

Circadian Rhythms and Homeostatic Mechanisms for Sleep Regulation <Chapter Heading>

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Abstract

This chapter examines circadian rhythms and homeostatic mechanisms for sleep regulation. It reviews the current evidence describing the two-process model of sleep regulation and how to assess disruption to either of these sleep drives. This chapter also reviews the role of the photic and non-photic resetting of the circadian rhythm and describes how some aspects of modern society can cause sleep and circadian disruption. Furthermore, this chapter describes how misalignment between the circadian rhythm and sleep homeostat, such as occurs during jet lag and shiftwork, can lead to sleep disruption. The short and long-term consequences of circadian misalignment are also reviewed.

Keywords

circadian rhythm, homeostasis, two-process model, sleep regulation, zeitgeber, circadian misalignment

Introduction <H1>

Most people understand that sleep is important for health and well-being, but less understood is the critical role that the mechanisms underlying sleep play in our lives.

Sleep is regulated by the build-up of homeostatic sleep pressure and an internal drive to sleep controlled by the circadian rhythm. These two distinct sleep drives work together to consolidate sleep at night and to allow people to maintain wakefulness during the day.

Sleep pressure is intuitive; it is the build-up of sleep need over time. Most people recognize that staying up too late or not getting enough sleep is associated with a feeling of sleepiness. When people do not get enough sleep to alleviate sleep pressure, a sleep debt occurs and persists until sleep pressure is relieved through an extended sleep bout.

Unlike sleep pressure, the role of the circadian rhythm in sleep is not intuitive. Our circadian rhythms may be thought of as a central body clock that coordinates many aspects of biological function, extending far beyond simply the drive to sleep. The circadian clock is intimately connected with the rotation of the Earth, so that under natural circumstances, the drive to sleep occurs to coincide with the solar night and waking is promoted during the day. Circadian rhythms are ubiquitous to life and are the central timekeepers for animals and plants alike. Even ocean-dwelling bioluminescent single-celled organisms have an internal circadian clock that synchronizes the timing of their glow (1). Importantly, the circadian clock is different between individuals, with some people having a longer than 24-hour circadian rhythm and other people having a shorter than 24-hour circadian rhythm. In order to stay synchronized with the 24-hour rotation of the Earth, our clocks must be reset each day in order to allow us to maintain sleep at night and wakefulness during the day. This resetting occurs through daily light exposure. Under normal circumstances, individuals do not need to do anything to stay

synchronized with the 24-hour day other than experience the natural pattern of light exposure during the day and darkness at night.

Although the maintenance of sleep and waking occurs naturally, many aspects of modern society can lead to disruption of sleep pressure and the circadian rhythm, which can in turn lead to sleep complaints, sleep disorders, or even other seemingly unrelated chronic conditions. For example, when people look at light-emitting screens at night, such as from smart phones, that light exposure is interpreted by the circadian clock as a cue to promote wakefulness. This causes modest circadian misalignment, which can lead to a shortened sleep episode and the accumulation of a chronic sleep debt. A more extreme example of circadian misalignment is night shift work. When individuals stay awake at night and try to sleep during the day, their circadian rhythms become offset from their behavioral cycle. In these cases, peripheral clocks, such as in the stomach, pancreas, and reproductive organs, become desynchronized from the circadian clock. This can lead to short-term consequences, such as daytime sleepiness or overeating, and long-term consequences, such as an increased risk of obesity, diabetes, and breast and prostate cancer.

In order to understand and treat disorders arising from sleep loss and circadian misalignment, it is important to understand the underlying mechanisms driving sleep. This chapter will describe how sleep pressure and the circadian rhythm interact to promote sleep. It will cover the underlying mechanisms associated with sleep pressure and the circadian system and then describe the consequences of perturbing either of these sleep drives.

