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The Physiology of the Circadian Rhythm

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Abstract

This paper discusses the importance and origin of the Circadian Rhythm. First recorded by Jean Jacque d'Ortous de Mairan in 1729, the Circadian Rhythm is understood to be a fundamental biological system that is tailored to Earth's axis. Having impacts on peripheral organs, sleep patterns, and hormonal balances, this process influences almost every aspect of the human body and several other mammals. Focusing on the Circadian Rhythm is vital to further understanding the "clock-like" patterns of the human body and future research and development of treatments could be the solution to current detrimental diseases and disorders.

Keywords

Circadian Rhythm, Melatonin, Sleep Disturbances

Disciplines

History of Science, Technology, and Medicine | Medicine and Health Sciences | Sleep Medicine

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INTRODUCTION

The Circadian Rhythm is a central biological system of living organisms and has adapted to the rotational pattern of the Earth's axis (Edery 2000). The concept of the system was first recorded by Jean Jacque d'Ortous de Mairan, a French astronomer, in 1729 while documenting daily leaf movement patterns that were placed in a dark cupboard (Rutter et al. 2002). His observations were vital as they showed the absence of light affected the rhythmic leaf movement patterns, which is now explained by the internal circadian clock.

With Latin etymologies that mean *circa* (around) and *diem* (day) (Blancas-Velazquez et al. 2017), the circadian rhythm is advantageous to organisms as it used to sync with the timing of organismal processes (Rutter et al. 2002). This synchronization is key because it allows for organisms to adapt to the cyclic changes in the external environment. Also known as a "master pacemaker," the internal clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Dibner & Schibler 2015). The SCN plays a key role in controlling the internal cellular clocks of periphery organs which are dependent on body temperature rhythms, feeding cycles, and oscillating bloodborne signals.

In mammals, the circadian system is coordinated with essentially all physiological processes such as metabolism cardiovascular activity and endocrine function (Dibner & Schibler 2015). In the past two decades, research has proven that almost every cell in the body has a circadian timekeeper which not only emphasizes the importance of this system but also how the circadian system is a commonality for a majority of species (O'Neill & Reddy 2011). Additionally, in the past two decades, researchers have traced more connections between different species and the circadian system, which has aided in the development of treatments for circadian rhythm malfunctions (Edery 2000).

CIRCADIAN TIMING SYSTEM

The circadian clock can be categorized into two main components: the central clock located in the SCN of the hypothalamus, and the peripheral clocks that are nearly in every tissue level and organ system (Richards & Gumz 2013). Additionally, circadian rhythms are defined by exhibiting three principal properties: reset by changes in external environmental conditions, persist with a period of around 24 hours in absence of extrinsic time cues, and withstand variation over a wide range of temperatures (Edery 2000). Feeding cues and light signals can entrain the central circadian clock and the peripheral clocks are synchronized as a result. As light enters through the retina of the eye, electrical signals pass through to the hypothalamus and are converted to chemical signals in the SCN. Although the two clocks can be entrained independently, meaning extrinsic stimuli can change or reset the phase of a circadian clock (Rutter et al. 2002), the character of their relationship can be described as the association between a conductor and orchestra (Dibner & Schibler 2015). Every peripheral clock can function independently, but the aid of the central clock helps the peripheral clocks synchronize.

The mechanism of the molecular clock is modeled by an oscillating transcription-translation feedback loop (TTO) (O'Neill & Reddy 2011). In overview, the feedback loop has clock proteins that negatively regulate their transcription, resulting in the production of the rhythmic clock gene expression. The two main proteins of the circadian system are CLOCK and BMAL1, which interact in the promoters of target genes and drive the positive transcription element of the TTO loop (Richards & Gumz 2013). Expression of these proteins inside the cell can influence the several signaling pathways that allow cells to pinpoint the time of day and perform applicable functions (Reddy et al. 2020). Majority of the clock genes program transcription factors and regulators, which then lead to rhythmic activation. There are three vital circadian promoter elements: E-boxes, D-boxes, and retinoid acid-related orphan receptor response elements (ROREs), which drive the expression of sizable programs of clock output genes related to specific tissues (Harder & Oster 2020). The clock output genes (CCGs) can translate "clock time" into ample physiological signals that can be understood throughout all systems of the body.

