Sleep and Immune Function

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Scientists are only beginning to fully understand the purpose of sleep and its underlying mechanisms. Lack of sleep is associated with many diseases, including infection, and with increased mortality. Lack of proper sleep is an important problem in the intensive care unit, and interventions have been designed to improve it. Sleep is associated with immune function, and this relationship is partially based on the physiological basis of sleep, sleep architecture, the sleep-wake cycle, cytokines and the hypothalamic-pituitary axis. (*Critical Care Nurse.* 2012;32[2]:e19-e25)

Sleep is one of the biggest riddles known. The knowledge that all animals sleep implies that sleep fulfills some basic physiological need. Yet, scientists are only beginning to fully understand the purpose of sleep[1] and the underlying mechanisms.[2] Lack of sleep is associated with many diseases and with increased mortality[1,3] and is an important problem in the intensive care unit (ICU).[4-8]

In this review, I describe the relationship between sleep and immune function. Understanding this complicated association requires knowledge of the physiological basis of sleep and the basic elements of immune function as applied to sleep. Therefore, I briefly review sleep architecture and the sleep-wake cycle. I also discuss immune function and cytokines and the hypothalamic-pituitary-adrenal (HPA) axis.

Although evidence linking sleep and immune function has come from studies of the sleep-wake cycle, cytokines, and the HPA axis, most investigators have relied on 2 basic approaches. In the first approach, laboratory animals and human volunteers are deprived of sleep and the consequences of the deprivation on immune responses, bodily systems associated with the immune system, and/or immune products are measured. In the other approach, laboratory animals or human volunteers are infected with pathogens or given substances that challenge the immune system, and the effects of these interventions on sleep are determined.[9] I present evidence provided by using both of these research strategies. Finally, I describe how sleep in the ICU affects patients' immune function and suggest interventions to improve patients' sleep.

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Sleep Architecture

Sleep has several sequential stages (Table 1). The first phase, nonrapid eye movement (NREM) sleep, consists of 4 stages. Stage 1 is a transitional stage between wakefulness and deep sleep. Stage 2 is a deeper sleep state; the sleeper is unaware of the surroundings but can be easily aroused. Stage 3 is the first stage of deep or slow-wave sleep (SWS), which has both fast and slow brain waves. Stage 4, the second phase of SWS, consists mostly of slow waves. Stages 3 and 4 are considered the deepest stages of sleep, when waking the sleeper is difficult. SWS is considered a time of energy conservation and renewal.[10,11] It is an anabolic state in which physiological repair occurs.[6] SWS has been widely studied in association with immune function. The next phase of sleep is rapid-eye movement (REM) sleep, in which dreaming occurs.[10]

The cycle of NREM sleep followed by REM sleep repeats 5 to 6 times per night for a period of 90 minutes per cycle. The relative amount of time spent in NREM and REM sleep changes during the night. NREM sleep takes up more time at the beginning of the night, and REM sleep occupies more time in the final sleep cycle.[11] The total amount and percentage of time spent in each cycle are species specific, but NREM sleep accounts for most of sleep in all animal species and in humans.[2] These cycles are part of the daily sleep-wake cycle.

The Sleep-Wake Cycle

The sleep-wake cycle is a 24-hour cycle associated with the biological

Table 1 Sleep stages in the intensive care unit[a]

Stage	State	Change in intensive care unit
Nonrapid eye movement		
Stage 1	Transitional state between wakefulness and sleep	Increased
Stage 2	Asleep but easily arousable	Increased
Stage 3	Slow-wave sleep Deep sleep Fast and slow brain waves	Decreased
Stage 4	Slow-wave sleep Deep sleep Primarily slow brain waves	Decreased
Rapid eye movement	Can include dreaming state	Decreased

[a] Based on Friese[5] and Hardin.[6]

rhythm of many bodily functions, including body temperature, hormonal secretion, metabolism and sleep[1] (see Figure). The biological clock is synchronized by a central pacemaker, the suprachiasmatic nucleus (SCN), located in the hypothalamus. The SCN neurons are entrained by environmental light coming from the retina. When a decrease occurs in the amount of light perceived, the neurons respond by stimulating the pineal gland to produce and release melatonin. Increased release of melatonin is associated with increased sleepiness.[3,11] Evidence[1] indicates that night-shift workers have a disruption in their biological rhythm and in their melatonin secretion cycle. Some researchers[1,14] have associated these changes in melatonin with an increased risk for cancer.