The Two-Process Model of Sleep Regulation <H1>

Understanding the mechanisms underlying the circadian rhythm and homeostatic drive for sleep is an important foundation for identifying and treating many sleep complaints and disorders. The interaction of these sleep drives has been described as the two-process model of sleep regulation (2), with process S and process C used to describe the homeostatic sleep pressure and circadian components, respectively (see Figure 1). When an individual maintains regular sleep and wake timing, with approximately eight hours in bed at night, process S and process C interact to promote a consolidated sleep episode. This process of synchronization to a light-dark cycle is called entrainment. When a person is entrained, the build-up of sleep pressure is very high at bedtime, while the circadian rhythm promotes sleep immediately prior to the habitual bedtime. The beginning of a normal sleep episode under entrained conditions is dominated by slow wave sleep (SWS), representing the repayment of sleep debt accumulated through the waking day ((3); described in more detail later in the chapter). As SWS subsides and sleep pressure is relieved, the circadian drive for sleep peaks, coinciding with the peak of melatonin production, nadir of body temperature, and an increase in rapid eye movement (REM) sleep (4). At the end of a typical entrained sleep episode, sleep pressure is low, and the circadian rhythm begins to promote wakefulness coinciding with the habitual wake time and circadian peak in cortisol production (5). Entrainment and consolidated sleep are maintained through regular wake-timing and regular light exposure following each sleep episode. The following sections will describe how sleep homeostasis and the circadian rhythm are controlled and what happens when these processes are altered.

<Insert Figure 1 about here>

Sleep homeostasis <H2>

Insufficient sleep is pervasive in modern society. Social, domestic, and work pressures are increasingly cutting into the time we have available to sleep. Even seemingly inconsequential decisions to stay up an extra hour to finish watching a movie, or get up an hour early to go to the gym before work can cut into valuable time that should otherwise be protected for sleep. Despite the focus on diet and exercise as pillars of health, a few hours' lost sleep can lead to both short- and long-term negative consequences for overall health. For example, chronic sleep restriction, that is, getting less sleep than you need over the course of a week or more, can increase the risk of developing cardiometabolic diseases such as diabetes, obesity, and heart disease. In the short-term, a night of poor sleep can increase the risk of motor vehicle and occupational accidents and, if nothing else, can put you in a really bad mood. When we lose sleep, the only thing to replace it is recovery sleep. Until this need is met, we exist in a state of sleep debt. The following section describes the underlying processes of sleep need, or the homeostatic drive for sleep.

The homeostatic drive for sleep accumulates across hours of wakefulness and dissipates with time spent asleep. The biochemical process underlying the build-up and relief of sleep pressure is associated with the build-up of the neuromodulator adenosine in the brain. During wakefulness, energy use is high, resulting in the depletion of energy stores, and the accumulation of associated metabolites (6). For example, adenosine levels accumulate during wakefulness due to the use of adenosine triphosphate (ATP) by active neurons. This build-up of adenosine is associated with a feeling of sleepiness.

Extracellular levels of adenosine are subsequently dissipated during sleep, particularly during slow wave sleep (7-9). Although this build-up of sleepiness is best alleviated by

sleep, millions of people worldwide do not get enough sleep and instead attempt to manage their sleepiness through the use of caffeine, which is an adenosine receptor antagonist. Caffeine doses of as little as 50 mg (the equivalent of a tea, or weak cup of coffee) can improve alertness and performance very quickly (10) and remain in the body for more than six hours. Despite the widespread cultural use and availability of caffeine, it should not be used as a replacement for sleep, because adenosine continues to build even during caffeine use and after the effects of caffeine have worn off, many people experience a “crash” in alertness. In addition, habitual caffeine use diminishes mood, decreases sleep duration, and changes sleep architecture making the sleep obtained while caffeine is circulating in the body less restorative than natural sleep (11, 12).

Biomarkers of sleep homeostasis <H3>

Early observations of the physiological markers of sleep homeostasis were derived from electroencephalographic (EEG) recordings of habitual sleep episodes. Slow wave sleep (SWS) was identified as a marker of Process S based on the observation that, like sleep pressure, SWS is predominant during the first few sleep cycles and then diminishes across the sleep episode (13). Furthermore, sleep pressure (e.g. under conditions of prior sleep loss and extended wakefulness) advances the onset of slow wave activity (SWA; EEG power density in the 0.75–4.5 Hz range) during non-rapid eye movement (NREM) sleep, and increases the amount of SWA in the sleep episode (13). For example, when people are allowed to take short naps during the day, the amount of prior wakefulness will determine the amount of SWA in the nap. That is, if you have been awake longer, you will have more SWA, or deeper sleep, in your nap (14). Conversely, if you take a late afternoon nap, this can reduce the amount of sleep pressure preceding your nighttime sleep period and, therefore, reduce the amount of overnight SWA (15, 16). The

homeostatic component of sleep is also evident under conditions of chronic sleep restriction. Under these conditions there is a conservation of SWS across restricted sleep episodes, and a conservation or increase in SWA (17). That is, if you only have 5 hours of sleep per night, your body will make sure to maintain the amount of SWA that would occur in an 8-hour sleep opportunity, sacrificing lighter sleep stages to preserve deep sleep.

