Chapter

Interaction between Melatonin, Sleepiness-Alertness and Body Temperature

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Abstract

Circadian rhythms confer a biological clock of all living beings, comprising oscillations in a range of physiological variables, including body temperature and melatonin, that regulate the sleep/wake cycle rhythmically. Both variables have been marked to influence the sleep/wake cycle; even so, the interrelationship among the triad (body temperature, melatonin & sleepiness/alertness) is still unknown. The current literature review is envisioned to examine the contemporary details regarding the interaction between melatonin, body temperature, and sleepiness/alertness. All the included information is procured from the latest review articles, systematic & meta-analytical literature reviews, and original research reports. Findings revealed that melatonin and body temperature collectively contribute to the formation of sleep. An increase in melatonin induces fluctuations in body temperature. Both physiologic variables serve as close indicators of sleepiness/alertness. However, modulating factors such as light, environmental temperature, and timing of melatonin administration (with the circadian clock) may impact the overall outcomes. A significant number of studies are required to infer the underlying processes by which these factors influence the circadian clock.

Keywords: Core Body Temperature (CBT), melatonin, sleepiness-alertness, circadian rhythm, light at night (LAN)

1. Introduction

Circadian rhythms are a biological trait shared by all organisms, comprised of oscillations in various physiological variables, such as melatonin, body temperature, motor activity, or cortisol production. These rhythms are observable in all members of a given species. Circadian rhythms exist in most human physiological processes, including CBT, heart rate, breathing rate, metabolic rate, activity in many brain regions, hormone release (including cortisol and melatonin), and the sleep-wake cycle. The circadian control of cognitive performance and sleep refers to the almost 24-h cycle of wakefulness and sleepiness. Daytime hours are characterized by heightened alertness and reduced sleepiness, while nocturnal hours display the inverse

pattern [1, 2]. These sleep-wake cycles revealed some relationship between body temperature and melatonin levels. Previously, studies have reported a drop in Core Body Temperature (CBT) in the early morning and peek in the evening. In contrast, melatonin levels rise at night and dropped to their nadir in the morning. Alertness refers to the high environmental consciousness and swings in a circadian pattern, having low concentrations during night that are augmented during the day. Studies have suggested dissimilar overlaps between CBT, melatonin, and alertness. Light-induced melatonin suppression has been shown to elevate the scores of alertness. In addition, alterations in CBT can potentially modulate the sleep/wake cycle [1]. These findings suggest some correlation between these three physiologic variables; sleepiness, melatonin, and body temperature. Accordingly, we aim to report the latest information regarding two research questions, (a) Is the alerting effect caused by the cumulative effort of melatonin and body temperature, (b) Does any correlation exist between the three variables?

2. Human sleep-wake cycle

A repeating pattern that alternates between waking and sleep is known as the human sleep-wake cycle. The body's intrinsic biological clock (circadian rhythm) and the buildup of sleep pressure (homeostatic factor) are two of the variables that control it. During wakefulness, various neurotransmitter systems promote alertness, while during sleep, different stages like rapid eye movement (REM) and non-rapid eye movement (NREM) facilitate rest and restoration. The NREM and REM sleep stages alternate in roughly 90-minute periods during the course of the night, reiterating the sleep-wake cycle. Understanding and maintaining a healthy sleep-wake cycle is vital for overall well-being and optimal functioning during wakefulness [3–5].

2.1 The neurophysiology of sleep and wake

By taking into account the sleep-wake cycle and the underlying neurological processes involved, it is possible to comprehend the neurophysiology of sleep and wakefulness. Rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep are the two basic sleep patterns that make up the human sleep cycle. N1, N2, and N3 are the three stages of NREM sleep (**Figure 1**). The N1 stage is the lightest stage, followed by N2 with sleep spindles and K-complexes and N3 with slow, high-amplitude delta waves as the deepest stage. The majority of dreams take place during REM sleep, which is distinguished by rapid eye movement and elevated brain activity. The sleep cycle starts with NREM sleep (N1-N2-N3) and then transitions to REM sleep. This cycle repeats throughout the night, lasting around 90–120 minutes per cycle. NREM sleep is more prominent in the first half of the night, while REM sleep becomes more significant in the later cycles [3, 4, 6].

Neurotransmitter systems play a role in promoting sleep or wakefulness. Sleep-promoting systems involve VLPO neurons, inhibiting wake-promoting systems. Cholinergic neurons promote REM sleep by activating the cortex and paralyzing muscles [7, 8]. Wake-promoting systems use neurotransmitters like acetylcholine and monoamines (serotonin, dopamine, norepinephrine, and histamine). ACh promotes wakefulness through direct projections to the cortex.

A flip-flop circuit model explains how wake- and sleep-promoting mechanisms are mutually inhibited, with the orexin system maintaining sleep-wake behavior [9].

