Biological Rhythms Workshop IC: Sleep and Rhythms

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Rhythms of sleep and wakefulness (typically measured as rest/activity rhythms) are among the most prominent of biological rhythms and therefore were among the first to be recorded in early chronobiological studies. These rhythms can provide useful information about the central biological clock, although an appreciation of the problems associated with using rest/activity to infer central clock function is important in the design and interpretation of chronobiological experiments in both animals and humans. Here, we review the anatomical and neurophysiologic bases of sleep regulation in mammals as well as similarities and differences between the sleep of humans and that of other organisms. We outline how human sleep is measured, the role of the circadian system in models of human sleep regulation, and human circadian rhythm sleep disorders. Although the function of sleep is still not completely understood, sleep has a critical role for human health, and we have attempted to outline the role that the circadian timing system has in regulating human sleep and in contributing to sleep disorders.

HISTORICAL USE OF REST/ACTIVITY RHYTHMS IN CHRONOBIOLOGY

The rest/activity cycle is one of the most prominent rhythms in most animal species (Fig. 1). Because this behavioral rhythm is easy to observe and measure, the rest/activity cycle has been used for decades as an index of clock function. Rest/activity cycles are also often used as an index of sleep/wake function, although the agreement between how closely rest/activity matches actual sleep/wake will depend on the method used to measure rest/activity and the species in question. In this chapter, we outline how the rest/activity cycle has been used as a measure of clock function in animal and human circadian rhythm studies, how the sleep/wakefulness cycle is controlled by the circadian timing system, and how rest/activity and sleep/wake differ between typical rodent models used in circadian research and humans.

TIMING OF THE REST/ACTIVITY CYCLE

Rest/Activity in the 24-Hour Natural Day

As described in the Biological Rhythms Workshop Introduction, in nature, most organisms are exposed to a 24-hour cycle of light and dark, and this daily fluctuation

of light and dark is the most powerful periodic environmental stimulus for entraining circadian rhythms. In most organisms, the periodic light/dark (LD) cycle normally synchronizes (or entrains) the near 24-hour endogenous circadian period to the exact 24-hour period of the environmental cycle (Pittendrigh 1961; Pittendrigh and Daan 1976a; Orth et al. 1979; Albers et al. 1984). Because the timing of the rest/activity cycle is determined (at least in part) by the circadian clock, the cycle of rest and activity (sleeping and wakefulness) is expressed as a 24-hour entrained rhythm in most organisms.

Although all organisms share the 24-hour LD cycle that entrains the circadian clock, and therefore the timing of the rest/activity cycle, the exact timing of rest/sleep and activity/wake varies between species. The most obvious difference in the timing of rest and activity is between nocturnal and diurnal organisms. Nocturnal animals have most of their activity during the biological night and spend most of the day resting, whereas diurnal animals are mostly active during the day and rest at night. The physiological mechanism of diurnality and nocturnality remains a mystery. Within nocturnal and diurnal groups, the exact timing of rest and activity can vary greatly among species and even among individuals within a species. This fact is only too apparent when one is awo-

Figure 1. Triple-plotted activity/rest record from a C57B6 mouse studied in DD. As is typical in mice, activity onset is earlier each day than the previous day, indicating a period shorter than 24 hours. (*Upper half*) Activity recordings are from a running wheel; (*lower half*) animal's running wheel was locked and the activity is from drinking at the water spout. The period was shorter when the animal was able to run in the wheel (23.05 hours vs. 23.50 hours), indicating that running-wheel activity was affecting the observed circadian period.

ken by the chirping of early-rising diurnal birds or kept awake by noisy neighbors!

The timing of a circadian-clock-controlled physiological or behavioral rhythm with respect to the LD cycle is referred to as the “phase angle of entrainment.” One such example of a phase angle is the time of activity onset relative to dawn in diurnal animals. In the natural environment, this phase angle of entrainment is determined by the endogenous period of the clock and its sensitivity to the phase-shifting effects of light. Given that both the endogenous period and light sensitivity are not static, nor is the day-to-day exposure to environmental light, phase angle can take on very different values among species, among individuals within a species, and even within a single individual.

Rest/Activity Independent of Light/Dark Cycles

Evaluation of rest/activity-sleep/wake timing in animals. It is a defining characteristic of endogenous circadian rhythms that they persist under constant conditions, without rhythmic input from external entraining agents such as the LD cycle. Initially, constant conditions were defined as constant environmental (external) conditions, hence long-term studies of animals in constant darkness (DD) or constant light (LL). In both DD and LL, circadian rhythms in rest and activity have been found to “free-run” with an endogenous period different from that of the 24-hour day. To place animals in a constant environment is still a widely used paradigm to quantify circadian phenotypes. The assumption underlying such experiments is that removal of periodic environmental cycles is sufficient to uncover the contribution of the circadian pacemaker to the observed rhythmicity. As we point out below, this assumption may not always be true.