While SWA is a primary biomarker of sleep homeostasis, it may not be practical to evaluate in a clinical setting. Other biomarkers of sleep pressure include self-reported sleepiness and sleep latency (the time it takes to fall asleep). Generally speaking, we know when we are tired, and self-reported sleepiness scales can be used to get a quick and easy subjective view of a person's sleep pressure at a given point in time (e.g. Karolinska Sleepiness Scale, KSS), or over a longer-term period (e.g. Epworth Sleepiness Scale, ESS). The KSS has been shown to correlate well with objective measures of sleepiness such as EEG, and performance measures such as standardized reaction time tests (e.g. psychomotor vigilance task, PVT) (18). It should be noted, however, that under some sleep loss conditions, self-reported sleepiness can be distorted, leading to a misleading view of underlying sleep pressure (19). Therefore, where possible, an objective measure of sleepiness is preferable.

A relatively easy to administer test of objective sleepiness is called the Multiple Sleep Latency Task (MSLT). This task measures how long it takes someone to fall asleep on a comfortable bed in a dark, quiet room. The task is terminated after sleep onset or after 20 minutes, whichever is sooner, and is typically repeated every 2 hours across a day.

Research suggests that falling asleep under these conditions within 5 minutes is indicative of clinically relevant sleepiness (20).

Circadian Sleep Drive <H2>

The circadian pacemaker is an endogenous oscillator located in the suprachiasmatic nucleus (SCN) of the hypothalamus that coordinates the action of many aspects of biological function. The term circadian was coined by Dr. Franz Halberg and comes from the Latin '*circa*' and '*diem*,' meaning 'about a day' (21). The average circadian rhythm has a period of approximately 24.2 hours (22), with about one-third of the population having a circadian period less than 24 hours and two-thirds having a period of more than 24 hours (23). The circadian rhythm is capable of resetting and entraining to periods that are close to the endogenous period through zeitgebers (time cues, from German, meaning 'time giver'), with the strongest zeitgeber being light. The resetting capability of the circadian rhythm is important, because it allows for the body clock to be flexible. Having a circadian rhythm that adapts to different light-dark cues allows us to be able to adapt to changes in time zones and allows us to be able to shift our sleep schedules when needed. Importantly, however, many people do not understand how the circadian rhythm works and as a result make choices that can cause sleep disruption. Understanding how the circadian rhythm works is an important component in treating modest sleep complaints.

Morningness-Eveningness Preference <H3>

Although daily light exposure is sufficient to synchronize the sleep-wake rhythms of most individuals to the 24-hour day, there is variation in how different individuals adapt to the day. Individuals with a longer circadian period tend to rate themselves as "night owls," while those who have a shorter circadian period tend to rate themselves as "morning larks (24)." Morningness-eveningness preference (also referred to as a person's

chronotype) has also been shown to change throughout the lifespan. Post-adolescent children and young adults tend to prefer later bed and wake times, while older adults tend to prefer earlier bed and rise times.

The underlying impact of morningness-eveningness preference on sleep relates to the differing phase angle of entrainment between larks and owls. Phase angle is the duration between bed or wake time and a marker of circadian phase, such as the melatonin peak (i.e., at the circadian nadir, the strongest circadian drive to sleep). If an owl and a lark went to bed at the same clock time (say, 11:00 PM), the lark, with an earlier circadian phase (e.g., circadian nadir at 2:00 AM), would have a bedtime closer to their circadian nadir and, therefore, a smaller phase angle (3h), than the owl, which has a later circadian phase (e.g., circadian nadir at 4:00 AM) and, therefore, a larger phase angle (5h) (25).