The T, B, and natural killer cells of the immune system also have internal biological clocks. These peripheral circadian clocks are based on a set of feedback loops in which proteins produced by a particular clock gene turn off their own transcription, resulting in messenger RNA and protein rhythms that are produced on a 24-hour cycle. The circadian rhythm of immune function is driven by the interaction between the central SCN clock and these peripheral clocks.[3,12] The synchronization of the central clock with the peripheral clocks is thought to occur via humoral and neural connections; however, the mechanism has not been elucidated[12] (see Figure).

The sleep or wakefulness status is thought to be determined by a complex balance between the sleep-promoting and arousal centers of the brain.[15,16] For example, wakefulness is promoted by the brain stem and hypothalamus. These systems are inhibited, at least in part, by the secretion of γ-aminobutyric acid during SWS by neurons near the arousal centers.[11] The ventrolateral preoptic nucleus also inhibits the arousal systems during sleep.[11] Products of the immune system, such as cytokines, also play a part in the balance between sleep and wakefulness.

Cytokines and Sleep

Cytokines are the principal messengers of the immune system. These proteins are produced by many different cells, including lymphocytes and macrophages, and unlike hormones, are not produced in special organs. One of the primary functions of T cells, a type of lymphocyte, is the production of cytokines. Different types of T cells exist, including T helper cells, T suppressor cells, and regulatory T cells. The different types produce different cytokines. For example, T helper cells are divided into 2 different categories: T_H1 and T_H2 cells. T_H1 cells produce cytokines that stimulate cellular immunity, such

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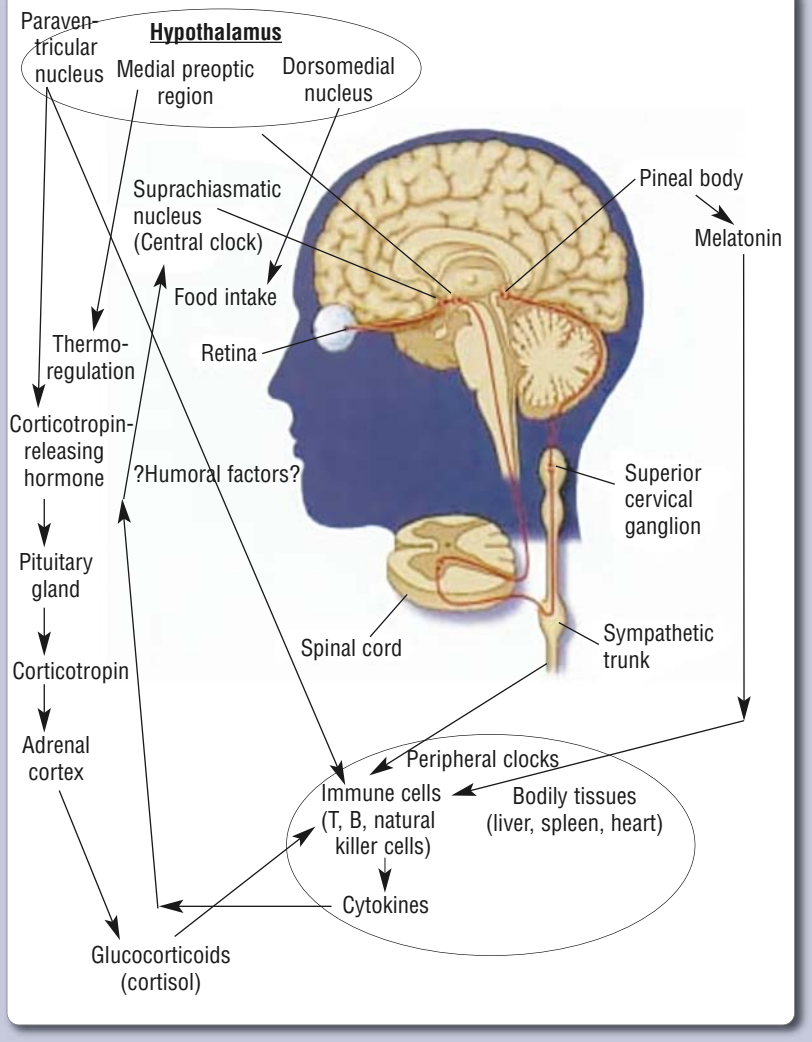

Figure Central and peripheral clocks. Perceptions of light and dark are transmitted from the retina to the central clock (suprachiasmatic nucleus), which stimulates various parts of the brain associated with circadian rhythms. The hypothalamus contains several centers associated with circadian rhythms, including thermoregulation and food intake. One hypothalamic pathway involves the paraventricular nucleus, which sends messages to various cells in the body that contain their own peripheral clocks. These cells then transmit feedback messages to the central clock via cytokines such that the central and peripheral clocks are somewhat synchronized.