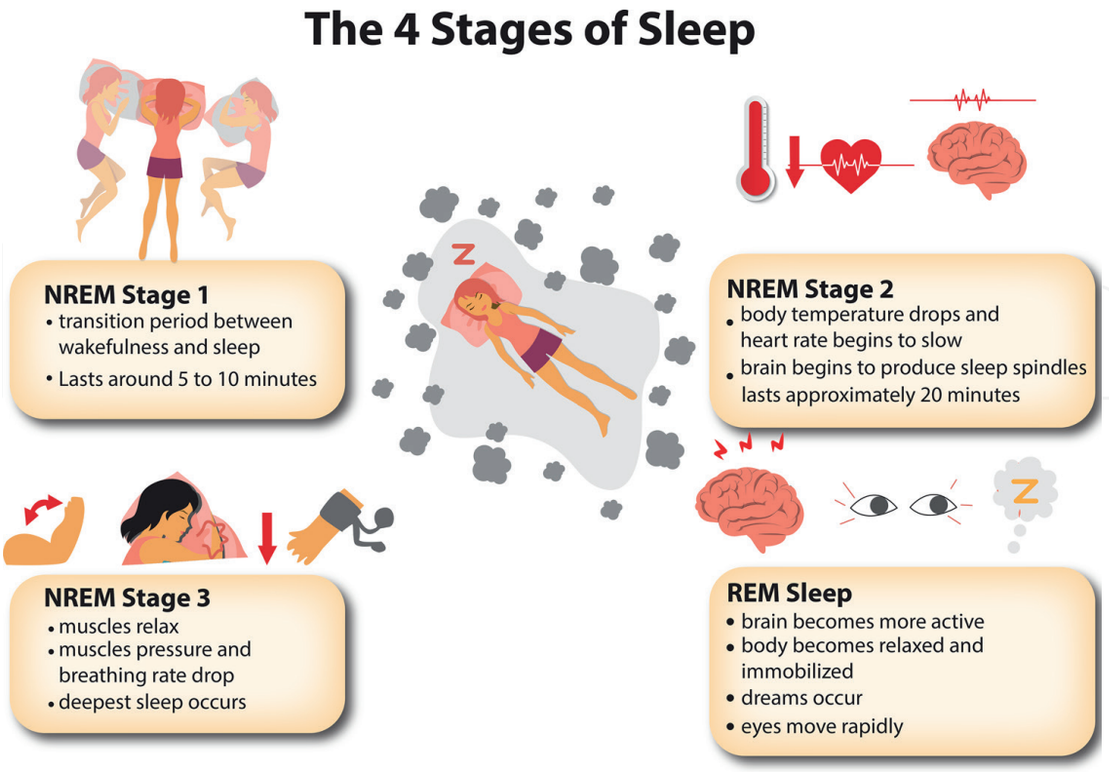

Figure 1.
The four stages of sleep. Figure 1 illustrates the four stages of sleep. The first three stages are known as non-rapid eye movement (NREM) sleep, whereas the fourth stage is known as rapid eye movement (REM) sleep. The brain transitions through four unique stages of sleep several times through the night. Each stage has a unique function and role in maintaining the brain's overall cognitive performance.

During waking hours, GABA and monoamine neurons are active; however, they are hardly active during NREM sleep and completely silent during REM sleep. The sleep-wake cycle causes changes in neurotransmitter activity. When we are awake, ACh neurons are active, dormant during deep (NREM) sleep, and only partially active during REM sleep. When you are awake, orexin neurons are active, and when you are asleep, they are not [3, 8].

2.2 Regulation of sleep-wake cycle: homeostatic and circadian regulation

Two processes, circadian regulation and homeostatic regulation, control the sleep-wake cycle. Process S, or homeostasis, is the process by which sleep pressure builds up during waking and is released during sleep. Adenosine, a substance in the brain, plays a role in increasing sleep pressure, promoting sleepiness. During sleep, adenosine levels decrease, reducing sleep pressure and promoting wakefulness [10].

The body's internal biological clock, also known as process C, is principally managed by the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN collects data on light exposure and assists in synchronizing the body's internal clock with the external cycle of day and night. The SCN controls how much melatonin the pineal gland secretes. Melatonin levels rise at night, encouraging sleep, and fall in the morning, indicating awakeness [11].

The interaction between homeostatic and circadian regulation is vital for maintaining a healthy sleep-wake cycle (**Figure 2**). The homeostatic process determines the need for sleep based on prior wakefulness, whereas the circadian process uses

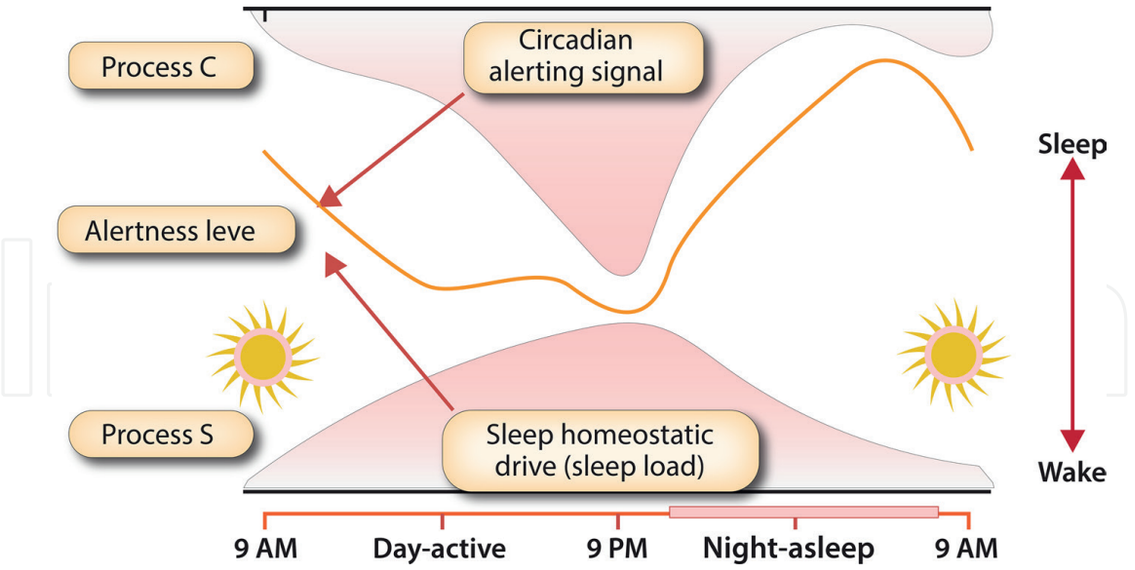

Figure 2.
Homeostatic and circadian regulation of sleep-wake cycle. Figure 2 indicates the two processes that regulate the sleep-wake cycle. Sleepwake cycle is controlled by circadian (Process C) and homeostatic (Process S). The interaction between homeostatic and circadian regulation is important to maintain a healthy sleep-wake cycle.

the light-dark cycle to predict when and how much sleep and wakefulness will occur. Disruptions of these regulatory processes can lead to sleep disorders and irregular sleep patterns [12].

3. Sleepiness and alertness; description, definition, and measure

Sleep is an elementary component of mammalian homeostatic mechanisms. The homeostatic regulation of sleep is fundamentally processed by the physiology of the circadian clock (sleep/wake cycle). Sleepiness and alertness are entirely distinct constructs. Sleepiness can be illustrated as a proclivity to fall asleep. It is a homeostatic measure characterized by a perpetual sleep-wake cycle in the absence of motivational and affective factors and can be modulated by circadian factors and sleep debt. However, alertness is the propensity of the brain to respond optimally to internal and external stimuli, and it may vary erratically. Neurophysiological substrates serve as a potential mediator that governs motivation, affect, and cognitive potential required for alertness [1].