Although the modest differences in phase angle as observed in owls and larks allows for a stable sleep episode, larger differences can lead to sleep disruption. Morningness-eveningness preference can be evaluated clinically using questionnaires, such as the Horne-Ostberg Questionnaire or Munich Chronotype Questionnaire. A common example of how morningness-eveningness preference can interfere with lifestyle occurs in night owls. About 2/3 of the population have a longer than 24-hour circadian rhythm, which makes it relatively easy to stay up too late. This may not be a problem for a person who has a mid- to late-morning work start time, but if an early work time is required, night owls may have a very difficult time waking up and performing at work. This can be a major problem for high school and college students who are at an age where circadian preference is later and social pressures may lead to a desire to stay up late, yet early

school start times prevent adequate sleep. These types of sleep complaints can be treated using light therapy (as described in the next section).

Light as a Zeitgeber <H3>

Light is the most potent synchronizer of the circadian rhythm. The light signal is transmitted to the SCN via a collection of intrinsically-photosensitive retinal ganglion cells (ipRGCs) that contain the photopigment melanopsin (26). These photoreceptors are separate from the visual photoreceptor system and project via the retino-hypothalamic tract to the SCN. The light signal is transmitted exclusively through the eyes (27) and totally blind individuals lacking the ipRGCs in the outer retina cannot synchronize with a 24-hour light/dark cycle (entrain) via light cues (zeitgebers) (28). The action of light on the human circadian pacemaker depends on the timing, intensity, wavelength, pattern, and duration of the light stimulus. These properties of light can be manipulated for therapeutic intervention, but inappropriate light exposure can lead to sleep and circadian disruption. The importance of each of these aspects of light is described below.

Timing of light exposure. The action of light on circadian timing follows a phase response curve (PRC), where light administered in the biological morning causes a phase advance of the system (shifting circadian rhythms, including the drive to sleep and wake, earlier), while light in the biological evening causes a phase delay of the system (shifting circadian rhythms later) (29) (see Figure 2). In simple terms, this means that when traveling a few time zones eastward (or shifting bedtime earlier), morning light exposure and evening light avoidance will accelerate adaptation, while evening light exposure and morning darkness is required when traveling a few time zones westward (or for shifting bedtime later).

Light Intensity. The magnitude of the effect of light depends on the intensity of the stimulus. Light levels as low as 1.5 lux (i.e., the equivalent of 1.5 candles burning 1 foot away) have been shown to facilitate entrainment in some individuals in laboratory environments (23), while brighter light levels elicit faster circadian phase shifts and are better for maintaining stable entrainment. When individuals are exposed to dim light during waking, it can be difficult to entrain to day lengths that are far from an individual's endogenous circadian period. Conversely, bright light of 10,000 lux has been shown to elicit phase shifts as much as three hours following a single, 6.7-hour light pulse (29). In practice, this means that individuals who do not receive a sufficient daily light stimulus (e.g., miners, individuals in care homes or hospitals) or those who expose themselves to light during the biological night (e.g., while viewing computer screens) may experience circadian misalignment and subsequent sleep disruption.

<Insert Figure 2 about here>

Wavelength. The human circadian pacemaker is most sensitive to short-wavelength light in the 460-480 nm range (30, 31). Low intensity blue light is capable of eliciting large phase shifts and melatonin suppression similar to those achieved with full-spectrum white light at much higher intensities (32, 33). In practice, these findings support the use of blue light for therapeutic interventions to improve the efficacy of treatment for disorders that involve shifting the circadian rhythm (e.g., advanced sleep phase syndrome, delayed sleep phase syndrome), but also highlight the importance of avoiding lights with blue peaks before and during the sleep episode.

Pattern and Duration. The pattern and duration of light exposure can also influence the magnitude of the phase shift incurred. Long light exposures of 3-7 hours are capable of

eliciting large phase shifts when timed near the circadian nadir (29, 34-36), while shorter light exposure sessions are capable of causing large phase shifts if the light is of sufficient intensity or spectral content (37). Recent evidence suggests that even millisecond flashes of light, pulsed between 2.5 and 30 seconds over an hour during wake or sleep, are capable of causing phase shifts of up to two hours (38, 39). Together, these data support the importance of educating patients on how very short light exposures are capable of causing phase shifts, and suggest that even very brief light exposure during sleep can influence the circadian system (e.g., checking a brightly lit phone screen, or turning on a bright bathroom light). These studies also highlight the importance of considering the timing and duration of light exposure regimes when administering light therapy to patients.