Exposure to LL and DD does not have equivalent effects on the timing of rest and activity. The rest/activity cycle is different in DD and LL, and within LL conditions, the observed free-running period depends on light intensity (“Aschoff’s rule”; Aschoff 1961). For nocturnal mammals, according to “Aschoff’s rule,” with increased light intensity, the period of the rest/activity cycle becomes longer and the length of time spent active decreases. For diurnal animals, the reverse tends to occur, with increasing light resulting in a shorter rest/activity cycle period and a longer active episode within each cycle. Furthermore, although the circadian period is usually stable upon entering DD, it has been found to take up to 60 days to reach a steady state while in LL (Pittendrigh and Daan 1976b).

Perhaps the most striking difference between the response to DD and LL is the effect on the integrity of the rest/activity rhythm. Although animals have been found to maintain stable rest/activity patterns throughout their life span in DD or very dim light (see, e.g., Richter 1968; Davis and Viswanathan 1998; Duffy et al. 1999a), bright LL is often associated with disruption of the rest/activity cycle, as outlined in Biological Rhythms Workshop IB (Pittendrigh and Daan 1976b; Honma and Hiroshige 1978; Shibata et al. 1984; Mason 1991; de la Iglesia et al. 2000; Jagota et al. 2000; Beaulé et al. 2003; Sudo et al. 2003). This is not surprising, because DD represents an absence of light input to the clock, whereas with bright

LL, there is constant exposure of the biological clock to a powerful entraining/resetting agent.

Given the disruptive effects of LL, when attempting to measure the endogenous rhythm in the rest/activity cycle of laboratory animals, the gold-standard method has been the measure of activity in DD. This method, however, is not without drawbacks. Activity itself has been demonstrated to be a powerful entraining agent. Phase shifts to acute presentation of a novel running wheel, eliciting intense locomotion, have been demonstrated in the hamster (Reebs and Mrosovsky 1989). Self-selected activity is also associated with an alteration of rest/activity timing. Increased locomotor activity has been shown to shorten the period of the rest/activity cycle in mice (Edgar et al. 1991) and rats (Yamada et al. 1988). An example of the effect of locomotor activity on the period of the rest/activity rhythm is presented in Figure 1, which shows the rest/activity rhythm of a mouse with access to a running wheel and with the running wheel locked. The period of the rest/activity rhythm was shorter when the animal was allowed access to the running wheel and lengthened when the wheel was locked and only drinking rhythms were measured (see also Cheng et al. 2004).

Feedback to the circadian system from the behavioral state of an animal is not limited to activity. Sleep has also been shown to affect the timing of the biological clock. Sleep deprivation has been shown to shift the phase of the rest/activity cycle (Antle and Mistlberger 2000). Sleep can also modulate the firing rate of suprachiasmatic nucleus (SCN) neurons (Deboer et al. 2003). The timing of both sleep and activity feeds back onto the core biological clock and affects the timing of these behaviors. It is therefore important to consider the behavior of the experimental organism when measuring circadian activity patterns and to understand that controlling environmental conditions does not consequently create a constant internal environment.

Although the timing of the rest/activity cycle tends to be fairly stable in DD, light exposure history has been found to have an effect on the period of the cycle once the light is removed. The period-altering effect of light exposure was first reported by Pittendrigh in 1960 (Pittendrigh 1961). Entrainment to LD cycles of various lengths has been shown to affect the circadian period such that the endogenous timing approaches that of the environment. For example, in a classic experiment, Pittendrigh and Daan (1976b) entrained mice to LD cycles of 23 and 25 hours, with half of each cycle light and the other half darkness. They increased or decreased the LD cycle by 10 minutes each day for 18 days, resulting in a final LD cycle of 20 or 28 hours, respectively. Following this, the mice were released into DD to have their circadian period assessed. The period was longer in mice following entrainment to a 28-hour LD cycle than in mice entrained to a 20-hour LD cycle, and these period values were longer and shorter, respectively, than the estimates of period for this species after exposure to 24-hour LD cycles. Such history-dependent effects on period, called “aftereffects of entrainment,” to longer and shorter than 24-hour day lengths have also been reported in hamsters (Reebs and Doucet 1997), albino rats (Stewart et al. 1990), and more recently humans (Scheer et al. 2007).

Aftereffects can also occur in response to different photoperiods. Using an LD ratio of 1:23 versus 18:6, four of five white-footed mice showed a shorter rest/activity cycle period after entrainment to the longer photoperiod (Pittendrigh and Daan 1976b), and the effects on period were observed to last for at least 300 cycles (nearly a year!) in some mice.

Aftereffects of light history on the timing of the rest/activity cycle have been demonstrated even after single exposures to light. Despite the wide array of species studied, findings are strikingly consistent: Aftereffects of light pulses on the timing of the rest/activity cycle depend on the magnitude and direction of the phase shift induced by the light. Delaying phase shifts produce a lengthening of period, and advancing light pulses produce a shorter period. The magnitude of the effect on period is positively correlated with the magnitude of phase shift produced (Pittendrigh 1961; DeCoursey 1964; Eskin 1971; Kramm 1971; Gerkema et al. 1993; Sharma and Daan 2002). The likely function of aftereffects is to stabilize entrainment when exposed to fluctuations of light input (Pittendrigh and Daan 1976b; DeCoursey 1989; Beersma et al. 1999), thus maintaining a fixed phase angle of entrainment to the environment.