An experience of feeling sleepy or alert is driven by perplexed interactions of neurophysiological pathways that exhibit dissimilar overlaps in different states of consciousness, impairment, and illness and can be influenced by numerous factors (external stimuli or stressors) [9]. These pathways can be modulated by melatonin, dopamine, hypocretin/orexin, serotonin, and norepinephrine. These neurohormones and neurotransmitters are also involved in the control of appetite, attention, fight-or-flight, and motivation [1, 9].

With time, various methods have been devised to quantify sleepiness or alertness. Multiple sleep latency tests (MSLT) can determine excessive daytime sleepiness or weakened alertness under controlled conditions [13]. The maintenance of the Wakefulness test is another objective test to ascertain a person's potential to stay awake during a defined period. It also helps to evaluate the success rate of the patient's

treatment plan [14]. Other alternatives include patient self-scoring questionnaires, namely ESS (Epworth sleepiness scale; 24 points), an instant KSS (Karolinska Sleepiness Scale; 9 points), THAT (50-points), ZOGIMA-A (50 points) and SSS (Stanford sleepiness scale; 7 points). ESS is instrumental in subjectively examining sleepiness [15]. The ZOGIMA-A is an alertness questionnaire that presents a level of alertness in the reflection of hypothetical scenarios (that may manipulate the subject's alertness) and a percentage rating scale of other activities (where alertness is required) [16]. Based on 50 points, the THAT questionnaire facilitates the retrospective investigation of the energy and concentration of the subject [17]. SSS helps in the estimation of subjective sleepiness [18].

3.1 Circadian rhythm and human sleepiness-alertness

The body's internal clock comprises 24-h circadian rhythm (CR) cycles that work in the background to carry out vital processes and functions. These rhythms are recorded oscillations influenced by physiological variables, such as melatonin, body temperature, cortisol secretion, and motor activities. The sleep-wake cycle is one of the most significant and well-known circadian rhythms [19].

Alteration in physiological variables can result in acute variations in these oscillations. For instance, when a mammal runs spontaneously to avoid a predator, the intense exercise boosts body temperature for a few minutes before the effect wears off and the temperature returns to its normal circadian range. These fleeting physiologic changes obscure circadian rhythms. The 24-h cycles (circadian rhythms) of sleepiness and alertness substantially influence cognitive performance and sleep. High alertness exists at daytime hours, and more sleepiness is observed at night [20].

According to the Posner and Rafal neuropsychological model, alertness constitutes four elements: sustained attention, selective attention, tonic alertness, and phasic alertness [21]. Sustained attention pertains to responding efficiently to an extended period (minutes to hours). Selective attention corresponds to the precise and selective response to every stimulus. Tonic alertness is an accustomed response to the environment induced by generic phenomena at any time. Phasic alertness refers to the response that generates following a warning signal, for example, a change of environment. The brain systems that chiefly contribute to upholding the alertness-linked circadian rhythms include the prefrontal, reticular, and parietal systems. The results of nearly all tests and tasks are compromised when attention-associated components are impacted by brain injury or any other disorder [21, 22].

The estimation of cognitive performance (alertness), regulated by the variations of circadian rhythms, can be performed by simple reaction or vigilance tasks. With reference to tonic and phasic alertness, Psychomotor Vigilance Test measured cognitive performance by modulating homeostatic and circadian rhythms, such as persistent routine, time of day, and forced asynchronism [23]. Reports corroborated an increase in reaction time, with lower response latency during the day and higher response latency at night. The frequency of lapses (omissions or responses with delayed reaction times) increased in the restive period and experienced circadian variations, with fewer lapses during the day and more at night [24, 25]. Variations in homeostatic (time awake) and circadian (time of day) cycles have remarkably influenced selective attention scores under the constant routine protocol. On providing a short interval among two stimuli (T1 and T2), progressive response latency was observed with the second stimuli (T2; lag 2, 200 ms) and the successive

independent stimulus (T2; lag 8800 ms) [26]. Assessment of sustained attention can be carried out by measuring three indices: stability in performance efficiency, time on task performance, and short-term stability. These variables can be examined by analyzing the variability of correct responses throughout the task. High stability can be depicted when the responses exhibit less variability. Accordingly, high attention scores were recorded during the day and less at night [27]. These investigations presented a direct relationship between time awake and the decline in alertness. Also, the dual task and task-switching performance was retarded due to sleep deprivation [2].

The impaired mechanisms of sleep generation may induce the propensity of acquiring SCRD (sleep and circadian rhythm disruption) disorder, ensued by comorbidity or lack of opportunity to sleep. The SCRD corresponds to the lack of optimal sleep duration, poor sleep quality, and improper sleep patterns. There are 83 types of sleep disorders listed in the ICSD (International Classification of Sleep Disorders), 3rd edition. The disruption of circadian rhythms eventuates in conditions that include Free-running sleep disorder (FRSD), Delayed sleep phase disorder (DSPD), Advanced sleep phase disorder (ASPD), Fragmented sleep disorder (FSD), and Insomnia. ASPD is characterized by falling asleep in the evening and trouble sleeping in the early morning. The DSPD appertains to the onset and offset of ≥3 h. sleep latency. FRSD is attributed to progressive sleep latency each day. FSD is observed in patients with complete loss of circadian clock. The term "insomnia" refers to a condition where a person has trouble falling or staying asleep [28].

4. Light and human sleepiness-alertness

4.1 Effect of LAN on alertness

Light exhibits acute alerting effects that can potentially influence the performance of night-shift workers. From a circadian standpoint, one of the possible underlying mechanisms is the suppression of melatonin ensued by high-intensity light exposure. However, the effects of light cannot be exacted as numerous factors, such as endogenous circadian phase, prior environmental light exposure, and duration of prior wakeful period, significantly affect the overall outcomes [29]. The majority of the studies have analyzed the impact during the night. To apprehend the correlation between light exposure and circadian and homoeostatic functioning, Chellapa et al. have reported a dramatic upsurge of subjective alertness and reduction in the objective markers of sleepiness (e.g. movement of the eye), even under high sleep pressure [30].