Many people expose themselves to light in ways that can cause sleep disruption. The prevalence of handheld tablets and phones in modern society can be blamed for many modest sleep complaints. Historically, one way people used to wind down for bed was by reading a book in bed by candle light or a bedside table lamp, but now, what was formerly an appropriate bedtime routine, has been replaced by people effectively staring at bright blue lights just before bed. The light generated from a tablet screen has been shown to cause a circadian phase shift by as much as 1.5 hours, leading to elevated sleepiness upon waking, relative to reading a book with a table lamp (40). Furthermore, looking at screens before bed doesn't simply cause a problem at the time of the exposure. The circadian pacemaker interprets the light signal from one night and uses that information to change the timing of the sleep drive for the next night. This means that if a person looks at a screen for one hour before bed tonight, it will be very difficult to go to

bed at that time the tomorrow. From a treatment perspective, simply teaching people to change their evening routines and turn off screens within two hours of their desired bedtime has the potential to greatly improve sleep outcomes for those with complaints of sleep onset difficulties and early morning sleepiness.

Influence of Non-Photic Cues <H3>

As described previously, light is recognized as the strongest resetting agent, but there are several other “non-photic” zeitgebers capable of shifting circadian phase in animal models, many of which have yet to be demonstrated in humans. It should also be noted that among the human studies that have been conducted to evaluate the impact of non-photic cues, no non-photic stimulus has been shown to be as strong as even dim light exposure. The primary non-photic cues that have been explored are described below.

Meal timing. Despite popular media articles suggesting scheduled meal timing as a panacea to jetlag, there is currently scarce evidence in humans that meal timing can enhance acute phase shifting beyond photic effects (41). To date, little is known about the efficacy of scheduled meal timing to shift circadian rhythms in humans, although meals misaligned with the circadian rhythm are associated with adverse health outcomes, as discussed in later in this chapter. It is difficult to assess the impact of meal timing in humans due to the influence of other exposures such as light and activity. Therefore, it is hard to say whether there is an independent effect of meal timing on human circadian phase, peripheral or otherwise. A study of morning versus evening carbohydrate rich meals demonstrated that the core body temperature rhythm, but not the melatonin rhythm, shifted earlier in the morning meal condition compared to the evening meal (42). This study suggests that there is the potential for meal timing to aid in shifting peripheral

clocks (discussed later in this chapter), but it appears to have less of an effect on central oscillations.

Exercise. Several studies have assessed the ability to entrain the circadian system through scheduled bouts of exercise. Early studies suggested that exercise might be capable of shifting the circadian rhythm, however, in those early studies light exposure was not strictly controlled and measures of circadian phase were not reliable, potentially confounding results. Recent studies have shown modest effects of exercise on circadian phase shifting, but only when individuals were kept in dim light. In addition, the influence of exercise on the circadian pacemaker is a short-term effect, with repeated cycles of exercise being required to maintain entrainment. Although there is evidence for exercise to produce a non-photic phase shift in humans, the duration and intensity of exercise required to make a significant contribution may not be viable in real-world settings such as the work place.

Independent of phase shifting, of note, it has been shown that regular exercise can improve sleep in humans (43) and short bursts of moderate to high intensity exercise can improve subjective alertness and objective cognitive performance in the short-term (44), which may be a more useful way of improving sleep and alertness than direct phase resetting.

Social and Behavioral Cues. Before light was accepted as a critical zeitgeber in humans, evidence of co-habiting individuals synchronizing circadian rhythms under conditions of self-selected bedtimes was interpreted as being driven by behavioral and social cues (45). It has since been shown that the self-selected light schedules in that study were probably the main driving force behind these observations. Co-habitation in dim light (<8

lux), by contrast, did not show any synchrony in circadian phases between subjects (46, 47). Social cues, therefore, are not a consistent entraining factor (48). Choosing to engage in social activities (or mandatory events, such as early work starts) is more likely to change circadian timing through other exposures such as light, food intake, and physical activity, or changing sleep/wake timing itself.

There is some evidence, however, that social cues and sleep-wake cycles alone can entrain circadian rhythms. Although rare, some blind individuals with no response to photic cues still exhibit a 24-hour rhythm (49). In these case studies, it is unknown which non-photic cues are responsible for entrainment. It is likely that only individuals with an endogenous period close to 24-hours are able to entrain to non-photic zeitgebers.