Together, these various findings demonstrate that even when an organism is studied under constant conditions, the recent history and internal physiological state, as well as the organism's periodic behavior, can influence the central pacemaker, thus affecting current observations and the outcome of any experimental manipulation.

Evaluation of rest/activity timing in humans. Early attempts to measure the endogenous timing of the human rest/activity cycle were performed by Aschoff and Wever (1962) in an isolation unit free from time cues. Several variables (including rest/activity) were shown to have a daily rhythm of about 25.1 hours. Longer-term experiments conducted in isolation units and caves also found that human circadian rhythms had a period close to 25 hours (Wever 1979, 1989; Aschoff and Wever 1981).

In retrospect, we now understand that the period estimates derived from these experiments were systematically confounded by the influence of self-selected light exposure (for review, see Czeisler 1995). This is because these early human studies were performed with two major differences from animal studies. First, many of the human studies were not conducted under constant lighting conditions (LL or DD), but instead in LD cycles. Second, unlike studies in other organisms where the organism under study had no control over the lighting, in these human studies, the experimental subjects were given control over some or all of the lighting, and the lighting levels used were bright enough (as we now know) to cause effects on the circadian system (Boivin et al. 1996; Zeitzer et al. 2000). This led to several factors that confounded the period estimates, although these confounds were not realized at the time.

First, humans, unlike most other organisms, have monophasic sleep (see below). This means that sleep generally occurs in one long bout each day, with waking occupying the remainder of the day. Light exposure (the

most powerful environmental signal to the internal clock) is therefore present at some circadian phases and absent at others when the lights are switched on upon waking and turned off for sleep. Even when lighting is kept on continuously, there is a change in light input to the central clock associated with eyelid closure upon sleep.

Second, under entrained conditions, the circadian rhythm of sleep propensity shows a paradoxical relationship to usual sleep/wake timing. Unlike what might be expected, there is a strong circadian drive for *wakefulness* just before usual bedtime in humans and a peak drive for sleep near the end of the usual sleep episode (see below for more detail). Humans who are studied in time-free environments and who are allowed to self-select their sleep/wake times routinely remain awake later than they do under entrained conditions (Czeisler et al. 1981; Zulley et al. 1981; Klerman et al. 1996). When they do so, the additional evening light exposure that they receive produces systematic phase-delay shifts due to the phase-dependent effects of light on the circadian system (Honma and Honma 1988; Czeisler et al. 1989; Minors et al. 1991; Khalsa et al. 2003). These systematic phase delays are further exacerbated by the fact that the sleep/dark episode is now extended into the usual morning time, when light exposure would normally counteract evening light exposure and produce a phase advance (for more detail, see Klerman et al. 1996).

The net result of these factors was that there was an overestimation of the period of the circadian system in those "free-running" studies in humans (Klerman et al. 1996). Development of a protocol (the "forced desynchrony" protocol [Czeisler et al. 1990] first proposed by Nathaniel Kleitman in the 1930s [Kleitman 1939]), in which these confounds are minimized, has subsequently shown that the period of the human circadian system is much closer to 24 hours (Middleton et al. 1996; Hiddinga et al. 1997; Waterhouse et al. 1998; Carskadon et al. 1999; Czeisler et al. 1999; Kelly et al. 1999; Wyatt et al. 1999) and far less variable among individuals than those initial free-running studies had suggested.

DEFINITION OF SLEEP

Sleep as an Altered Behavioral State

The alternating succession of sleep (or rest) and wakefulness is a ubiquitous, evolutionarily conserved behavior, and has been shown in invertebrates, vertebrates, and humans (Campbell and Tobler 1984; Tobler 2005). In invertebrates and lower vertebrates (fish and amphibians), sleep is assessed by quiet resting behavior, typical body position, reduced reactivity to external stimuli, and by the relatively rapid reversibility of these states. In birds, reptiles, and mammals, sleep and wakefulness are further ascertained in characteristically dynamic changes of electrical brain activity. More recently, it has also become possible to assess sleep- and wake-dependent differences in brain activity of very small invertebrates such as fruit flies (*Drosophila melanogaster*; Nitz et al. 2002). These characteristics allow the differentiation between sleep and quiet wakefulness and between sleep and other vegetative states such as torpor, hibernation, or coma.

In most animals, the entire brain enters the sleep state, but this does not occur in all animals. In aquatic mammals such as cetaceans (whales and dolphins), only one brain hemisphere sleeps at a time, and the other half remains awake (Mukhametov et al. 1977). By sleeping with only half of their brain at once, these aquatic mammals can periodically swim to the surface to breathe during sleep. Interestingly, in those animals that exhibit aquatic and terrestrial living across their life span (e.g., fur seals; subfamily *Arctocephalinae*), sleep patterns change from unihemispheric to symmetric hemispheric sleep and vice versa, depending on the medium in which the animal is currently living (Siegel 2005).