Some studies have additionally credited the attenuation of SCN (suprachiasmatic nucleus) depending on mechanisms caused by melatonin. It may regulate and stimulate the arousal of cortical and behavioral states at certain points in circadian cycles. A study aimed to determine the comparative influence of alertness for three different light conditions; continuous bright light, intermittent bright light (alternative exposure of dim light and bright light), and dim light with a 3-h exposure, rendered insignificant differences between continuous and intermittent bright light exposure; however, KSS scores were remarkably lower in intermittent light conditions than in dim light conditions. Over time, a progressive decline of subjective alertness was observed among all exposures; however, the objective alertness was

considerably higher in the cohort of intermittent exposure compared to the subjects that experienced dim light conditions. In comparison with dim light conditions, intermittent and continuous light exposures scored low for total sleep time and sleep efficiency, but the sleep pattern was marginally affected [31]. Similarly, subjective alertness was significantly lower during dim light and/or melatonin administration in comparison to bright light exposure [32]. Contrarily, some studies did not evidence any light-inducing alerting effects (AE) or melatonin suppression during the day or night. Thus, the presence of additional mechanistic activities can be a plausible explanation for this phenomenon. Light intensity is significant for ideal synchronization of the two variables (sleepiness or alertness), as more than 1000 lux polychromic light may escalate AE, irrespective of timing (day or night). It transposes the scientists to secondary analysis, i.e. Calculation of the Light Intensity Threshold that renders AE [31].

4.2 Effect of light intensity/wavelength on alertness

Ocular light exposure poses adverse effects on the human circadian clock. In particular, specific light intensities (wavelengths) can potentially synchronize (entrain) endogenous circadian rhythms to the 24-h day and eventuate in a variable alerting effect. Sunde et al. investigated the comparative alerting effect of a 455 nm- short wavelength narrow bandwidth light and 625 nm- long-wavelength narrow bandwidth light, subjected with a similar photon density (~2.8 × 1014 photons/cm^2/s) throughout the nocturnal shift. With long wavelengths, the subject's sleepiness and efficient task performance were more critically influenced than with the subjects exposed to shorter wavelengths. In contrast to long-wavelength light exposed subjects, Psychomotor Vigilance Task (PVT) test displayed more attentive scores in short-wavelength light, characterized by the quick response time, quick response time in the optimal range, and less attentional lapses. In addition, the inception of melatonin was more phase delayed in short-wavelength light than in long-wavelength light. It infers that alertness and performance can be improved with short-wavelength narrow-band light [33]. Blue light (shorter wavelength; 450–495 nm) manifested increased alertness and reaction latency in slightly more than two third of the studies, while decreased sleep efficacy and increased sleep latency among half and slightly less than half of the studies, respectively [34]. This research is consistent with the CDC report regarding the impact of blue light on sleep. Among blue, white, red, and yellow, blue strongly influence the sensitive period (sleep) featured by the inability to fall asleep and stay asleep [35]. Lin et al. dug more to apprehend the impact (AE) from short wavelength on four different frequency bins; theta alpha (5–9 Hz), lower alpha (8–9 Hz), higher alpha (11–13 Hz), and beta (13–30 Hz). Significant associations were established at theta alpha and beta ranges; however, lower alpha and higher alpha presented an insignificant effect. A descriptive posthoc comparison of the beta range accentuated a significant difference between 80 lux and 160 lux, 40 lux and 160 lux, and Dim and 160 lux blue lights. However, a lower AE was observed at 40 lux and 160 lux blue lights. The beta range (160 lux) revealed a remarkable difference compared to the three lighting conditions. According to a KSS score, Subjective sleepiness was considerably reduced in 160 lux conditions than in dim light conditions, affirming a high alerting effect [36]. These findings delineate that short wavelengths, except for a few frequency bins, induce less alertness than longer wavelengths.

5. Body temperature and sleep

5.1 Physiological regulation of body temperature

Thermoregulation is a term that refers to the maintenance of body temperature. Two types of systems mainly regulate the body temperature: physiological and behavioral. Heat is produced or lost by physiological effectors, which are mostly autonomic and involuntary. The main physiological reactions to cold exposure involve heat production by skeletal muscle contractions, brown adipose tissue (BAT) thermogenesis, and the vasoconstriction (constriction of blood vessels), that inhibits heat loss. However, exposure to warmth induces a set of thermoregulatory autonomic mechanisms, such as sweating (water evaporation) mediated heat loss, repression of thermogenesis, and vasodilation (blood vessels dilation). Different species employ distinct mechanisms to attain similar physiologic effect. For instance, humans utilize sweating to relieve ancillary heat, rodents spread saliva on their fur, and dogs perform panting. Despite these apparent differences, it is believed that a shared set of neuronal substrates that are conserved across mammalian species controls the major physiologic responses [37–39].

Sensory neurons that measure body temperature are the main input source for the thermoregulatory system. Most of these sensory neurons have axons that extend outside their cell bodies to measure the temperature of vital thermoregulatory tissues (e.g. spinal cord, the skin, and abdominal viscera). Also, the temperature of the hypothalamus is sensed and measured by a different set of sensory neurons present in the brain itself.

The thermoregulatory system maintains the temperature set point, which can be modulated by internal and external influencers. They mainly reflect interactions with other physiologic systems. For instance, a controlled body temperature increases (fever) in response to infection. Sleep is another physiological process that imparts modification in and is influenced by the thermoregulatory system. The temperature decline of the body is closely related to sleep onset. During sleep, RED (Rapid Eye Moment) accompanies a near-total inhibition of thermoregulatory responses in most of the species. Long durations and CR-induced diurnal-thermal fluctuations overlay the sleep effects. Neuronal circuits (located in the anterior hypothalamus) control the triad (circadian rhythms, sleep, and body temperature), but the interrelationship of these neural circuits is yet to determine [38, 39].