Melatonin and Pharmacological Agents. Studies of treatment of non-24-hour circadian rhythm disorders, particularly in the blind, have shown exogenous melatonin administration to be successful in entraining circadian rhythms (50). Similarly, a clinical trial of tasimelteon, a melatonin receptor agonist, was successfully used to advance circadian rhythms more rapidly than placebo (51) and to entrain blind individuals (52). Melatonin has also proven useful in shift workers to help adapt to daytime sleep patterns (53). The effects of melatonin, like light, follow a phase response curve, with greater efficacy when delivered during naturally low levels of endogenous melatonin, that is, during the day/light period for humans (54).

Until recently the phase shifting effects of caffeine had only been investigated in animal studies, and with mixed results (55, 56). Recently, however, caffeine has been shown to shift circadian rhythms in humans (57, 58). The phase shifting properties of stimulants (i.e., methamphetamines), and hypnotics (i.e., benzodiazepines), may be due to their

effects on behavior (increase activity or sleep, respectively). While changes in sleep-wake patterns are only weak zeitgebers, this may be enhanced through pharmacological agents, which may also act through additional pathways to enhance re-entrainment.

Outputs of the Circadian Rhythm <H2>

Many people understand that the circadian pacemaker controls the drive to sleep at specific times of day, less known are the other aspects of biological function that are under circadian control. One important feature of the circadian rhythm is that it also controls the drive to be awake. The strongest drive to be awake occurs in the hours just before one's habitual bedtime and has been dubbed the "wake maintenance zone." The purpose of the wake maintenance zone is to dampen the high homeostatic sleep pressure that occurs near the end of the day in order for people to make it to a bedtime that will allow for a consolidated nightly sleep episode. Under normal circumstances, the wake maintenance zone is important in helping to maintain entrainment. However, the wake maintenance zone can lead to sleep complaints when individuals try to sleep during it. For example, when an individual needs to wake up at 4:00 AM to work or catch a flight, s/he would need to go to bed at 8:00 PM in order to have eight hours available for sleep. If that person normally goes to bed at 10:00 PM, then 8:00 PM will fall during the wake maintenance zone and it will be very difficult to sleep at that time. Similarly, a three hour advance in bedtime, such as the phase shift that occurs during jet lag when crossing three time zones eastward, can lead to sleep fragmentation at the beginning of the sleep episode due to the intersection of the imposed bedtime with the wake maintenance zone (59).

Although the circadian pacemaker controls many aspects of biological function, melatonin is the hormone most often measured as a biomarker of circadian phase. When

a person is entrained, melatonin is produced just prior to one's habitual bedtime. Optimal sleep initiation follows the onset of melatonin production. On average, melatonin peaks approximately six hours after sleep onset and is not produced during the waking day (see Figure 3). The timing of the melatonin onset or peak can be used to determine whether an individual's circadian rhythm is optimally timed relative to their sleep opportunity. Many researchers and clinicians use the dim light melatonin onset (DLMO) to assess circadian phase in individuals who are suspected to have circadian rhythm sleep issues. DLMO is collected by asking an individual to remain in dim light for up to six hours before, and up to three hours after, their habitual bedtime. Melatonin is typically measured by taking hourly saliva or blood samples (although urine samples can be used to evaluate the melatonin peak over a 24-hour duration). Clinicians may find it beneficial to measure DLMO for confirmation of diagnosis in individuals suspected of having advanced or delayed sleep phase disorder. It may also be beneficial to measure DLMO in individuals who have sleep onset or early waking insomnia. Modest circadian misalignment is apparent in as many as 20% of individuals diagnosed with insomnia (60). In these cases, if the timing of DLMO occurs very late (e.g., after midnight in someone who desires to sleep at 10:00 PM), then the person has a phase delayed circadian rhythm and will require either exogenous melatonin treatment before bed or bright light therapy in the morning or both to align the circadian rhythm with the individual's desired sleep time. In cases where the timing of DLMO occurs very early (e.g., before 7:00 PM in a person who desires to sleep at 10:00 PM), then the person has a phase-advanced circadian rhythm. In this case, bright light treatment in the evening would be required to align the circadian rhythm with the sleep opportunity.

