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Egypt J Neurol Psychiatry Neurosurg (2022) 58:34
https://doi.org/10.1186/s41983-022-00468-8

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

REVIEW Open Access

The neurophysiologic basis of the human sleep–wake cycle and the physiopathology of the circadian clock: a narrative review

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Abstract

The objectives of this review were to explain the neurologic processes that control the human sleep–wake cycle as well as the pathophysiology of the human circadian clock. Non-rapid eye movement and rapid eye movement sleep are the two main phases of sleep. When triggered by circadian input from the anterior hypothalamus and sleep–wake homeostatic information from endogenous chemical signals (example, adenosine), the ventrolateral preoptic nucleus initiates the onset of sleep. Arousal in which there is a conscious monitoring of the surroundings and the ability to respond to external stimuli is known as wakefulness. It contrasts the state of sleep, in which receptivity to external stimuli is reduced. The higher the synchronous firing rates of cerebral cortex neurons, the longer the brain has been awake. Sleep–wake disturbances induced by endogenous circadian system disruptions or desynchronization between internal and external sleep–wake cycles are known as circadian rhythm sleep–wake disorder (CRSWD). Patients with CRSWD usually report chronic daytime drowsiness and/or insomnia, which interferes with their activities. CRSWD is diagnosed based on the results of some functional evaluations, which include measuring the circadian phase using core body temperature, melatonin secretion timing, sleep diaries, actigraphy, and subjective experiences (example, using the Morningness–Eveningness Questionnaire). CRSWD is classified as a dyssomnia in the second edition of the International Classification of Sleep Disorders, with six subtypes: advanced sleep phase, delayed sleep phase, irregular sleep–wake, free running, jet lag, and shift work types. CRSWD can be temporary (due to jet lag, shift work, or illness) or chronic (due to delayed sleep–wake phase disorder, advanced sleep–wake phase disorder, non-24-h sleep–wake disorder, or irregular sleep–wake rhythm disorder). The inability to fall asleep and wake up at the desired time is a common symptom of all CRSWDs.

Keywords: Sleeping habits, Sleep stage, Sleep monitoring, Circadian rhythm sleep disorders

Background

The 24-h internal clock in our brain that regulates cycles of alertness and sleepiness by responding to light variations in our surroundings is known as the circadian rhythm [1]. Melatonin is a hormone produced mostly during the dark period in the pineal gland and inhibited by light exposure. It affects circadian rhythms and the sleep–wake cycle [2]. Aging is associated with circadian disruption, such as sleep disruption and inflammation, which leads to metabolic problems [3]. As a result, sleep cycle disruptions result in a lot of pathophysiological alterations that hasten the aging process [4–11]. In different organisms, the circadian clock developed to integrate external environmental changes with physiological processes [12–15]. The clock gives the host chronological accuracy and a remarkable capacity to adjust to its environment. Whenever circadian rhythms are disrupted or distorted because of sleeplessness, rotating shifts, or other lifestyle variables, negative health repercussions emerge, and the risk of diseases like cancer,

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cardiovascular disease, and metabolic disorders rises [16–18]. Although the detrimental effects of circadian rhythm disruption are now commonly recognized, there is still a lack of substantial evidence on how to take full advantage of, or correct, biological timing for medical benefits. The objectives of this narrative review were to explain the neurologic processes that control the human sleep–wake cycle as well as the pathophysiology of the human circadian clock.

Methods for literature search

Original studies, book chapters, and review articles that reported on the neurologic processes that control the human sleep–wake cycle as well as the pathophysiology of the human circadian clock were searched in the following electronic databases: PubMed, Scopus, and the Web of Science. The following Medical Subject Headings were used to search for articles in the above-mentioned databases: Sleeping Habits, Sleep Stage, Sleep Monitoring, Circadian Rhythm Sleep Disorders. Full articles were assessed, and relevant information was extracted.