5.2 Body temperature variation with the sleep-wake cycle

Sleep is triggered by a temporal variation in the brain and core body, regulated by a conserved circadian rhythm; however, dissociation from this phenomenon is referred to as Insomnia. A plunge of sleepiness, reduced rapid eye moment and latency of sleep are the stereotypical effects of heat or cold exposure. The environmental influence of temperature induces the thermoregulatory mechanisms linked to sleep. The sleep stages are also affected by the type of bedding or clothing. Heavy clothing and bedding impart high heat exposure, resulting in increased wakefulness, sleep latency, and decreased rapid eye moment. Exposure to humid heat aggravates sleep by escalating thermal load. Contrastingly, cold exposure, with appropriate clothing and bedding conditions, revealed an insignificant impact on the sleep cycle; even so, cold exposure profoundly impacts autonomic responses of the heart without

modulating subjective sensations [40–42]. In another study, temperature variation was substantially observed in the morning (post-wakeup) and the evening (pre-sleep). In particular, a transitory state was noted from 6:00 to 10:00 (early to mid-morning) and 18;00 to 22:00 (evening). These transitions are attributed to heat gain in the morning (CBT rises) and loss of heat in the evening (CBT drops). In addition, light considerably contributes to the modulation of thermo-physiological responses in the morning and evening.

In contrast, no change was observed in the core body and distal skin temperature during the afternoon. These results establish a positive association between cold temperatures to increase sleep propensity, whereas hot and humid temperatures may result in less and delayed sleep induction. Furthermore, transitory periods are fundamental in thermo-physiological variations. The thermo-physiological variations can be inferred by collecting 24 h data, with the admissible error rate from inter-individual and exogenous differences, such as irregular eating and sleeping patterns, irregular patterns of light exposures, and jetlag [43].

5.3 Regulation of body temperature and sleep

Mammals possess a conspicuous thermal preference for sleep, such as a thermo-neutral environment (27–30°C) and minimal expenditure of energy. These behaviors drive the thermal decline of the circadian cycle (following light and dark cycles) to stimulate sleep. The thermoregulatory mechanisms and sleep are coherently connected with the neural circuits. These circuits employ the warmth to gate sleep, with a simultaneous elevation of circadian cooling of the body to generate the first non-rapid eye moment (NREM). Similar neurons directly connect the NREM initiation to decrease the body temperature [44, 45]. This phenomenon explains the transitional mechanisms that convert wakefulness to NREM sleep, followed by an instant reduction of brain temperature and a subsequent Rapid Eye Moment (REM). A rewarming effect is induced to reverse the phenomenon. NREM is originated in the preoptic hypothalamus (PO) and is activated by warm stimuli. The NREM sleep-inducing brain cooling mechanism and the coordination of circadian rhythm to regulate core temperature are significant to generate efficient sleep [44, 46].

Sleep-stimulating neurons exist all around the brain. It may integrate the autonomous and behavioral nervous systems that cumulatively govern the circadian and homeostatic sleep drive. For instance, the suppression of VTA (ventral tegmental area)-dopamine neurons produces an encouraging effect for sleep initiation [47]. The behavioral, circadian, homeostatic, and autonomic systems generate a cumulative input to gate sleep.

Inefficient thermal systems may modulate the energy-consuming mechanisms and the urge to consume food. Thus, it may solely influence the sleep networks. After a meal, leptin is released by adipocytes. This hormone inhibits hunger and function through multi-stream procedures in the hypothalamic nucleus. In this region, leptin restricts the expression of Neuropeptide Y (NPY), expressing Agouti-related protein (AgRP). The activity of these neurons is repressed to promote sleep. Leptin receptors are also present in the PO hypothalamus. The leptin receptors residing on PO glutamatergic neurons get excited upon arousal of ambient temperature [47, 48].

Consequently, inhibited thermogenesis results in less food consumption and reduced energy dissipation. According to a recent analysis, circulatory leptin and

insulin inhibit the AgRP neurons. AgRP neurons are referred to as "hunger sensors" because they can detect energy input. However, Proopiomelanocortin (POMC) neurons exhibit an opposite mode of action. AgRP activates food-seeking behavior by compromising sleep. However, in the case of food deprivation, AgRPs are repressed to secure sleep at the expense of food; sleep deprivation radically alters the energy balance and thermoregulatory mechanisms [44, 49]. From a rat study, the selective REM and chronic sleep deprivation led to detrimental physiological effects and subsequent death [50]. Earlier, high metabolic activity was observed, accompanied by high food consumption and an ascension in body temperature. Then, a sudden drop in temperature ensued in hypothermic conditions among rats [51]. Over time, deepened sleep deprivation results in the progressive rise of body temperature. This data reveals that a range of thermoregulatory mediators, either directly or indirectly, plays a significant part in the stimulation of sleep, depending upon different environmental and bodily conditions [44].

5.4 Regulation of body temperature by SCN

The suprachiasmatic nucleus (SCN), which is controlled by the circadian rhythm, is essential in controlling body temperature. The SCN receives information from the eyes regarding the light-dark cycle, which aids in synchronizing the body's internal clock with the outside world. Timing the changes in body temperature is one of its primary duties (**Figure 3**).

Normally, body temperature follows a circadian rhythm, with a decrease at night and an increase during the day. The SCN orchestrates this rhythm by initiating cooling processes during the evening and nighttime. This drop in temperature promotes sleep onset and facilitates restorative sleep. Hormones and neurotransmitters, such as melatonin, are released by the SCN to influence thermoregulation [3, 52].