Monophasic versus Polyphasic Sleep

One of the major differences between rest/activity and sleep/wake cycles of typical rodent models of circadian rhythmicity and humans is in the distribution of sleep and wakefulness across the 24-hour day. Most animal species have polyphasic sleep, with sleep and wakefulness distributed in frequent bouts, often with a predominance during the dark (diurnal species) or light (nocturnal species) phase (Tobler et al. 1990a). For example, the nocturnal Syrian hamster (*Mesocricetus auratus*) spends about 78% of the light period and 51% of the dark period sleeping (Tobler and Jaggi 1987), and Sprague-Dawley rats (an outbred strain from *Rattus norvegicus*) sleep during about 69% of the light period and 27% of the dark period (Franken et al. 1991). The rabbit (family Leporidae) spends 55% of the light period and 40% of the dark period sleeping (Tobler et al. 1990b), whereas the diurnal Siberian chipmunk (*Tamias sibericus*) sleeps during only 27.5% of the light period but spends 74% of the dark period sleeping (Dijk and Daan 1989). Guinea pigs (*Cavia porcellus*) seem to have little phase preference, spending 30% of the dark phase and 35% of the light phase asleep (Tobler et al. 1993).

In contrast, adult humans and a few other primates (e.g., some species of New World monkeys) exhibit monophasic sleep, spending nearly all of the light phase awake and most of the dark phase (depending on LD cycle duration) asleep, resulting in only one (or two) major bouts of sleep and wakefulness each 24-hour cycle. A major difference between these primates and other animals is that they can maintain wakefulness for an extended duration without any special environmental influence or intervention, with their consolidated sleep likely resulting from their ability to consolidate wakefulness. Due to artificial illumination, modern humans control their LD cycle, typically spending about one third of each 24-hour day sleeping. Whether the distribution of sleep and wakefulness into one bout per day, and the relative duration of sleep (about one third) and wakefulness (about two thirds) within the daily cycle, reflects a biological process or is instead an artifact of access to artificial lighting is not entirely clear, but some laboratory studies provide hints. Wehr (1991, 1996, 2001) conducted a study in which they kept human subjects in bed in complete darkness for 14 hours each day for 4 weeks. After many nights of increased sleep duration (attributed to recovering from prior sleep deprivation), most of the subjects established a pattern in which they slept for about 8.4

hours per night, but this was divided into two major bouts, with several hours of wake in the middle of each 14-hour night. These findings suggest that although the relative sleep/wake ratio (1:2) seen in adults may reflect an average biological sleep need, the relative consolidation of adult human sleep into one major bout per day may be an artifact of photoperiod and/or how long we attempt to or are able to remain awake each day and that under the right conditions, human sleep may tend to be polyphasic.

In designing and interpreting studies of circadian rhythmicity, study conditions that result in sleep/wake and light/dark cycles being potentially confounded, and/or when rest/activity could have a feedback effect on the system under study, the effects of sleep itself and the species differences in sleep become important considerations.

Measurement of Human Sleep Architecture and Sleep EEG

Before technology allowed for the measurement of brain electrical activity (electroencephalogram, EEG), it was thought that the brain, like the rest of the body, was inactive during sleep. The EEG, first described in rabbits and monkeys by Caton in 1894, and later in humans (Berger 1929), reflects summated potentials of large cortical neuron groups, recorded from the surface of the scalp or from the cortex, in a voltage-time domain. Brain wave activity differs between sleep and wakefulness (Loomis et al. 1935, 1937), and during sleep itself, there are substantial differences in the neuronal firing pattern with ultradian changes across the sleep episode (Dement and Kleitman 1957).

A normal 8-hour sleep episode in humans consists of four to five sleep cycles, with each cycle lasting for about

Figure 2. Schematic representation of the human sleep episode. The x axis indicates time within the sleep episode, and the y axis indicates the vigilance state. As is typical for a healthy, well-rested young adult, sleep onset occurs within 10–30 minutes of attempting to initiate sleep, and there is a quick procession through the lighter NREM stages to deep NREM sleep and then into REM sleep. As the night progresses, NREM and REM sleep cycles alternate about four to six times, with REM episodes getting progressively longer and NREM episodes containing fewer of the deeper stages toward the end of the night. There are a few brief awakenings, and spontaneous awakening occurs mostly from REM (as shown here).

Figure 3. EEG waves in different vigilance states recorded from a 23-year-old man. (A) Alpha waves characteristic of quiet wakefulness with eyes closed; (B) Stage 1; (C,D) Stage 2. In panel C, the arrow indicates a sleep spindle, and in panel D, the arrow indicates a “K complex”; both of these EEG waves are characteristic of Stage 2. (E) Slow waves characteristic of Stages 3 and 4 sleep; (F) REM sleep. Note that as sleep progresses, the EEG slows down and the amplitude increases, reflecting synchronization of the underlying cortical neurons.

90–100 minutes (Fig. 2). These cycles are composed of two distinct states, rapid eye movement (REM) sleep and nonrapid eye movement (NREM) sleep. Visual scoring of the sleep EEG is defined according to standardized criteria (Rechtschaffen and Kales 1968). According to these somewhat arbitrary criteria, brain waves in the frequency range between 8 and 12 Hz (alpha waves) typically occur

during quiet rest with eyes closed. At the transition from wakefulness to sleep, there is a gradual lowering in frequency and concomitant increase of amplitude in the EEG, and this general slowing of EEG frequency and increase of EEG amplitude continues as sleep initially progresses, reflecting a rising level of synchronization in cortical neurons. As these EEG changes progress, specific EEG frequency and amplitude criteria are used to subdivide sleep into NREM Stages 1 (the transition between wakefulness and sleep) through 4 (deep sleep) (Fig. 3).