The neurophysiology of sleep

There are two major phases of sleep: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep [19]. The ventrolateral preoptic nucleus contains gamma-aminobutyric acid (GABA) and galanin, and when triggered, initiates the onset of sleep via circadian input from the anterior hypothalamus and sleep–wake homeostatic information from endogenous chemical signals (example, adenosine), which accumulate in proportion to time spent awake [19]. As an individual falls asleep, the electroencephalogram (EEG) primarily changes from a state of high frequency and low voltage waves in the waking state to higher voltage and slower waves signifying NREM sleep. Thereafter, another transition occurs from NREM into REM sleep, characterized by lower voltage and higher frequency action [19]. Circadian and homeostatic signals are integrated in the diencephalic structures to initiate sleep [19]. Once sleep is initiated, an ultradian oscillator in the mesopontine junction modulates the usual alternation of NREM and REM sleep [19]. During NREM sleep, there is decreased sympathetic tone and increased parasympathetic activity that creates a state of reduced activity [19]. REM sleep is characterized by increased parasympathetic activity and adjusted sympathetic activity [20]. NREM sleep occurs in 3 stages. Stage 1 of NREM sleep is the switch from wakefulness to sleep, which usually lasts less than 10 min; it is a light sleep stage characterized by slow breathing and heartbeats and muscle relaxation [21]. Stage 2 of NREM sleep is also a light sleep stage, preceding the deep sleep stages of NREM sleep. Breathing and heartbeats become slower, with more relaxation of muscles and slower brain activity. This stage lasts for about 30–60 min [21]. Stage 3 involves deep sleep, where breathing and heartbeats become very slow. In this stage, muscles are relaxed, and brain waves are even slower. This stage lasts for about 20 to 40 min [21].

REM sleep is the final phase of sleep before a new cycle begins. Breathing and heartbeats are faster in this phase, and most dreaming occurs during REM sleep [22]. NREM sleep is associated with significant reductions in blood flow and metabolism, while total blood flow and metabolism in REM sleep is comparable to wakefulness [22]. Growth hormone secretion usually occurs during the first few hours after sleep onset while thyroid hormone secretion increases later [22].

Neurophysiology of wakefulness

Wakefulness is a state of arousal in which there is a conscious surveillance of the environment and the ability to respond to external stimuli [23]. It juxtaposes the state of sleep in which there is decreased sensitivity to external stimuli [23]. The longer the brain has been awake, the higher the synchronous firing rates of cerebral cortex neurons. However, after prolonged periods of sleep, both the speed and synchronicity of the neurons' firing are reduced [24]. Wakefulness reduces glycogen in astrocytes, which delivers energy to neurons, and this is replenished during sleep [25]. Wakefulness occurs via communication between several neurotransmitters arising in the brainstem and ascending through the midbrain, hypothalamus, thalamus, and basal forebrain [26]. The posterior hypothalamus contributes importantly to cortical activation that triggers wakefulness [26]. Neural communications involving the posterior hypothalamus control shifts from wakefulness to sleep and vice versa [26]. Histamine neurons in the tuberomammillary nucleus and adjacent posterior hypothalamus project into the whole brain and impact wake-selective brain networks [27]. Orexin-containing neurons in areas adjacent to histamine neurons project extensively to most brain areas and are linked to arousal [28]. Orexin insufficiency has been associated with daytime sleepiness and unexpected bouts of sleep [29]. Orexin and histamine neurons work synchronously to regulate sleep and wakefulness by contributing to wakeful behaviour and wakefulness and cortical activity, respectively [30, 31].

Homeostatic regulations of sleep

Sleep homeostasis occurs during prolonged wakefulness [32]. Sleepiness and sleep tension increase, and when sleep is allowed, adequate duration and volume of sleep are intended to compensate [32]. Adenosine in the basal forebrain is a prominent physiological mediator of sleep

homeostasis [32, 33]. Adenosine is an endogenous factor produced in neurons and glia by the metabolism of adenosine triphosphate [34]. Adenosine accumulates in the extracellular space, where it can prompt regulatory actions on the sleep–wakefulness cycle circuits [34]. Adenosine acts on the purinergic receptors A1 and A2 [34].

