meticulously calibrated to achieve the desired adjustment in the circadian rhythm, whether it involves an advancement or a delay.[31]

Dark therapy involves wearing blue and blue-green blocking goggles during evening hours to prevent the suppression of melatonin production. Medications like melatonin, modafinil, and Tasimelteon are used for treatment, and sleep phase chronotherapy helps adjust sleep timing.[32]

Seasonal Affective Disorder (SAD)

The most evident manifestation of seasonality in human behavior is observed through recurring major depressive episodes, interspersed with periods of remission. Despite its association with cyclic patterns, is not recognized as a standalone mood disorder in formal psychiatric classifications. Instead, its diagnosis is contingent upon meeting the criteria for a major depressive episode. In other words, individuals must exhibit symptoms consistent with major depression before their condition can be classified as SAD. Following this, meticulous evaluation is conducted to determine the presence of seasonal pattern specifier criteria, thereby aiding in the diagnostic process for SAD.[33]

Seasonal affective disorder is diagnosed when there is a consistent temporal correlation between the onset of major depression episodes and particular seasons of the year, regardless of any apparent season-related psychosocial stressors. Alongside these episodes, which may feature complete remissions or transition to states of mania or hypomania, discernible temporal patterns emerge, aligning with distinct times of the year. Diagnosis requires the occurrence of two major depressive episodes within the preceding two years, each meeting specified criteria, with the absence of nonseasonal episodes during this period. Additionally, individuals diagnosed with SAD experience a higher frequency of major depressive episodes during specific seasons compared with nonseasonal episodes throughout their lifetime.[34]

Winter Blues

This condition delineates a type of depression characterized by recurrent episodes of low mood, usually encountered in the winter. Recurrent episodes of low mood in the autumn and winter are the hallmark of SAD, a kind of depression, with symptoms like low energy, oversleeping, weight gain, and social withdrawal. As spring and summer bring longer daylight hours, symptoms often improve. With a prevalence ranging from 4 to 9% in the general population, women are disproportionately affected, being four times more likely than men. The SAD patients often exhibit a delayed phase in their circadian clock. Treatment commonly involves daily exposure to broad-spectrum ultraviolet-filtered white light with high irradiance (5,000–10,000 lux) for 45–90 minutes. Recent studies have suggested augmented efficacy when combined with cognitive–behavioral therapy and occasionally supplemented with monoamine oxidase inhibitors (MAOIs).[33,35]

Circadian Rhythm and Bipolar Disorders

Variations in the sleep–wake cycle are key indicators in diagnosing bipolar disorder, characterized by reduced sleep requirements during manic episodes and insomnia or hypersomnia during depressive episodes. Disruptions in biological rhythms, including fluctuations in body temperature, cortisol levels, and hormone secretion, contribute to the pathogenesis of bipolar disorder. The social zeitgeber theory posits that these irregularities precipitate mood episodes, increasing the risk of relapses and worsening prognosis. Therapeutic interventions targeting the circadian system, such as behavioral strategies and pharmacological approaches, offer promising avenues for managing bipolar disorders.[13,36–38]

Circadian Rhythm and Depression

Individuals with depression commonly exhibit a myriad of disruptions in their sleep architecture, while those genetically predisposed to either "eveningness" or "morningness" display an increased vulnerability to depressive symptoms. Moreover, a decrease in the quantity of deep sleep preceding the onset of depression is frequently observed.[39] Therefore, it is imperative to adhere to a consistent schedule, ensuring regularity in bedtime and waking hours, thereby maintaining a stable duration of sleep each night.[40] For those inclined toward early rising, maintaining a consistent schedule becomes especially vital, as their circadian rhythms demonstrate reduced flexibility toward behavioral changes. However, following the commencement of antidepressant or mood stabilizer therapy and subsequent patient recuperation, normalization of these rhythms is observed.[41]

Circadian Rhythm and Schizophrenia

The ability of insomnia to endure through different situations in terms of both sleep induction and maintenance, regardless of medication or clinical stage. It notes changes in the sleep architecture, particularly reduced time in the N3 stage of deep sleep and reduced time in the REM stage of sleep. These disruptions in the circadian rhythm, coupled with difficulties in falling and staying asleep, are hypothesized to be associated with an overactive dopaminergic system and impaired functioning of the GABAergic system.[42,43]

Substance Effects

Substance abuse significantly disrupts the central circadian pacemaker, leading to perturbed rhythms and disturbed sleep patterns in affected individuals. These alterations may increase vulnerability to continued substance misuse and relapse. Genetic and environmental factors can further modify the sleep–wake cycle, potentially heightening susceptibility to addiction. However, stabilizing sleep patterns and circadian rhythms could mitigate this vulnerability, thereby reducing the risk of relapse.[44,45]

Circadian Rhythms in Cancer

Numerous investigations have revealed a concerning trend: cancer patients with disrupted daily rhythms tend to exhibit poorer survival outcomes compared with those with more stable 24-hour rhythms.

An increased risk of colorectal and breast cancer is associated with extended shift employment, a correlation attributed to the inhibition of nocturnal melatonin production induced by nighttime light exposure. This may contribute to the heightened incidence of breast cancer observed among shift workers, potentially via augmented estrogen production. Moreover, individuals in professions involving frequent transmeridian flights, such as flight attendants, often experience disturbances in circadian sleep–wake rhythms, further amplifying their susceptibility to breast cancer.[46–48]

Metabolic Complexity in Obesity

Experimental investigations have elucidated the intricate interplay between the circadian rhythm and blood lipid, glucose, and insulin levels. Shift workers, in particular, demonstrate a heightened susceptibility to metabolic syndrome, a condition characterized by a spectrum of metabolic disturbances including elevated blood sugar levels (hyperglycemia), diminished insulin levels (hypoinsulinemia), dysregulated lipid profiles (dyslipidemia), visceral adiposity, and the ensuing complications arising from these metabolic aberrations.[49,50]

Future Advancers

Unraveling the intricate mechanisms governing the transmission of phase information among biological oscillators offers a promising path toward mitigating circadian desynchronization.

These findings possess the potential to guide the creation of precise pharmacological interventions and behavioral interventions tailored to reestablish circadian equilibrium. Furthermore, recognizing how the circadian system affects the effectiveness of medication marks a notable advancement in the field of chronotherapy.

Summary

Circadian rhythms are fundamental cyclic patterns that govern a diverse array of physiological functions, including behavior, sleep, and hormonal regulation, persisting over a 24-hour cycle. Orchestrated by the circadian clock, nestled within the hypothalamus, these rhythms are finely tuned by environmental cues, notably Sundown and sunrise transitions of the morning–night cycle. Diurnal rhythms align closely with natural daylight cycles, while ultradian rhythms operate on shorter timescales, and infradian rhythms extend beyond 24 hours. Disruptions to the sleep cycle induced by abrupt routine changes or jet lag can disrupt normal rhythmicity, alongside seasonal transitions that affect melatonin secretion and sleep patterns. Such disturbances can precipitate mood disorders, including seasonal affective disorder and depression, underscoring the intricate relationship between biological rhythms and mental health. Despite ongoing research, a comprehensive understanding of this relationship remains elusive, but continued exploration holds promise for uncovering novel therapeutic approaches to mitigate disruptions in biological rhythmicity and their associated health implications.

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