Stages 3 and 4 together are commonly referred to as slow-wave sleep (SWS) and are defined as containing >20% delta waves (EEG waves with a frequency between 0.75 and 4.5 Hz and a peak-to-trough difference of at least 75 μ V). There is clear evidence that delta waves are generated through synchronized rhythmic thalamocortical circuit activity, whereas very slow oscillations (<1 Hz) are excited within the neocortex (Steriade et al. 1993). Additional phasic EEG events, such as sleep spindles (12–14 Hz, see arrow in Fig. 3C) and K complexes (e.g., during Stage 2, see arrow in Fig. 3D) or vertex sharp transients (Stage 1) are also typical during NREM sleep.

REM sleep (also known as paradoxical sleep) was first described by Aserinsky and Kleitman (1953) and is mainly characterized by rapid eye movements (measured in the electrooculogram), a loss of muscle tone (measured in the electromyogram), and a low-voltage mixed EEG frequency (1–7 Hz) pattern (Fig. 4).

As the alternation of NREM and REM sleep continues across the night, the proportion of each sleep stage changes, with most SWS at the beginning of the night and longer REM sleep episodes and more Stage 2 sleep toward the end of the night. Visual scoring of the sleep polysomnogram (Rechtschaffen and Kales 1968) subdivides sleep into discrete stages (1–4, REM) and thus allows only limited quantification of the sleep EEG and the underlying physiological changes in the neuronal firing pattern of the cortex. There are more quantitative methods of analyzing the sleep EEG, such as fast Fourier transformation (FFT), which enables continuous analyses

Figure 4. Thirty-second recording during REM sleep from a healthy 72-year-old woman. The upper recording line shows the electromyogram (EMG), the next four recording lines show the EEGs recorded from central (C3, C4) and occipital (O1, O2) sites, and the two lower recording lines show the electrooculograms (EOGs) from the left (LOC) and right (ROC) eyes. Characteristic of REM sleep, EMG activity is extremely low and there are several rapid eye movements within this 30-second epoch. The typical low-voltage mixed EEG frequency (1–7 Hz) pattern can also be seen here.

in the power/frequency domain (Dietsch 1932; Borbély et al. 1981).

It is now clear that during sleep the human brain exhibits regional differences in electrical activity (EEG power density in different frequency bands) (Werth et al. 1996; Finelli et al. 2001; Knoblauch et al. 2003), and there are age-dependent differences in this (Landolt and Borbély 2001; Münch et al. 2004). In addition, there is both EEG and neuroimaging evidence that during sleep, the brain shows use- and experience-dependent deactivation and reactivation in different areas (Braun et al. 1997; Hofle et al. 1997; Maquet et al. 1997), and such regional variation in activity during sleep may be associated with learning and memory-related processes in which sleep has a role (Kattler et al. 1994; Huber et al. 2004; Schmidt et al. 2006).

Neuroanatomic and Neurophysiologic Basis of Sleep

The ascending reticular activating system (ARAS) of the brain stem, first described by Moruzzi and Magoun (1949), is involved in maintaining cortical activation and behavioral arousal during wakefulness. The ARAS largely originates from a series of well-defined cell groups, including the laterodorsal tegmental (LDT) and pedunculopontine (PPT) nuclei, the locus coeruleus (LC), the dorsal and medial raphe nuclei (DR), the tuberomammillary neurons (TMN), and dopaminergic neurons in the periaqueductal grey matter (Saper et al. 2001). In animals, these nuclei of the ARAS in the brain stem receive various inputs from visceral, somatic, and sensory systems and project mainly via two different pathways to the cerebral cortex (for review, see Jones 2000). Excitatory neurons of the dorsal pathway in the ARAS project from the upper brain stem via relay and reticular neurons of the thalamus to the cerebral cortex. The ventral pathway projects directly to the cortex via the lateral hypothalamus (LH) and the basal forebrain (BF) (Jones 2000; Saper et al. 2005b). The firing rate of glutaminergic ascending reticular neurons and monoaminergic cell groups, as well as excitatory peptidergic neurons of the posterior hypothalamus and the LH (which synthesizes the wake-promoting hormone orexin/hypocretin), is crucial for maintaining cortical activation and behavioral arousal during wakefulness (Jones 2000; Saper et al. 2005b). The intralaminar and midline nuclei of the thalamus are also believed to have a role in cortical arousal (Berendse and Groenewegen 1991; Saper et al. 2005a).

During sleep, neurons in the ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus inhibit neuronal activation of the ARAS, BF, and cerebral cortex (Sherin et al. 1996; Jones 2000; Saper et al. 2005a). The VLPO receives afferents from each cell group of the monoaminergic system via the subparaventricular zone of the dorsomedial hypothalamus, thus mostly indirectly receiving input from the SCN. There are also mutual connections between the VLPO and orexin neurons (Chou et al. 2002). The VLPO consists of at least two subregions: a dense cell cluster projecting to the TMN and a diffuse cell region (eVLPO), which projects to the LC, DR (Lu et al. 2000, 2002), and probably also REM sleep-activating sites in the mesopontine tegmentum (Lu et al. 2006).

