Sleep and Circadian Rhythms: Basic and Clinical Findings

In modern society, there are many factors that challenge the sleep/wake system, the circadian timing system, or both. The human body is remarkable in its capacity to cope with these problems on an acute, short-term basis. When prolonged, however, these challenges can lead to significant impairments in the area of waking neurobehavioral functioning. Neurobehavioral functions include such domains as cognitive performance, psychomotor abilities, subjective mood state, and waking psychophysiological parameters.

Sleep is often thought of as an appetitive process. Throughout the course of normal bouts of sustained wakefulness (e.g., 16 hours), sleep drive builds up in a relatively linear manner, but begins to taper its rate of accumulation during longer bouts of wakefulness. During a subsequent sleep episode, this sleep pressure is satiated in a rapid manner, such that the majority of sleep pressure, following a 16-hour wake episode, is satiated during the early hours of the sleep episode. 

Taken as a whole, this accumulation of sleep pressure during wakefulness and its abatement during sleep can be thought of as an active maintenance of a balance state, or a homeostasis, as one may think of hunger or osmolarity.

In an individual living with a relatively regular sleep/wake cycle (e.g., sleeping from 10 pm to 6 am and being awake from 6 am to 10 pm), the central nervous system's circadian timing system has a somewhat paradoxical, albeit beneficial relationship with the sleep homeostatic system. Without a circadian system, one would become increasingly sleepy across the course of a normal 16-hour wake episode. Similarly, one would have difficulty maintaining sleep for a full 8-hour sleep episode. However, the circadian timing system, the primary pacemaker of which is located in the suprachiasmatic nucleus of the hypothalamus, actively promotes wakefulness in an increasing manner across the course of normal wakefulness, such that this wake-promoting signal is maximal shortly prior to habitual bedtime. In addition, the circadian timing system maximally promotes sleep toward the second half of the habitual sleep episode. With the normal phase relationship (timing) between the sleep homeostat and the circadian timing system, humans are able to sustain a relatively constant level of alertness and cognitive performance throughout a 16-hour wake episode during the day. Similarly, they are able to obtain a consolidated, 8-hour nocturnal sleep episode.

There are many disease states and behaviors that challenge the sleep homeostatic system, the circadian system, or the phase relationship between these two systems. Primary sleep disorders, such as obstructive sleep apnea, pose challenges to both sleep itself and to subsequent waking neurobehavioral functioning. In obstructive sleep apnea, repetitive partial or complete airflow reductions are associated with decreases in blood oxygenation and partial arousals from sleep, as well as excessive daytime sleepiness. Various behavioral (weight loss), mechanical (nasal continuous positive airway pressure, or CPAP), and surgical (uvulopalatopharyngoplasty) interventions have shown varying degrees of success in alleviating the apneic episodes and consequently, improving daytime alertness. A behavior that challenges the ability to have a consolidated nocturnal sleep episode is daytime napping. Napping decreases homeostatic sleep pressure, and hence, takes away from the sleep drive that normally provides the impetus for the first half of the nocturnal sleep episode. Consumption of caffeine is another behavior that appears to alter the expression of sleep homeostatic pressure. Caffeine is an adenosine receptor antagonist. Animal models have shown that adenosine builds up in the central nervous system (CNS) during the course of normal wakefulness and is cleared during the course of subsequent sleep. Adenosine has therefore been implicated as a putative, endogenous sleep-promoting substance. In human investigations, the ingestion of caffeine has been shown to increase the amount of time required to fall asleep, alter the rapid eye movement/nonrapid eye movement (REM/NREM) distribution during sleep, and even alter the spectral composition of the sleep electroencephalogram. In an opposite manner, naturally-occurring (e.g., in medical house staff when taking in-house call) or experimentally enforced sleep loss (e.g., sleep deprivation or sleep restriction experiments) has been shown to increase self-reported sleepiness and impair waking neurobehavioral functioning. This can be thought of as continuing the buildup of sleep homeostatic drive well beyond the levels encountered during a

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normal, 16-hour bout of wakefulness.