Based on Bollinger et al,[3] Nader et al,[12] and Hong et al.[13]

as interferon- γ (IFN-γ) and tumor necrosis factor (TNF), whereas T_H2 cells stimulate humoral immunity associated with antibody production. T_H2 cells therefore produce cytokines such as interleukins (IL) 4, 6, and 10.[17-19]

Many other types of cells, including neurons in the brain and the periphery, as well as lymphoid tissue, have surface receptors for cytokines. The activity of one cytokine may overlap with the activity of another cytokine, including the synthesis and secretion of other cytokines.[17]

Although more than 20 different cytokines have been described, only a few are present in the circulating blood of healthy people,[17] making these proteins difficult to study in humans. In addition, cytokines are characterized by rapid utilization and degradation, quick binding to cellular receptors, and the effect of natural inhibitors.[18] Many cytokines are associated with sleep in animals and humans, including ILs 1, 2, 4, 6, 8, 10, 13, and 18; IFNs α, β, and γ; transforming growth factor; and TNF.[19,20] Table 2 is a summary of the effect of these cytokines on sleep.

Two cytokines, IL-1 and TNF-α, have been studied extensively in research related to sleep. Neurons in the hippocampus, hypothalamus, brain stem, and cortex have receptors for these cytokines.[18,20,23-25] Administration of the cytokines causes an increase in NREM sleep in several species in lower doses and a decrease in higher doses.[20] If an animal is given a substance that suppresses or antagonizes the action of the cytokine, such as an antibody to or a soluble receptor for the cytokine, the level of NREM sleep is increased.[19,20] Mice bred so that they do not have the gene responsible for coding IL-1β type 1 or TNF-α receptors (called knockout mice) have less NREM sleep than do control normal mice.[19,26] In humans, IL-1 levels are highest at the onset of sleep.[27]

HPA Axis, Sleep, and Immune Function

The circadian pacemaker, the SCN, also affects hormonal secretion, including that of the HPA axis[1] (see Figure). The HPA axis is associated with the body's response to stress. The hormones secreted by the HPA axis—corticotropin-releasing hormone, corticotropin,

Table 2 Influence of cytokines on sleep[a]

Enhances sleep	Inhibits sleep	Mixed influence on sleep[b]
IL-1	IL-4	IL-6
IL-2	IL-10	IFN-α
IL-8	IL-13	
IL-18	TGF-β	
TNF-α		
IFN-γ		

Abbreviations: IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.
[a] Based on Kapsimalis et al,[17] Ranjbaran et al,[21] and Friese et al.[22]
[b] Literature on the effects of the cytokine are mixed: cytokine may enhance, inhibit, or have no effect.

and cortisol—inhibit sleep[17,18] and stimulate wakefulness,[17] whereas SWS inhibits activity of the HPA axis and the secretion of cortisol.[2] For example, plasma levels of corticotropin and cortisol are lowest during sleep and highest during periods of wakefulness.[25-27] Cortisol levels are elevated when normal sleep is frequently interrupted.[31] Therefore people, including ICU patients, who are under stress have higher circulating levels of hormones associated with the HPA axis and lower levels of sleep.

Sleep Deprivation and Immune Function

The strategy of depriving human volunteers or animals of sleep, administering a pathogen, and then determining the effects of the pathogen on cellular, antibody, and cytokine responses has been productive for describing the relationship between sleep and immune function.[18] For example, sleep deprivation increased secretion of IL-6,[32] TNF-α,[32] IL-1,[33] and IL-2.[33] However, the direction of the response (whether the infection increases or decreases various immune functions) varies widely. This variability is due to differences in the methods used to produce sleep deprivation, the duration of deprivation, the immune functions tested, the methods used to measure the functions, the experimental conditions, and the population tested.[2,5] However, a general conclusion is that sleep deprivation shifts immune activity toward cell-mediated immunity (T_H1 activity) rather than toward humoral immunity (T_H2 activity).[2] Optimal immune function involves both of these types of immune activity. If the balance between T_H1 activity and T_H2 activity is altered, immune function can be compromised. This shift has clinical implications: ICU patients can have altered sleep quality and quantity (as described later), leading to a potentially altered balance between cellular and humoral immunity and compromised immune function.