Caffeine, an adenosine receptor antagonist, is a widely used stimulant. Caffeine promotes a state of alertness by centrally blocking adenosine A2A receptor, a G-protein-coupled receptor that is important for regulating myocardial oxygen consumption, coronary blood flow, and central nervous system neurotransmitters [34]. Nitric oxide, a neuromodulator, is synthesized by inducible nitric oxide synthase in the basal forebrain during prolonged wakefulness [35]. Inducible nitric oxide synthase is produced during inflammation, and there is an association between prolonged wakefulness and activation of the immune response [36]. The influx of histamine, a cortex-activating neurotransmitter, into the basal forebrain increases wakefulness and reduces sleep [31–37]. Persistent wakefulness lengthens the cycle of neuronal activity in various brain areas and consequently increases energy consumption. During energy depletion, the concentration of adenosine increases [38]. Sleep homeostasis may be linked to energy exhaustion because of prolonged neuronal activation during prolonged wakefulness [38]. Recovery sleep after sleep restriction improves less in older animals. Moreover, increases in adenosine, nitric oxide, and lactate concentrations have been found to be blunted in older individuals, signifying that the main regulators of sleep homeostasis and homeostatic sleep responses are affected by aging [39, 40].

Circadian regulations of the human sleep–wake cycle

The daily regulation of sleep/wakefulness relies on the circadian clock involving the suprachiasmatic nucleus (SCN) [41]. SCN neuronal activity displays circadian variations. The SCN connects transcription–translation negative feedback loops to generate circadian rhythms in clock gene expression (involving such clock genes as *Per*, *Cry*, and *Bmal1*) within a period of approximately 24 h [42, 43].

The electrical activity of the SCN is higher during daytime and lower at night [44]. Neurotransmitters and hormonal factors control the circadian rhythm in the SCN. For example, the endogenous rhythm of melatonin secretion, a hormone synthesized and secreted by the pineal gland at night under dark conditions, is harmonized by the SCN and attuned to light/dark cycles. More specifically, blue light (460–480 nm) is capable of suppressing melatonin biosynthesis during the night [45]. However, a key physiological role of melatonin is to carry information regarding the daily cycle of light and darkness to body structures [45]. This information is utilized for the harmonization of physiological activities that react to adjustments during the period of exposure to light [45]. SCN neurons project to specific brain regions, including the sub-paraventricular region and dorsomedial nucleus of the hypothalamus, to control multiple physiological activities. SCN neurons also contribute importantly to the regulation of sleep and wakefulness [46]. The sleep–wake cycle progresses from intervals of wakefulness to NREM sleep to REM sleep. Each alertness stage reflects functioning in several neuronal systems, including the mesolimbic dopamine system [47]. Activating neurons containing glutamatergic nitric oxide synthase 1 promotes wakefulness via projections to the nucleus accumbens, and the lateral hypothalamus, whereas lesioning glutamate cells decreases the initiation of wakefulness [47]. However, activation of GABAergic neurons in the ventral tegmental area promotes long-lasting non-REM-like sleep resembling sedation, whereas lesioning these neurons promotes wakefulness [48].

A two-process model has been posited for the regulation of sleep and wakefulness. These processes (S and C) are powered by homeostatic mechanisms and the circadian clock, respectively [49]. More specifically, process S signifies sleep pressure, which rises as a function of the duration of wakefulness, whereas process C is regulated by the circadian clock, and it relies on the cycle of circadian rhythms in the body [49].

Pathophysiological processes associated with sleep deprivation and an altered circadian clock

Sleep disorders are very common in the global population, and many people who suffer from them go undiagnosed and untreated [50]. A variety of factors, including lifestyle, physiological, psychological, and genetic factors, have been linked to sleep disorders [50]. Sleep–wake cycle disruptions frequently have an impact on mental health [51]. Disruptions in sleep may be precursors to neurodegenerative diseases [52].During normal aging, sleep changes include decreases in total sleep time, REM sleep, and deep NREM sleep, as well as increases in time spent in light NREM phases [53].

However, some oscillatory patterns of sleep alterations mostly decrease slow wave activity and spindle density. Alteration in slow oscillation-sleep spindle coupling and theta-gamma coupling are linked to biomarkers of Alzheimer's disease. Sleep irregularities are associated with amyloid beta and tau protein, suggesting that sleep disruption might reflect early symptoms of Alzheimer's disease [53].