In the thalamus, progressive hyperpolarization of reticular neurons gates thalamocortical inputs to the cortex. When a certain level of hyperpolarization is achieved, those neurons change their firing pattern from single-spike mode to a rhythmic burst mode (Steriade et al. 1993). These oscillations are then relayed on other nuclei within the thalamus and lead to rhythmic inhibitory postsynaptic potentials in thalamocortical neurons. Consequently, the thalamocortical neurons fire rebound bursts of action potentials that are transferred to the cortical pyramidal cells, where they in turn induce excitatory postsynaptic potentials, thereby generating EEG sleep spindles. This results in an inverse firing pattern in reticular and thalamocortical neurons during these oscillations. Depending on the degree of hyperpolarization in the reticular cells, either sleep spindles or slow-wave oscillations are generated. Therefore, the progressive hyperpolarization of thalamocortical cells at sleep onset first leads to the generation of sleep spindle oscillations, which are replaced by slow-wave oscillations as deepening of sleep proceeds and a certain low-voltage range in thalamocortical neurons is reached. These slow-wave oscillations become synchronized in the cortex in large neuronal assemblies by a network of synchronizing factors (Steriade et al. 1993; Amzica and Steriade 1998; Steriade 2003).

The switch between REM and NREM sleep is thought to be modulated through interaction of monoaminergic with cholinergic neurons, although these mechanisms and their function are not fully understood. The monoaminergic neurons fire faster during wakefulness than during NREM sleep and show virtually no firing activity during REM sleep, whereas the cholinergic system is most active during wakefulness and REM sleep by preventing reticular cells in the thalamus from hyperpolarization (Aston-Jones and Bloom 1981).

Saper et al. (2001) have proposed the so-called “flip-flop” model of sleep and wakefulness (see Fig. 5). In this model, monoaminergic nuclei such as the TMN, LC, and DR promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep-promoting neurons of the VLPO. During sleep, the VLPO inhibits monoaminergic-mediated arousal regions through GABAergic and galaninergic projections (Saper et al. 2001). Thus, intermediate states between sleep and wakefulness are prevented by the reciprocal inhibition of VLPO neurons and monoaminergic cell groups that concomitantly disinhibit and reinforce their own firing rates. Orexin-containing neurons seem to have an important stabilizing role in the proposed flip-flop mechanism. In addition, it has also been suggested that there is a flip-flop switch for REM/NREM sleep, with mutually inhibitory neurons in the brain stem, also under the influence of orexin (Lu et al. 2006). Several neuronal pathways of the SCN to and from sleep and wake-regulatory neurons have been described in the last few years (Deboer et al. 2003; Saper et al. 2005b), and there is strong evidence that information from peripheral oscillators, such as feeding and temperature regulation and even emotional states, are integrated in the modulation of the endogenous circadian timekeeping system in animals and humans (for review, see Saper et al. 2005b).

Figure 5. A flip-flop model for reciprocal interactions between sleep- and wake-promoting brain regions. (Red) Inhibitory pathways; (green) excitatory pathways. (DR) Dorsal raphe nucleus; (HIST) histamine; (LC) locus coeruleus; (LDT) laterodorsal tegmental nuclei; (PPT) pedunculopontine tegmentum; (REM) rapid eye movement; (TMN) tuberomammillary nucleus; (VLPO) ventrolateral preoptic nucleus. A flip-flop switch promotes the system to be in one state or the other and prevents the system from being in an intermediate state for long durations. (Reprinted, with permission, from Saper et al. 2001 [© Elsevier].)

SLEEP REGULATION IN HUMANS

Interaction of Two Major Regulatory Processes: Borbély-Daan Model of Process C and Process S

Several models have been proposed to understand how consolidated sleep and waking can be achieved in humans. In the early 1980s, Borbély proposed a model with two interacting processes—a homeostatic Process S and a circadian Process C—that counterbalance each other to allow for a long consolidated bout of sleep each night and a long bout of wakefulness during each 24-hour day (Borbély 1982; Daan et al. 1984).

According to this two-process model, Process S (the level of sleep pressure) builds up during wakefulness with respect to the duration of time awake (Fig. 6, lower panel) and then that sleep pressure is dissipated during the course of the following sleep episode. Markers of this homeostatic process are the increase of EEG theta activity (4.5–8 Hz) during wakefulness (Cajochen et al. 1995, 1999b; Finelli et al. 2000) and the decrease of EEG slow-wave activity (0.75–4.5 Hz) during the following sleep episode (Werth et al. 1996; Cajochen et al. 1999a; Finelli et al. 2001). Process S has been shown to be operative in both animals and humans, and the predictions of the model, based on mathematical simulations, fit the experimental data (Borbély 1982; Daan et al. 1984; Achermann et al. 1993). The neurobiological correlates of the homeostatic process are not known, and although sleep homeostasis may be functionally linked to restoration, the underlying

mechanisms remain to be elucidated (Benington and Heller 1995). There is mounting evidence that genetic factors (Retey et al. 2005; Viola et al. 2007) and processes related to synaptic plasticity (Tononi and Cirelli 2003, 2006) are also involved in homeostatic sleep regulation.