When the body transitions from light to dark, inputs are sent to the retinohypothalamic pathway. In the light cycle, axons in the retinal ganglionic cells deliver signals to activate the suprachiasmatic nucleus through the optic nerve, cranial nerve II. After, the SCN carries a signal through the inhibitory transmitter, gamma-amino-butyric acid (GABA), to hinder the paraventricular nucleus. When these inhibitory signals are relayed, they have repressive effects on the sympathetic nervous system, and as a result, melatonin does not get released from the pineal gland into blood circulation. As the night hours approach, the absence of light signals the retinal ganglion cells to inhibit the suprachiasmatic nucleus, activate the paraventricular nucleus, resulting in stimulating the sympathetic nervous system, and tiredness is induced (Pritchett & Reddy 2015).

Building upon the mechanism of the central circadian system, the SCN also synchronizes the numerous cellular clocks in peripheral organs by utilizing several signal transduction pathways, dependent on feeding cycles, body temperature rhythms, and oscillating hormones (Dibner & Schibler 2015). The most dominant zeitgebers (time givers) for a majority of peripheral organs are feeding cycles. The SCN pacemaker is pretty resilient to various feeding rhythms and maintains its original composition, the peripheral clocks are uncoupled from the SCN. If there is a conflict with the feeding cycles, the SCN takes a more direct approach to counteract the dominant signals that depend on the metabolic cycles of the body. Once the conflicting feeding rhythms are subdued, the SCN promptly resumes its role as master pacemaker and can adjust the phase of the oscillators in the periphery organs within two to three days.

DEVELOPMENT OF CIRCADIAN SYSTEM

Accounting for the significant role the circadian system plays in the body, its development and progression are quite interesting, as they have postnatal natures (Harder & Oster 2020). While in the womb, the fetus is not yet exposed to external stimuli, on entrainment, so neonates are born with “an immature functioning system” (Edery 2000). Within the first four-month of life, the newborn has to rapidly adapt to new physiological changes and environments. The establishment of the circadian rhythm is known to be heavily associated with core body temperature, which is one of the most firmly controlled systems in the body. Although little variation occurs in the womb, the newborn is exposed to the perception of night and day, within the first few weeks out of the womb. This exposure helps with the development and control of melatonin and aids in permanently establishing a newborn’s circadian rhythm, within the first three months.

FACTORS AND CONSEQUENCES ON CIRCADIAN RHYTHM

Under typical conditions, the circadian rhythm is synchronized to the 24 hours cycle and is extremely sensitive to alterations in various inputs like light exposure, dietary choices, and work shifts. Exposure to light in the evening or early morning hours significantly affects the circadian clock (Dijk & Landolt 2019). Later hours of the night delay the clock and the rise of melatonin will likely occur while the early morning hours will advance the clock and trigger the cortisol rhythm to occur earlier (Duffy & Wright 2005). These light input variations not only contribute to sleep disturbances, but they alter the hormonal releases of melatonin and cortisol.

Unfortunately, the timing of the circadian clock is increasingly more jeopardized because of the insufficient exposure to daylight as humans spend more hours of their day indoors (Huang et al. 2011). Low levels of exposure to daylight, particularly in the winter months, will have a direct correlation to the increase in the delaying effects of artificial light.

DISORDERS AND DISEASE

Quite often, disorders and diseases linked to the circadian rhythm are often overlooked and can have extremely detrimental effects on the human body. Sleep disorders are known to typically manifest as a misalignment between an individual's sleep timeline and the 24-hour external environment cycle (O'Neill & Reddy 2011). These malfunctions are associated with numerous disorders such as manic-depression, seasonal affective disorder (SAD), chronic sleep disturbances, and diseases of specific body systems (Kim et al. 2018). Through several studies that have been conducted in rodents and humans, the results have demonstrated the important role the circadian clock plays in cardiovascular disease. In a study conducted by Martino et al., a mouse transverse aortic constriction model was used to disrupt the circadian clock in mice, which resulted in reduced contractility and increased cardiac hypertrophy. This model additionally showed that several genes that are associated with cardiac remodeling, i.e. glycolysis, and fatty acid metabolism, had significant alterations. This study emphasizes the correlation between desynchronization and disease development: desynchronization leads to an increased risk for cardiovascular occurrences (Martino et al. 2007).