In 2 different studies[34,35] with healthy volunteers, the antibody response to vaccination (to hepatitis A virus[34] and influenza virus[35]) was significantly lower among volunteers who were sleep deprived than among controls who were not ($P < .02$ for both hepatitis A virus and influenza virus). In another study[36] of 153 healthy men and women, those who reported a mean of less than 7 hours of sleep per night were almost 3 times more likely to acquire a cold than were those with 8 or more hours of sleep. In that study,[36] the participants were asked to record their sleep duration for 14 days as a baseline. They were then quarantined, administered nasal drops containing a rhinovirus, and monitored for the development of a cold for 5 days after exposure.

In addition, sustained sleep deprivation in rats was associated with increased mortality.[37,38] Sleep-deprived rats entered an unexplained hypercatabolic state, with increased metabolic rate, increased plasma levels of norepinephrine, and signs of malnutrition. Everson[37] cited the development of opportunistic infections leading to death, and Rechtschaffen and Bergmann[38] cited hypothermia, breakdown of body tissue due to catabolism, organ failure, and bacteremia.

A common method used to measure immune function is to expose lymphocytes in vitro to substances called mitogens that stimulate DNA synthesis and cellular reproduction. The mitogens are components of bacterial cell walls, endotoxin, or plant proteins (lectins). Two common plant mitogens are phytohemagglutinin and concanavalin A. Lymphocytes that are less able to reproduce in response to mitogen stimulation are considered to have lower immune function, because the ability of an immune cell to reproduce when stimulated is considered a basic and important immune function. The mitogen method was used in several early sleep deprivation studies with volunteers.[33,39] The results indicated that cellular reproduction and DNA synthesis in response to mitogen

stimulation was significantly decreased after sleep deprivation.

Infection and Sleep

The second major method used to investigate the relationship between sleep and immune function is measurement of sleep in animals and humans infected with various bacteria, viruses, fungi, and protozoa. Differences in the route of administration, dose and invasiveness of the infectious agent, and the type of animal model affect the magnitude of the sleep response. However, in general, animals infected with low doses of these pathogens had increased NREM and SWS and decreased REM sleep, and animals infected with higher doses had decreased NREM sleep.[2,5,19]

The response to low doses of pathogen is similar to the response described as sickness behavior, or an adaptive response of the host to an infectious organism in which products from immune cells (eg, cytokines) mediate nonspecific behaviors that include malaise, fatigue, sleepiness, anorexia, and apathy.[40] For example, when a person catches cold, the immune system responds with increased production of cytokines such as IL-1, IL-6, and TNF.[40] These cytokines make the person "feel sick." Humans with rhinovirus infection,[41] mononucleosis,[42] and HIV infection[43,44] have reported increased feelings of sleepiness and have increased SWS. Therefore, sleeping is one of the body's responses to infection.

Imeri and Opp[20] have theorized that the body's response to infection is part of the acute-phase response that includes changes in sleep, fever, and sickness behavior. They base their theory on research on the relationship between sleep and cytokines, in which cytokines mediate changes in sleep induced by infection. They suggest that in response to infection, an increase in cytokine production is associated with increases in body temperature and immune function. These changes create an unfavorable environment for the invading pathogen. Increased internal temperature not only leads to an increase in cytokine production but also to increases in metabolism and energy demand. The investigators[20] suggest that the body tries to compensate for this loss of energy by stimulating sleep, a state in which energy expenditure is decreased.