The circadian process (Process C) in the model describes the 24-hour periodicity of sleep propensity resulting from the neuronal and/or humoral influence of the biological clock, with strong sleep propensity at some and weaker or absent sleep propensity at other circadian phases. This waveform of sleep propensity in humans is associated with melatonin secretion from the pineal gland (Lavie 1997), and the circadian sleep propensity waveform is influenced by light via the retinohypothalamic tract to the SCN (see Biological Rhythms Workshop IB). As has been reported in many animal species (see Biological Rhythms Workshop IB), the biological night in humans seems to be extended when photoperiods are shorter (Wehr 1991, 1996, 2001).

Another phenomenon in humans is that of different chronotypes, whereby the relative sleep timing of some individuals is earlier (morning types) or later (evening types) than average (Kleitman 1939). This preference for different sleep times has been shown to be associated with differences in circadian period (Duffy et al. 2001), with individuals with shorter circadian periods showing a pref-

Figure 6. Model of human sleep regulation. This schematic incorporates the “two-process model” proposed by Borbély (Borbély 1982; Daan et al. 1984), with features of the “opponent process” model of Edgar (Edgar et al. 1993; Dijk and Edgar 1999) and additional features proposed by others (for review, see Mistlberger 2005). (Lower panel) Borbély’s proposed homeostatic Process S builds up during wakefulness and dissipates during sleep (shaded box). (Upper panel) Wake-promoting function of Process C (from signals from the SCN) as proposed by Edgar peaks toward the end of the wake episode (Cw), acting to counteract the buildup of sleep pressure during waking. (Middle panel) Another proposed function of the circadian system, which is to actively promote sleep toward the end of the sleep episode to allow for a long consolidated bout of sleep (Cs).

erence for morningness and those with longer periods showing a preference for eveningness. Consistent with these period differences are reports that morning and evening types have differences in their phase angle of entrainment, such that they are not only sleeping at different clock times, but also sleeping at different biological times (Duffy et al. 1999b; Baehr et al. 2000). Morningness-eveningness has been shown to be associated with clock gene expression (Katzenberg et al. 1998; Archer et al. 2003; Carpen et al. 2005, 2006; Mishima et al. 2005), lending further support to the idea that chronotype preference can be the result of fundamental differences in the circadian system. More recently, human chronotypes have also been shown to differ in their homeostatic sleep regulation (Mongrain et al. 2006).

Regulation of Sleep by the Circadian Pacemaker

As described in detail in Biological Rhythms Workshop IB, the SCN represent the endogenous circadian pacemaker, and one role this group of neurons has is to synchronize the circadian oscillations of behavior. Among other factors, SCN lesions result in arrhythmicity of the rest/activity and sleep/wake cycles in animals. In fact, although SCN lesions cannot be done in humans, the anterior hypothalamus was identified as a locus of sleep/wake control as early as the 1920s, based on data from patients with tumors in that region of the brain (Fulton and Bailey 1929; von Economo 1930). Such patients continue to show patterns of sleep and wakefulness, although no longer on a consistent 24-hour basis and often no longer in consolidated bouts (Fulton and Bailey 1929; von Economo 1930; Schwartz et al. 1986; Cohen and Albers 1991; Bloch et al. 2005; Triarhou 2006), suggesting a role for the human SCN in maintaining 24-hour patterns of sleep and wakefulness.

The Borbély-Daan Two-process Model hypothesized a Process C emanating from the circadian pacemaker, and later researchers confirmed that it was indeed the SCN serving such a function by studying sleep/wake regulation in SCN-lesioned animals. Edgar (Edgar et al. 1993) studied the circadian control of sleep/wake function in SCN-lesioned squirrel monkeys (*Saimiri sciureus*, diurnal animals who exhibit monophasic sleep) and proposed an “Opponent Process” model of sleep/wake regulation to describe how the SCN promotes wakefulness during the subjective day (for review, see Dijk and Edgar 1999) to counterbalance the buildup of sleepiness. Others have since extended this by suggesting that the SCN not only promotes wakefulness during the subjective day, but also promotes sleep during the subjective night (for review, see Mistlberger 2005; Fuller et al. 2006).

A precise interaction between sleep/wake homeostatic (Process S) and circadian processes is required to maintain wakefulness throughout the biological day and sleep throughout the biological night. As homeostatic sleep pressure builds throughout wakefulness, the circadian pacemaker is thought to send an increasingly strong wake-promoting signal, allowing wakefulness to be maintained (Fig. 6, upper panel). Similarly during sleep, as sleep pressure dissipates across the night, the biological

clock may send a strong sleep-promoting signal, allowing sleep to be maintained (Fig. 6, middle panel). Evidence supporting both processes (C and S) in these models came from studies using the forced desynchrony protocol.