Genes also play an important role in the pathogenesis of sleep disorders [54]. A mutation in *hPer2*, a human

Period gene essential for resetting the central clock in response to light, is linked to familial advanced sleep phase syndrome, an autosomal dominant ailment with early morning waking and early sleep times [55]. Some regulators of gene expression (methylases and acetylases, core clock genes, and ribosomal proteins) are affected by sleep disruption [56].

Mistimed sleep disrupts circadian regulation of the human transcriptome by altering molecular processes of the circadian rhythm system. Proper sleep timing may thus help to organize the human transcriptome's temporal organization [56]. In one study, four days of simulated night shifts diminished temporal coordination between the human circadian transcriptome and external environment, providing insight into mechanisms underlying unfavourable health impacts linked to night shift work [57]. Rhythmic metabolites are misaligned relative to the endogenous circadian system during night shifts, and this could be a factor underling poor metabolic health among shift workers [58]. Given that sleep and mood disorders have been associated with poor performance among healthcare workers [59], mechanistic insight may help intervention development.

Classification of circadian rhythm sleep–wake disorders

Circadian rhythm sleep–wake disorder (CRSWD) is defined as sleep–wake disturbances caused by endogenous circadian system disruptions or desynchronization between internal and external sleep–wake rhythms [60]. CRSWD patients frequently complain of chronic excessive daytime sleepiness and/or insomnia, which interferes with their activities [60].The diagnosis of CRSWD is based on the outcome of some functional assessments that involve assessing the circadian phase using core body temperature, timing of melatonin secretion, sleep diaries, actigraphy, and subjective experiences (example, using the Morningness–Eveningness Questionnaire) [61]. Treatment may include personalized sleep scheduling, circadian phase shifting/clock resetting, and/or the use of hypnotics and stimulant drugs [61]. Epidemiological studies suggest that up to 3% of the global adult population experiences CRSWD [62]. An estimated 10% of adults and 16% of adolescents with reported cases of sleep disruption may have a delay in the sleep–wake cycle of about 3–6 h later than desired [62]. The second edition of the International Classification of Sleep Disorders classifies CRSWD as a dyssomnia, with six subtypes including advanced sleep phase, delayed sleep phase, irregular sleep–wake, free running, jet lag, and shift work types [63]. CRSWD can also be transient (caused by jet lag, shift work, or illness) or chronic (caused by delayed sleep–wake phase disorder (DSWPD), advanced sleep–wake phase disorder (ASWPD), non-24-h sleep–wake disorder (N24SWD), and irregular sleep–wake rhythm disorder (ISWRD) [64]. The major proven feature of all CRSWDs is the inability to fall asleep and wake up at the desired time [64]. It is considered that CRSWDs evolve from problems with internal biological clocks and/or misalignment between the circadian timing system and the external 24-h environment [65].

DSWPD is a common CRSWD. While widespread, it represents a small fraction of severe insomnia. Individuals who are affected report difficulty falling asleep and waking up during normal working hours [66]. Approximately 10% of individuals with insomnia who have sought treatment in hospitals have DSWPD [17]. Higher percentages have been reported based on surveys and telephone sampling. Integrated skewed and unbiased measures estimate the prevalence of DSWPD among the global population to be 0.13–3.1% [67]. DSWPD is more prevalent in girls than in boys [68].

ASWPD is characterized by persistent early evening sleep onset and early morning awakening, although the condition of awakening earlier than anticipated is common among older adults [69]. The prevalence of ASWPD has been estimated to range from 0.25 to 7% [70]. An advanced sleep phase phenotype was found among 0.33% of patients registered in a sleep clinic, and an estimated 1 in 2500 patients evaluated for sleep disorder has ASWPD [71].

N24SWD is a cyclic, often devastating CRSWD characterized by severe difficulties sleeping on a 24-h schedule [72]. Individuals isolated from a 24-h light–dark cycle exhibit sleep–wake cycles different from 24 h [72]. N24SWD is more common among totally blind individuals because of the lack of light information reaching the circadian pacemaker in the hypothalamus [72]. N24SWD is unusual among sighted individuals. It has been associated with delayed sleep–wake rhythm disorder or mental disorders [72].