Sleep and Disease

Probably the most well-known infection in humans that affects sleep is human African trypanosomiasis, otherwise known as African sleeping sickness. This disease can be fatal if left untreated.[45,46] Humans and animals infected with the protozoan *Trypanosoma brucei* produce increased levels of inflammatory cytokines, especially IL-1β, TNF-α, and IFN-γ, both in the brain and in the periphery.[45,46] The total amount of sleep does not increase; rather, the distribution changes during the course of 24 hours. An increase occurs in sleep during the day, a decrease at night, and an increase in REM sleep with decreased NREM sleep. An unusual indication of the disease is frequent periods in which patients go directly from wakefulness into REM sleep, without the NREM phase.[19,45,46]

Other studies[3,47,48] have also shown the association between sleep and disease. For example, in a 22-year, prospective, population-based, cohort twin study, men and women who slept either less than 7 hours or more than 8 hours per night had an increased mortality risk compared with men and women who slept between 7 and 8 hours (hazard ratios for men: <7 hours, 1.26; >8 hours, 1.24; for women: <7 hours, 1.21; >8 hours, 1.17).[3] In another population-based study,[47] participants who slept less than 5 hours per night were 2.5 times more likely to have diabetes than were participants who slept 7 hours or more. A significant positive correlation was found between sleep duration and the incidence of coronary heart disease.[48] Women who slept 4 hours or less per night had a 2.32 hazard ratio for cardiovascular disease mortality compared with women who slept 7 hours. Long sleep duration (>10 hours) in men and women was associated with a 1.5- to 2-fold increase in cardiovascular disease mortality compared with a shorter duration (7 hours).[48]

Sleep disturbances also worsen in chronic inflammatory conditions such as asthma, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease.[21] In a review of the literature on autoimmune diseases, Ranjbaran et al[21] found that a change in the sleep-wake cycle was one of the first responses to acute inflammation and infection. They suggested that poor sleep can affect chronic conditions via increases in the production of proinflammatory cytokines. However, in these chronic inflammatory conditions, it is difficult to separate worsening of the chronic condition and its association with an increased level of pain and

discomfort that leads to decreased sleep from decreased sleep that worsens the chronic inflammatory condition due to changes in immune function.

Decreased Sleep in the ICU

The preceding review of the literature indicates that people who are ill have a decreased quality of sleep and that sleep deprivation is a risk factor in the development of disease. Promotion of good-quality sleep can therefore be considered a primary prevention strategy for all patients, including patients in the ICU.

As stated previously, animals infected with high doses of pathogens have decreased NREM sleep.[2,5,19] Patients in the ICU also tend to be infected with high doses of pathogens, and therefore it is not surprising that recent review articles have presented strong evidence that sleep in the ICU is severely compromised. The reviews cite a wide range of total sleep time, ranging from 1.7 to 19.4 hours in a 24-hour period.[4,5] The distribution of this sleep was abnormal; more than 40% occurred during the day.[4,5] Both the progression and the distribution of the stages of sleep were altered; patients had more stage 1 and stage 2 sleep and less SWS (stages 3 and 4) and REM sleep.[4-6] For example, in a sleep study[21] in which surgical and trauma patients were compared with healthy volunteer controls, the patients had significantly more stage 1 and stage 2 sleep (96% vs 55% for healthy controls) and less stage 3, stage 4, and REM sleep (4% vs 45%). The patients also had a high amount of interrupted sleep, with a mean of 6.2 awakenings per hour.[21] Similar results were presented in reviews of the sleep of ICU patients: from 42 to 51 interruptions per night[7] to up to 49 arousals or awakenings per hour.[4]

Interventions to Improve Sleep in the ICU

Many causes of poor sleep in the ICU have been suggested.[4-8,10] Factors include noise, light, nursing care, severity of illness, pain, anxiety, mechanical ventilation, medications such as benzodiazepines and opioids, and sedation. Interventions to improve sleep in the ICU include decreasing noise (eg, limiting the use of televisions and telephones, keeping patients' doors closed, lowering white noise levels when possible, and reminding staff and visitors to minimize the volume of their conversations), lowering light levels, minimizing the use of medications that inhibit sleep and using those that promote sleep, and allowing uninterrupted time for sleep by decreasing nursing care during the night whenever possible (eg, minimize bathing, dressing changes at night).[6,22]

Summary and Conclusion

Studies with different experimental approaches in both animal and human models have indicated a link between sleep and the immune system. Cytokines play a major part in this connection. Although many of the mechanisms that promote this connection are known, others are only beginning to be understood. Patients in the ICU have altered sleep, potentially compromising their immune function. Several interventions have been suggested to improve sleep in the ICU and thereby improve immune function.

ICU nurses have the authority and responsibility to provide and support patients' optimal sleep, even if the interventions include decreasing the amount of nursing activities at night or suggesting the use of different medications that have less of an impact on sleep, thereby hopefully improving patients' immune function and overall outcome. CCN

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Financial Disclosures
None reported.

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