In forced desynchrony studies, the timing of the sleep/wake cycle is uncoupled from the timing of the circadian system by scheduling human subjects to live on a rest/activity schedule that is much shorter (typically 20 hours) or much longer (typically 28 hours) than the near 24-hour period of the underlying circadian system. This protocol results in sleep and wake episodes distributed across all circadian phases, with similar scheduled durations of wakefulness preceding each sleep episode. Therefore, homeostatic (Process S) and circadian phase-dependent (Process C) effects on sleep can be separated and quantified.

In the first such study, Dijk and Czeisler (1994) found that the sleep/wake homeostat and the circadian pacemaker contributed about equally to sleep in young men. As had been suggested by earlier studies (Weitzman et al. 1974a,b; Carskadon and Dement 1975; Webb and Agnew 1975; Lavie 1986), the circadian sleep propensity rhythm was lowest near habitual bedtime under entrained conditions (“wake maintenance zone”), and circadian sleep propensity was greatest at phases corresponding to usual wake time under entrained conditions. Furthermore, they showed that it was only with a very precise relative timing between these two sleep regulatory processes that sleep could be maintained for a consolidated 8–9-hour sleep episode.

CIRCADIAN RHYTHM SLEEP DISORDERS

Circadian rhythm sleep disorders represent situations in which the relationship between the timing of sleep and wakefulness and the timing of the underlying circadian system is misaligned. This misalignment can be transient, such as in jet lag or during night shift work, or the misalignment can be chronic, as in advanced or delayed sleep phase disorders (ASP, DSP) or non-24-hour sleep/wake disorder. In jet lag and during night shift work, sleep and wake are attempted at nonoptimal biological times, resulting in difficulty falling asleep and/or difficulty in maintaining sleep. In contrast, ASP and DSP patients often do sleep at appropriate biological times, but those times are inappropriate socially, and when the patients try to change their sleep timing to a more acceptable social time, they have trouble remaining awake (ASP), falling asleep (DSP), or maintaining sleep. In most cases, patients with these disorders have a reduced sleep duration, resulting in decrements in performance, mood, and alertness during their wake episodes (for a recent review, see Lack and Wright 2007).

A similar situation affects many totally blind individuals. Due to a lack of light input to the biological clock, many blind people are unable to entrain to the 24-hour day, and thus experience non-24-hour sleep/wake disorder (Sack et al. 1992). The circadian system of these blind individuals typically cycles in and out of synchrony with the time of the external world, and thus at some times, they

are able to sleep at night and maintain alertness throughout the day, whereas at other times, they have great difficulty sleeping at night and remaining awake during the day.

CHRONOPHARMACOLOGY

The biological clock surely serves to do more than properly time sleep and wakefulness. Coordination of temporal information throughout the whole organism is thought to be crucial for maintaining optimal health, with the central pacemaker located in the SCN serving to maintain synchrony among peripheral oscillators and with the external environment. This suggests that disruptions of this internal synchrony will not only affect the function of many organ systems, but also affect how the whole organism responds to challenges, and there is evidence of this from both animal and human studies. Experiments performed in the early 1980s demonstrated that the circadian time of administering a lethal drug dose to rats could influence mortality or long-term survival. Rats were administered *cis*-diamminedichloro-platinum (cisplatin) at different times of the day in an "LD₅₀" test, and depending on the time of drug administration, there were differences of threefold to eightfold 50% mortality rate and a nearly threefold difference in long-term survival (Hrushesky et al. 1982). In more recent studies, when such cytotoxic medications are given to human cancer patients, the drugs show a higher efficacy when administered at an ideal circadian time, allowing a reduced dose to be used, thereby reducing side effects (see, e.g., von Roemeling et al. 1990). The circadian timing of drug administration likely contributes to pharmacokinetic variability, which in the past has been attributed only to such factors as age, gender, ethnicity, or organ functioning (Undevia et al. 2005). In fact, many clinicians and scientists now suggest a custom-tailored therapy for an individual patient, including assessing circadian phase and taking into account the sleep/wake cycle (for review, see Lévi and Schibler 2007).

CONCLUSIONS

As we have outlined in this review, rhythms of sleep and wakefulness (typically measured as rest/activity rhythms) are among the most prominent of biological rhythms and therefore were among the first to be recorded in early chronobiological studies. These rhythms provide useful information about the central biological clock, but there are problems inherent in their use, and an understanding of those potential problems is important in the design and interpretation of chronobiological experiments. Furthermore, a more comprehensive understanding of sleep/wake-regulatory differences among species is important for the design and interpretation of chronobiological experiments and for extrapolating observations from animal studies to studies of human chronobiological disorders.

We have also described the anatomical and neurophysiological bases of sleep regulation in mammals and briefly outlined how sleep in humans is measured. The interaction of circadian with homeostatic sleep regulating processes to allow for consolidated sleep and wakefulness in humans has been described. Finally, we briefly sum-

marized how circadian rhythm sleep disorders in humans occur. Although the function of sleep is still not completely understood, sleep has a critical role for human health, and we have attempted to outline the role of the circadian timing system in human sleep and sleep disorders, as well as similarities and differences between the sleep of humans and that of other organisms.

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