Behavioral challenges to the circadian timing system include such recent developments as rotating or fixed night shift work and jet lag. When someone rotates from a regular schedule to a night shift, they are required to be awake and perform at a time when the circadian timing system is actively promoting sleep, and impairments of alertness and performance are seen.15,16 Furthermore, shift workers try to sleep during the hours of daylight, when the circadian timing system is actively promoting wakefulness such that sleep disruption and shorter sleep times are commonly observed.17 In jet lag, depending on the number of time zones crossed, the individual will have a temporary misalignment between the new sleep/wake schedule at the destination and the intrinsic circadian system. For example, in an individual traveling from the East Coast of the United States to Europe, the new local sleep/wake schedule occurs 5–6 hours earlier than the old sleep/wake schedule. Thus, the person attempts to fall asleep during a time when the circadian system is actively promoting wakefulness. Also, the new schedule will require the traveler to awaken at a time when the circadian system is now actively promoting sleep.

Fortunately, for shift workers and jet travelers, much has been learned during the past 20 years about the scientific application of artificial bright light as a countermeasure to circadian phase misalignment with the desired sleep and work schedules. Light to the retina is the primary means by which the human circadian timing system is reset to the external light/dark cycle18 and therefore keeps the circadian system adjusted to promote wakefulness during the daytime and sleep at night. In the example given above, the application of bright light after arrival in Europe, in the mid- to late-morning hours would "phase advance" the circadian system, allowing for as much as 1–2 hours of adaptation per day. Thus, after just a few days the individual could have an appropriate phase alignment between the new sleep/wake schedule and the intrinsic circadian system.

Shift work is also an example of a behavior that affects both the sleep homeostatic system and the circadian system. As mentioned above, there is a misalignment of the new sleep and work schedules with the intrinsic circadian timing system after switching from a daytime to a nighttime work schedule, resulting in impairments of both sleep and waking alertness. The resultant sleep loss leads to an increase in sleep homeostatic drive during the hours of work. Shift workers commonly attempt to counteract this impaired alertness through the use of stimulants (e.g., caffeine, nicotine) and the impaired sleep through CNS depressants (e.g., alcohol, sleeping pills). Such behaviors merely mask the true, underlying physiologic problem.

In assessing waking neurobehavioral functions to look for modulation from sleep homeostatic and/or circadian systems, researchers have developed a wide array of testing protocols. The Multiple Sleep Latency Test19 has become the most widely used measure of true, physiologic daytime sleepiness, allowing for the quantification of sleep drive at measured intervals throughout the waking day. Computerized cognitive testing batteries3 with sound psychometric properties have been developed, allowing for efficient, repeated assessment of mental functioning in both laboratory and field studies. Ambulatory measurement of the waking electroencephalogram and slow eye movements provides a minimally intrusive, on-line, physiologically based measure of alertness in the CNS.20 Taken as a group, these behavioral and physiologic measures have produced data that allow for mathematic modeling of the various factors that affect waking functioning, in hopes of both better understanding the underlying biologic processes and how they manifest under a variety of natural and artificial conditions.21

There are many promising developments in the areas of sleep and circadian rhythms research, which will eventually provide greater assistance for people with sleep and/or circadian rhythm disorders. Pharmaceutical and neuropharmacologic research continues to identify both putative endogenous sleep substances and medications that may induce a more normal sleep episode, as opposed to older medications that consolidate sleep but tend to produce sleep dissimilar to that which occurs naturally. Knowledge of the interaction between the circadian and sleep homeostatic systems has led to the appearance of consultants who can advise public, private, and governmental agencies on the optimal timing of travel and work schedules, and also warn of times when sleep and/or alertness may be impaired. The application of artificial bright light has been tested as a method for adapting actual rotating shift workers, both in normal industry and in such high-profile operations as manned space flight. In addition, research has shown that melatonin, a hormone released by the pineal gland during the hours of darkness, may play a role in attenuating the wake-promoting signal from the circadian timing system.22 Exogenous melatonin administration has been shown to increase the ability to fall asleep and extend sleep duration, when the sleep episode falls during the hours that the circadian timing system is actively promoting wakefulness,23 suggesting potential applications to enhance sleep in shift workers or in jet travel.

Future scientific investigations would be welcome in many areas. Studies should investigate the generalizability of laboratory findings regarding neurobehavioral deficits encountered with challenges to the sleep and circadian systems to the real workplace. Clinical research studies must address not only the development of new and better treatments for primary sleep disorders, but also the poor level of patient compliance that is by no means limited to
pharmacologic or behavioral treatment of sleep disorders. Finally, basic research must continue to elucidate the underlying physiologic and pharmacologic processes that support sleep and circadian rhythms, and how these processes act (or fail) when given behavioral or pharmacologic challenges.