Along with cardiovascular events, the circadian system also has demonstrated that there is a connection between its malfunctioning and the development of diabetes. In recent studies, there appears to be an association between melatonin signaling and diabetes. In a study conducted by Mantele et al., three groups of men (obese nondiabetic, lean, and obese Type 2) had their melatonin levels observed to conclude if there was a correlation between melatonin levels and diabetes. Nondiabetic obese men had significantly higher plasma melatonin levels than the other two groups. The conclusions from this study provide evidence that the inhibitory characteristics of melatonin cause lowered insulin levels, and therefore can contribute to a diagnosis of diabetes (Mantele et al. 2012). Although this research requires more investigation to completely establish the connection between the circadian clock, melatonin, and diabetes, the aforementioned studies have emphasized the significance melatonin and the circadian clock have in diabetes and glucose regulation.

COUNTERMEASURES

To counteract the disruption to the circadian rhythm, several natural and artificial countermeasures can help with ameliorating the aforementioned disorders and diseases (Potter et al. 2016). Melatonin, a natural hormone produced by the pineal gland, is under circadian regulation and is known to have significant alleviation of disorders associated with disruptions to the circadian rhythm (Edery 2000). The release of this hormone is closely synchronized with the routine hours of sleep and alterations in synchronization are correlated with sleep disturbances. The alterations essentially disrupt the release of melatonin from the pineal gland which affects sleep propensity, the speed of falling asleep, and the quality and disruption of sleep (Brzezinski 1997). In the study conducted by Brzezinski, in young adults, the oral administration of 5 mg of melatonin had a significant increase in the duration of rapid-eye-movement (REM) sleep propensity and sleep propensity. The results from this study indicate that increasing melatonin concentrations can trigger the onset of sleep regardless of the internal circadian rhythm.

In addition to the non-pharmaceutical intervention, melatonin, the introduction and research of blue light have been key to understanding how to counteract circadian rhythm disruptions (Mohawk et al. 2012). As discussed in Czeisler's study, the artificial light that strikes the retina between the hours of dusk and dawn inhibits sleep-promoting neurons and suppresses the sleep-inducing hormone melatonin. Solid white light, otherwise known as artificial light, is habitually rich in blue light which is short in wavelength and creates the most sensitivity to the rods and cones in the eye (Czeisler 2013). The prolonged exposure to blue light from technological devices, light-emitting diode (LEDs), were found to be more disruptive to circadian rhythms and melatonin secretion than incandescent lighting. From this discovery, several strategies and preventions have been developed to ameliorate the disruptions caused by harsh blue light exposure. Besides turning off electronic devices two to three hours before sleeping, wearing orange-tinted glasses has been evaluated and effectively reduced the emission of short-wavelength blue-enriched light (Var der Lely et al. 2015). Van der Lely et al, discussed that blue-enriched light exposure in evening hours led to amplified alertness and high cognitive performance in adolescents. More importantly, they found that the results of their study show that blue light glasses attenuate the suppression of melatonin and overall prevent light-induced suppressive effects.

In contrast to the non-pharma and therapeutic interventions, like melatonin and blue-light blocking glasses, there are pharmaceutical medications that have been researched as additional countermeasures for circadian rhythm disruption. The progression of circadian rhythm disorders, whether intrinsic (aging, sleep disorders) or extrinsic factors (work shifts), has led to the development of chrono-biotics (Cardinali et al. 2006). The term is defined as "a substance capable of shifting the phase of the circadian system thus re-entraining circadian rhythms," (Cardinali et al. 2006). The first use of chrono-biotics was H.W. Simpson in 1973 but it was not understood until much later that it could specifically affect the physiological regulation of biological temporal structures, and more importantly circadian rhythms (Dawson & Armstrong 1996). Overall, chrono-biotics help synchronizes the sleep-wake cycle in individuals that are suffering from a delayed sleep cycle, like jet lag (Cardinali et al. 2006).

CONCLUSION

The circadian rhythm is a system that is the internal clockwork and biological pace making foundation of several species and has evolved independently in various species lineages (Loudon 2012). The findings and results of the studies mentioned, and all of the ongoing research, suggest that there is ample amount of evidence that the circadian clock is a potential new drug target for various disorders (Richards & Gumz 2013). With continued research, drug development to ameliorate disruptions to the circadian rhythm could be the breakthrough of understanding detrimental diseases like Alzheimer’s disease, insomnia, and diabetes.

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