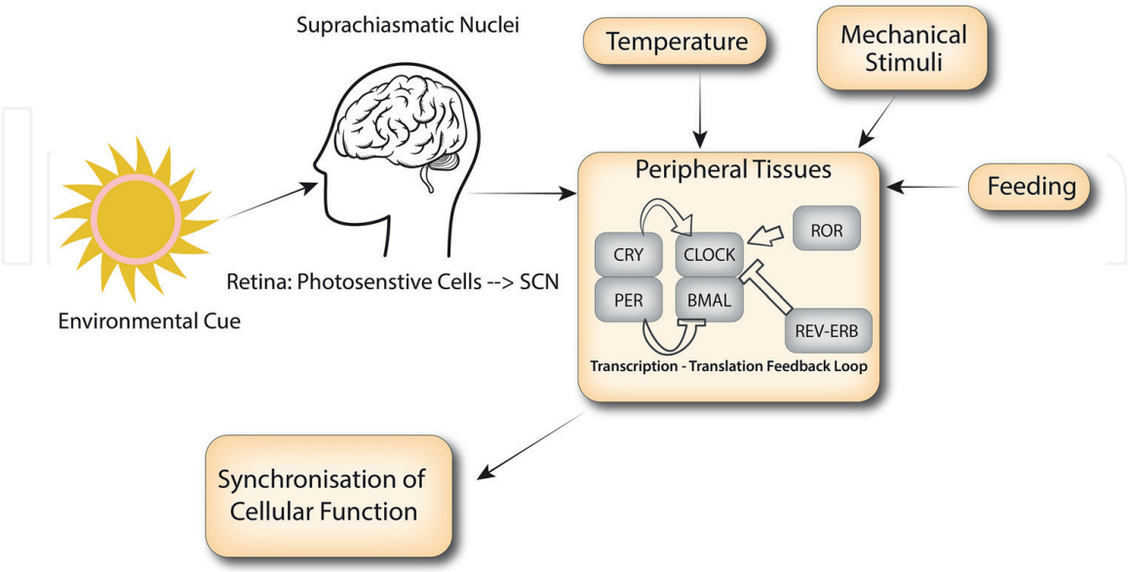

Figure 3.
Schematic summary of circadian synchronization. Figure 3 demonstrates the summary of circadian synchronization. The photic zeitgeber entertains the central clock, which in turn regulates the peripheral clock. The non-photic zeitgebers such as mechanical stimuli, temperature, and feeding mainly entertain the peripheral clock.

In the morning and throughout the day, as light exposure increases, the SCN triggers the warming process, leading to a rise in body temperature. This promotes wakefulness and alertness. Hormones and neurotransmitters, like cortisol, are released to support wakefulness.

The SCN's regulation of body temperature involves complex interactions with other brain regions and physiological systems. It communicates with areas responsible for thermoregulation, such as the hypothalamus, to coordinate temperature changes throughout the body [12, 52]. Disruptions to the SCN's regulation of body temperature can occur due to factors like jet lag, shift work, or sleep disorders. These disruptions can affect the adjustment to new time zones, disrupt the body's temperature rhythm, and contribute to sleep disturbances.

5.5 Circadian rhythm of human body temperature

Human body temperature exhibits a circadian rhythm characterized by 0.8–1°C oscillation that fluctuates between a nocturnal minimum and a diurnal maximum. The circadian rhythms are governed by the hypothalamic SCN (chief thermoregulatory hub in animals) that deploys the TRPs (transient receptor potential; family of ion channels) to detect temperature. Thermal TRPs are frequently expressed in sensory neurons and are triggered at specific temperature thresholds. The subtype TRPV3 detects heat, while the subtype TRPM8 sense cold. Consequently, pre-entering the hypothalamus, thermal information from the integumentary surface, core organs, peripheral tissues, and the neuronal axis itself is combined at multiple levels. The hypothalamic thermoregulatory center receives a rhythmic input from hypothalamus to synchronize with CRBT (Circadian Rhythm of Body Temperature) [53]. Nam et al. demonstrated that the synthesis and metabolism of brown adipose tissue serve as a critical organ for thermal regulation and are coordinated by the circadian clock [54]. Additionally, the seasons could be a possible source of body temperature variation. A large-scale investigation demonstrated that the human circadian cycle exhibits a temperature difference of ~0.2°C between winters and summers. These ambient effects reside within the thermo-tolerable ranges [55]. The circadian system endures significant changes during an individual's lifetime, notably during early old age and in early ontogenetic development. Some reports are evident that daily temperature level and amplitude decrease with age. These changes might be induced due to inefficient intrinsic thermoregulatory mechanisms. They could also be linked to chronic diseases, a sedentary lifestyle or medications and may influence other circadian functions [56]. Furthermore, gender is another substantial factor mainly influenced by sexual hormones. During ovulation, a 0.25–0.5°C rise in body temperature is commonly observed in females. In the luteal phase, the average daily body temperature rises by nearly 0.4°C compared to the pre-ovulatory follicular phase. It is unprecedented that the menstrual event can potentially alter the CRBT [57]. However, progesterone reduces the amplitude and possibly delays the phase of the circadian rhythm in the luteal phase, than in the follicular phase, hence blunting the drop in nocturnal temperature. An altered thermal CR can also result from a disturbed environment, sickness, ambient temperature, sleep, meals, physical activity, or medicines. Night workers display significant CR anomalies including thermal dysregulation of the body, which persists even after retirement [58].

5.6 Acute light effects on body temperature

5.6.1 The direct impact of LAN on body temperature

Our circadian temperature is synchronized with the ambient light-dark cycle through the influence of light. Hence, circadian photoentrainment may potentially alter human thermal responses. From 15 studies, evening bright light exposure revealed less decline of CBT compared to dim light conditions. Moreover, a smaller decrease in CBT (0.2°C) was observed with shorter wavelengths than with longer wavelengths [59]. Among 15, two studies documented a decreased melatonin concentration with increased CBT [60, 61]. Two studies reported that longer wavelengths could not reduce CBT in the evening [60, 62]. It advocates the intercedence of pRGCs (photosensitive retinal ganglion cells) that impedes the light induced-natural CBT decline during the night, similar to the CR-phase shifting, where the impact is especially vulnerable to the shorter wavelengths [63]. In another study, 100-lux light exposure was relatable to 10-lux light exposure [63]. Regarding morning exposures, an earlier rise of CBT was observed (0.1°C, by the end of the morning, 0.2°C; during the afternoon, 0.1°C; evening), post bright light exposure in the morning.