<Insert Figure 3 about here>

Although melatonin is the output rhythm most commonly associated with the circadian pacemaker, the production of many other hormones and body temperature are also under circadian control. For example, there is a daily rhythm in the production of cortisol, which peaks in association with waking in entrained individuals. This morning cortisol peak is referred to as the cortisol awakening response (CAR). The hormone leptin, which is associated with appetite suppression is also under circadian control, with a peak during the night. Similarly, body temperature follows a predictable circadian rhythm. Core body temperature drops in conjunction with an individual's habitual bedtime and reaches a nadir during the night, approximately six hours after sleep onset, coinciding with the strongest circadian drive to sleep. Skin temperature follows an opposite pattern and reaches a peak during the night. These daily patterns can only shift in conjunction with careful control of light and darkness, so if a person who is normally entrained stays up all night, s/he will still experience these fluctuations in biological rhythms.

Peripheral Clocks <H2>

The central circadian pacemaker in the SCN is the master clock of the body, but many organs and tissues also contain circadian clock genes, which organize their activities in conjunction with the master clock. When the SCN is removed, these clocks continue to oscillate, but become desynchronized from one another (61). Peripheral clocks control a myriad of processes including the circadian secretion of myokines (e.g., interleukin-6) by skeletal muscle, through to daily fluctuations in gene expression in reproductive organs. The importance of these peripheral clocks is increasingly being recognized. For example, disruption of peripheral clock genes in reproductive organ tissue leads to a decrease in

fertility in animal models. Many metabolic functions are also under circadian control through peripheral clocks in the pancreas, gut, and liver. There is a peripheral clock in the pancreas that coordinates the timing of insulin secretion, promoting insulin production approximately 4 hours after the peak in melatonin (early morning) (62). Similarly, the conversion of glucose to glycogen in the liver is controlled by a peripheral clock that synchronizes glucose regulation and storage. This coordination and synchrony across organs and tissues within the body allows for an appropriate metabolic response to food consumed during the day, with better glucose tolerance occurring in the morning compared to the evening (63).

Under conditions of shift work, meal timing often occurs out of phase with these coordinated circadian clocks. Peripheral clocks are more sensitive to phase changes induced by non-photic cues such as food intake, and can shift at different rates to the SCN, and other tissues. This can lead to desynchrony across tissues, and between the peripheral and central clocks, essentially disrupting the otherwise synchronized physiological functions coordinated for processing of food. This can lead to reduced insulin sensitivity and impaired glucose tolerance when eating at night. Recent studies suggest that avoiding large meals on night shift can help to reduce the impact of circadian misalignment on these metabolic outcomes (64).

Circadian Misalignment <H2>

Circadian misalignment occurs when a sleep-wake or light-dark cycle is desynchronized from the body's internal circadian clock. This desynchrony can lead to a host of short- and long-term neurobehavioral and physiological changes. Shiftwork is a common example of circadian misalignment as workers are often required to be active during the

night, leading to desynchrony between the work-rest cycle and their endogenous circadian rhythms. Other common examples of circadian misalignment include jet lag due to transmeridian travel, and social jet lag resulting from changing sleep behaviors on weekends compared to weekdays, or extreme chronotypes (i.e., night owls) with regular office hours (65). The impact of circadian misalignment on short- and long-term health and well-being is far reaching, as described below.

Performance and alertness (neurobehavioral effects) <H3>

The neurobehavioral outcomes of atypical working hours have been well documented. Shift work is associated with sleep loss, sleepiness, and increased error rates. Circadian misalignment affects neurobehavioral outcomes in two ways: (1) attempting to maintain wakefulness at times when the circadian pressure for sleep is high (e.g., 02:00–06:00 AM); and (2) attempting to sleep during the day when the circadian rhythm is promoting wakefulness (66). Workers on both permanent night shifts and rotating night shifts only partially adapt to the nocturnal work pattern and maintain a degree of misalignment between their endogenous rhythms and work-rest cycle (67, 68). Those who do partially adapt to night work may have better alertness on shift (69), but may also find it harder to revert to being awake during the day on days off, therefore experiencing misalignment both during work days and days off (70, 71). It is worth noting that, although the sleep loss caused by circadian disruption plays a role in the consequences observed in shift work, the desynchrony of circadian and environmental cycles has independent effects on physiological factors and has been shown to further exacerbate the effects of sleep loss itself (72, 73). Therefore, even though a nightshift worker might report being able to sleep relatively well during the day, they may still suffer from the effects of circadian

misalignment on other physiological outcomes such as gastrointestinal complaints from eating at night.