ISWRD is a circadian rhythm disorder characterized by multiple bouts of sleep within a 24-h period [73]. Individuals report symptoms of insomnia, including difficulty either falling or remaining asleep, and daytime excessive sleepiness [73]. ISWRD is associated with neurological illnesses. It is usually diagnosed among children with neurodevelopmental disorders, patients with neuropsychiatric disorders, and, most usually, older adults with neurodegenerative disorders [73].

Potential risk factors for circadian rhythm sleep–wake disorders

Genetic influences contribute significantly to nearly all types of CRSWD, including DSWPD [74]. A length polymorphism in *hPer3* has been associated with severe diurnal preference [75]. A polymorphism of the gene

coding for arylalkylamine N-acetyltransferase and the leucocyte antigen DR1 have been linked to DSWPD in small studies [76]. Individuals with neurodegenerative disorders (Alzheimer's, Parkinson's, or Huntington's disease) are more likely to experience ISWRD [77]. Blindness or visual impairment is a major risk factor for N24SWD given deficiencies in light perception [78]. The presence of artificial light, noisy environments, and higher room temperatures may impair sleep quality and are vital factors to consider in the management of sleep disorders [79]. Trans-meridian travel predisposes flight attendants to jet lag, a consequence of circadian misalignment that occurs after crossing time zones quickly and outpacing the circadian clock [80].

In addition to genetic factors, physiological and behavioural factors contribute to CRSWD. Changes in sensitivity contribute to the vulnerability of developing CRSWD [81]. Zeitgebers are normal, occurring events functioning as time cues to help regulate the circadian rhythm and thus maintain the sleep–wake cycle [82]. Zeitgebers such as light, eating, and physical activity provide feedback to the circadian clock [82]. However, distorted, or disrupted sensitivity to zeitgebers may increase the risk of CRSWD [83]. The habitual intake of psychoactive substances (example, caffeine) at night may prolong sleep latency, reduce total sleep time, impair sleep efficiency, and worsen perceived sleep quality [84]. Night-shift work also increases the likelihood of experiencing CRSWD because it can disrupt the synchronous relationship between the body's internal clock and the environment [85].

Summary of the clinical features of circadian rhythm sleep–wake disorders

Insomnia, daytime somnolence, sleep disturbances, poor sleep quality, depression, poor concentration, decreased job performance, headaches, reduced cognitive function, and poor coordination are common symptoms of CRSWDs [86–88]. According to the third edition of the International Classification of Sleep Disorders, insomnia is described as a problem with either initiating sleep, maintaining sleep continuity, or experiencing poor sleep quality [89]. Despite advances in the clinical management of CRSWDs, clinical diagnosis of circadian disruption remains complex [90]. Diagnostic specification involves analysing fluctuations of plasma melatonin levels over time, necessitating sequential sampling, typically in the evening and in dim light [90]. However, blood assays have been merged with computational techniques to detect markers of circadian timing, providing accurate assessment of circadian phases [90].

Conclusions

Humans' sleep is characterized by a loss of consciousness and a condition of absolute inertia in a supine position with the eyes closed. The suppression of activity in the ascending arousal systems is necessary for the onset and continuation of sleep. The inhibitory neurons of the ventrolateral preoptic region are responsible for this. CRSWDs are a subset of sleep disorders that are characterized by changes in the circadian system, its synchronization processes, or a lack of alignment of the internal circadian rhythm with the surrounding environment. The primary sleep period is either earlier or later than expected, is irregular from day to day, and/or sleep occurs at the wrong chronological period in CRSWDs. Dysregulation may occur at the SCN, resulting in rhythm mistiming.

Abbreviations

ASWPD: Advanced sleep-wake phase disorder; CRSWD: Circadian rhythm sleep-wake disorder; DSWPD: Delayed sleep-wake phase disorder; GABA: Gamma-aminobutyric acid; ISWRD: Irregular sleep-wake rhythm disorder; N24SWD: Non-24-h sleep wake disorder; NREM: Non-rapid eye movement; REM: Rapid eye movement sleep; SCN: Suprachiasmatic nucleus.

Acknowledgements

None.

Authors' contributions

The author did the literature search, wrote the manuscript, drafted the manuscript, and revised the manuscript critically. The author read and approved the final manuscript.

Funding

This study received no funding.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

Received: 29 September 2021 Accepted: 4 March 2022
Published online: 18 March 2022

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