Concerning Skin temperature (ST), evening exposure to intense light elevated the mean ST by 1.0°C, compared to light exposure with <50 lux intensity. In contrast, the ST of the foot was approximately −2.0°C lower when exposed to bright light exposure in the evening compared to dim light [64, 65]. Evening's bright light could be the contributing factor that increases Proximal Skin Temperature (PROX-ST) and decreases Distal Skin Temperature (DIST-ST). Regarding DPG (distal to proximal SKT gradient), it was discovered that monochromatic light at both 460 and 550 nm prevents the nighttime temperature decline by 0.7°C. Similar effects on DPG were observed following the bright light exposure in the evening and throughout the night [60, 66]. Melatonin concentration appeared to be reduced at night post-bright light exposure. Evening reduction of melatonin led to an increase in proximal temperatures, a decrease in distal temperatures, and a greater DPG [59].

The impact of Sweat (SW) was analyzed under three experiments. No significant difference was noticed between the effects of blue and red light on SW. However, the bright light exposure in the morning resulted in sweating at −0.1°C, indicating a lower CBT value than in dim light. Sweating may have initiated at the same time and with a similar ST from both light exposures, although bright light exposure reflected lower CBT and no significant difference in ST was observed throughout both exposures. However, bright light exposure revealed lower CBT levels than in dim light [67, 68]. In summary, these findings indicate that evening bright light exposure suppresses melatonin, CBT, and proximal ST while decreasing distal ST. Light exposure in the morning causes an earlier rise in CBT and a quicker drop in melatonin levels. Studies conducted in the afternoon found no correlation between light exposure and CBT or SKT. These results suggest that the influence of bright light on DPG, SKT, and CBT varies with the time of day, the intensity, and the photo-spectral composition. However, future studies are required to examine the persistence of these effects independent from CR-linked phase alteration or melatonin suppression [59].

5.6.2 Hypothermic effect of melatonin on core temperature

Melatonin (MLT), a result of pineal gland secretion, significantly contribute in the human circadian clock and exhibits hypothermic and soporific effects. The spike in

nocturnal melatonin levels translates into the nadir of CBT. The fact that exogenous MLT exhibits hypothermic qualities are well-documented, although the mechanisms behind this phenomenon is still under investigation. Scientists have observed that MLT promotes peripheral vasodilation without affecting heart rate or cerebral blood flow, suggesting that melatonin operates on peripheral vascular receptors [69].

Likewise, Cook et al. observed that MLT enhanced forearm blood flow and reduced renal blood flow, though cerebral blood flow remained unchanged. These changes in vascular blood flow reflect that heat loss processes primarily drive the hypothermic effects of MLT. The average decrease in CBT after receiving melatonin was calculated to be 0.21°C (0.18–0.24°C) [70]. Cagnacci et al. showed that daytime melatonin administration ensured a quick increase (within 20 minutes) in endogenous MLT and a concurrent reduction in CBT [71]. According to Van den Heuvel et al., MLT suppresses morning CBT for at least 1–2 h after plasma melatonin levels recover to regular daytime values [72]. Researchers discovered that low-dose melatonin injections prevented the body's typical daytime rise in core temperature for *30–90 minutes. Satoh and Mishima observed that the exogenous melatonin's hypothermic effect existed for ~3 h. The extent of suppression was significantly associated with endogenous melatonin levels. Thus, a logarithmic pattern of dose-response was established between MLT doses and their hypothermic effect. A 5-mg dosage of MLT resulted in a *0.2 C drop in body temperature. Higher dosages did not remarkably augment this hypothermic effect; however, they possibly manifest soporific side effects [69, 73].

6. Interaction between melatonin, sleepiness-alertness, and body temperature

The relationship of the triad (melatonin, sleepiness/alertness, body temperature) establishes a complex pattern. MLT is chiefly synthesized in the pineal gland, and SCN controls its release. MLT theoretically mediates the communication between the products of the circadian pacemaker and the sleep-wake cycle system. Observed nocturnal periods of sleep inclination under an ultrashort sleep-wake cycle appears to coincide with an increase in melatonin release close to the habitual bedtime. Another study from this review evinced a strong relationship between melatonin suppression with increased alertness, circadian phase shifting, and nocturnal decline [1]. In 2006, blue light (460 nm) exposure enormously suppressed melatonin, accompanied by the decline of subjective sleepiness and increased cognitive performance. In the same year, Lockley et al. established an inverse proportionality between melatonin suppression and arousal of alertness [74]. Contrastingly, Lin et al. expressed a pronounced stimulatory effect of red light for the arousal of alertness while conserving melatonin levels [36]. These studies are consistent with Plitnick et al. and Figueiro et al., where red light elicited subjective alertness, but not at the expense of melatonin [75, 76]. Likewise, Foster RG signified melatonin as a biological marker of the dark that is regulated by a light-inducing mechanism. It has the potential to reduce sleep latency and improve sleep duration. Still, melatonin-deprived individuals (for instance, tetraplegic individuals, pinealectomized patients, and people on beta-blockers) exhibit a rhythmic sleep/wake cycle with marginal alteration [28]. These studies corroborated that melatonin possibly establishes a close association with sleep-inducing mechanisms; however, some additional factors have also facilitated sleep generation.

While exploring coupling mechanisms between the circadian pacemaker and sleep, one alternate theory argues that an indirect influence of melatonin on the sleep-wake cycle mediated by temperature may be crucial, as melatonin has a substantial effect on the temperature rhythm [30]. This theory was formerly evidenced in 2006, where post two hours of melatonin administration revealed a decline of PROX-ST (skin temperature of stomach, thigh, forehead, and infraclavicular skin regions), and an upsurge of DIST-ST (skin temperature of hand and feet) [77]. A laboratory experiment envisioned to examine the kinetics of melatonin.

degradation plotted a graph between temperatures; 60, 70, 80, and 90°C against the function of time. From a function-of-time standpoint, the highest degradation of melatonin was observed at maximum temperature. In addition, the lowest melatonin levels were recorded in the presence of light at (RT) room temperature. Due to the increased kinetic energy of the reactant molecules, the pace of a reaction typically increases with temperature [78]. In 2019, a study orchestrated the correlational attributes of melatonin, sleepiness/alertness, and temperature. Following melatonin ingestion, subjective sleepiness and DSTL-ST were elicited. On light exposure and post-melatonin administration, PROX-ST increased, and DIST-ST decreased, while alertness scores remained unaffected [79].