Cardiometabolic disorders <H3>

A higher incidence of metabolic and cardiovascular disorders such as obesity, type 2 diabetes, and coronary heart disease have been observed in shift work populations compared to day time workers (74-76). There is some evidence to suggest that shift workers eat more poorly with higher fat content and higher calories per day compared to day workers, which may explain this epidemiological observation (77). However, a meta-analysis comparing the 24-hour energy intake of shift workers versus day workers found no difference between these two populations, suggesting that other factors may be contributing to this epidemic (78). The timing, rather than content, of meals has since been the focus of research to probe the physiological mechanisms underlying the pathologies seen in the shift working population. Indeed, laboratory studies of simulated shiftwork have shown that eating at night can impair glucose tolerance and metabolism (79, 80), which is a risk factor for obesity and type 2 diabetes. Furthermore, young adults who eat closer to their biological night have higher percent body fat and BMI (81). These studies suggest that the misalignment of meal timing with internal circadian rhythms can lead to metabolic dysfunction with effects observed after both acute and chronic misalignment.

Cancer <H3>

Epidemiological studies have shown modest yet inconsistent associations between shift work and cancer risk (82-85). While breast cancer has received the most attention, studies of colorectal, endometrial, and prostate cancer have also emerged. In 2007, based on a review of both animal and human studies, the International Agency for Research on

Cancer (IARC) classified shift work associated with circadian disruption or chronodisruption (CD) as a “probable human carcinogen” (86).

The primary mechanistic link between circadian misalignment and cancer appears to involve the increased exposure to light during the biological night, which leads to the suppression of melatonin (87). Melatonin has been shown to exhibit tumor-suppressing actions and acts as a mediator in estrogen signaling pathways (88). In rodents, studies have shown that light at night (LAN) reduces melatonin and increases markers of tumor progression, whereas exogenous replacement of melatonin in LAN conditions rescued these effects (89, 90). In humans, the association between LAN and cancer is less consistent. A recent prospective study of 105,866 participants in the UK Generations Study found no significant association between LAN exposure and cancer risk (91). However, an earlier meta-analysis showed an increased relative risk of breast cancer with high artificial light exposure, but not ambient light exposure (87). Therefore, the intensity of the light exposure and relative reduction in melatonin may account for discrepancies in reported associations. Furthermore, increased methylation of tumor-suppression factors (92) and shortened telomere length (93), both risk factors for cancer, were only observed in workers with long and/or intense shift work exposure, suggesting greater exposure to LAN. Epigenetic studies suggest that interactions between circadian genotypes and shiftwork exposure may put some shift workers at a greater risk of developing cancer, further obscuring the effects of circadian misalignment due to shiftwork in the general population (92, 94). Together these studies suggest that the effects of light-suppressed melatonin due to shift work on cancer risk may be mediated by genotype (e.g., light sensitivity, chronotype) (94).

Mental health <H3>

Surveys of shift workers report greater negative impacts on stress (95, 96), mental health (97), mood (98), and family–life satisfaction (99). Controlled laboratory studies of rats suffering from circadian misalignment show expression of depressive behaviors during the active period suggesting a direct link between circadian desynchrony and mental health (100). In humans, the independent contribution of circadian misalignment on depression and other mood disorders has yet to be disentangled from the myriad factors contributing to overall mental health.

Summary <H1>

A daily, consolidated sleep episode is achieved through stable entrainment of the circadian rhythm to a robust light-dark cycle. Such entrainment, with regular sleep-wake timing, allows for the predictable build-up of homeostatic sleep pressure during the waking day and maintenance of sleep during the night, as described by the two-process model of sleep regulation. Light is the most potent synchronizer of the circadian rhythm, while timed feeding, exercise, and social interaction have a weak to no influence on circadian entrainment in humans. Desynchronization of the homeostatic and circadian drives for sleep, such as that which occurs with jet lag, shiftwork, or insufficient light exposure, leads to sleep loss and sleep fragmentation. Persistent circadian misalignment, such as that which occurs during many years of shiftwork, can lead to an increased risk of an array of negative health outcomes including metabolic syndrome, cancer, and negative mental health effects. Together, these findings support the importance of encouraging patients to maintain stable sleep timing, in addition to sleep of adequate duration, in order to realize short- and long-term health benefits.

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