Bright light exposure following MLT administration did not alter subjective or alertness scores. Even so, body and PROX-ST increased while DIST-ST decreased. Light exposure unremarkably affects these parameters in the placebo condition. These results confirm a significant association of melatonin in sleep induction, while the thermal association of melatonin still requires additional inquiry. A meta-analysis of 30 datasets revealed a mean drop of 0.21C at 5 mg exogenous melatonin. High soporific effects were recorded at >5 mg dose, though no further temperature decline was observed [69]. With a 5 mg dose, an increase in subjective sleepiness and DSTL-ST was noticed. Following light exposure, DSTL-ST was decreased, and PROX_ST was increased [1]. In a different study, light-induced melatonin declines conferred timing-related thermal fluctuations, where light exposure in the evening revealed a delayed reduction of CBT and decelerated the rise of DST-ST, a morning exposure resulted in a rapid decrease of melatonin and subsequent increase of CBT [59]. An investigation devoid of melatonin accentuated NREM initiation at the steepest rate of decline in body temperature (**Figure 4**) [44].

Conclusively, sleep generation is a cumulative effort of melatonin and body temperature. Also, the rise of melatonin revealed a fluctuation in body temperature. High amounts of MLT correspond to a drop in CBT and PROX-ST, and a rise in DIST-ST. However, the influence of light inhibits the MLT release and subsequently prevents the decline of temperature. Both physiologic variables (body temperature and MLT) serve as close indicators of sleepiness/alertness. However, modulating factors such as light, environmental temperature, and timing of melatonin administration (with reference to the circadian clock) may alter the overall outcomes. Studies constituting large sample sizes are required to infer the underlying mechanisms through which these factors may modulate the circadian clock (**Table 1**).

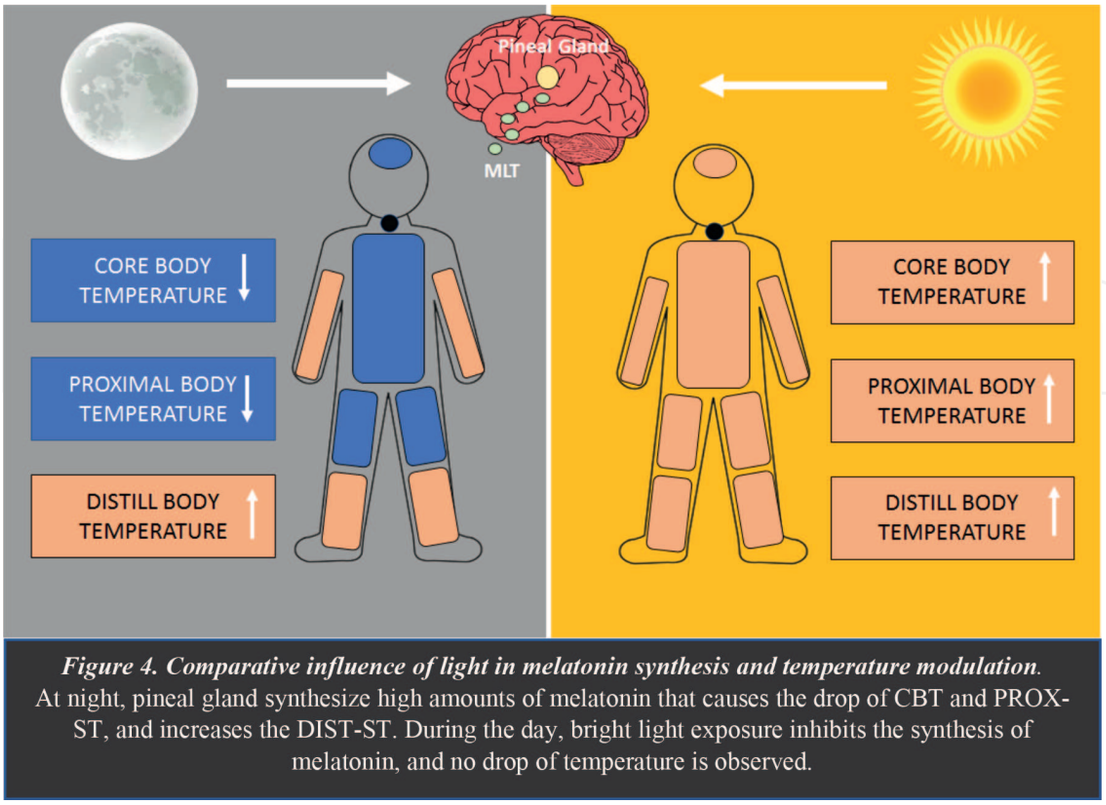

Figure 4. Comparative influence of light in melatonin synthesis and temperature modulation.
At night, pineal gland synthesize high amounts of melatonin that causes the drop of CBT and PROX-ST, and increases the DIST-ST. During the day, bright light exposure inhibits the synthesis of melatonin, and no drop of temperature is observed.

Figure 4.
Comparative influence of light in melatonin synthesis and temperature modulation. At night, pineal gland synthesizes high amounts of melatonin that cause the drop of CBT and PROXST and increases the DIST-ST. During the day, bright light exposure inhibits the synthesis of melatonin, and no drop in temperature is observed.

Author	Article type	Study year	Studies included/ no. of subjects	Melatonin (MLT)	Sleepiness (S)	Body temperature effect €
Marrin et al. [17]	Review Article	2013	30/193	5 mg MLT ▲	Unknown (Un)	CBT ▼
				>5 mg MLT ▲	S ▲	No effect
te Kulve et al. [16]	Review Article	2016	48/Un	MLT ▼	—	CBT ▲
Hardling et al. [20]	Review Article	2019	~160/Un	—	S ▲	CBT ▼
Lok R. et al. [1]	Research Article	2019	10 subjects	5 mg MLT ▲	S ▲	DSTL-ST ▲
						PROX-ST ▼
Krauchi et al. [18]	Research Article	2006	11 subjects	5 mg MLT ▲	S ▲	DSTL-ST ▲
						PROX-ST ▼

Table 1.
Interplay of melatonin, sleepiness, and body temperature. Table 1 illustrates the collection of research articles demonstrating the interaction between melatonin, sleepiness, and body temperature.

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