Chapter
26

Sleep and Host Defense

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Chapter Highlights

- Sleep is altered during sickness; this has been known for millennia. Yet systematic and controlled studies aimed at elucidating the extent to which sleep is altered in response to immune challenge have only been conducted during the last 30 years.
- Substances historically viewed as components of the innate immune system are now known to be involved in the regulation or modulation of physiologic sleep-wake behavior in the absence of immune challenge. Changes in sleep during immune challenge are actively driven and result from amplification of these physiologic mechanisms.
- Although the precise changes in sleep-wake behavior depend on the pathogen, route of infection, timing of infection, host species, and other factors, altered sleep during immune challenge is generally characterized by periods of increased non–rapid eye movement (NREM) sleep, increased delta power during NREM sleep, and suppressed rapid eye movement sleep. Infection-induced alterations in sleep are often accompanied by fever or hypothermia.
- Altered sleep has been studied in humans during pathologies and/or infections with pathogens, including human immunodeficiency virus/acquired immunodeficiency syndrome, rhinovirus (common cold), streptococci, trypanosomes, prions, and sepsis. Laboratory animal models include sepsis, influenza and other viruses (gamma herpesvirus, vesicular stomatitis virus, rabies, feline immunodeficiency virus), several bacterial species, trypanosomes, and several prion diseases.
- Mechanisms that link sleep to innate immunity involve a biochemical brain network composed of cytokines, chemokines, growth factors, transcription factors, neurotransmitters, enzymes, and their receptors. Each of these substances and receptors is present in neurons, although interactions with glia are critical for host defense responses to immune challenge. Redundancy, feed-forward, and feedback loops are characteristic of this biochemical network. These attributes provide stability and flexibility to the organismal response to immune challenge.

INTRODUCTION

Most individuals have experienced the lethargy, malaise, and desire to sleep that may occur at the onset of infection. Further, most have been admonished to "get plenty of rest, or you will get sick." Conventional wisdom and personal experience suggest a connection between sleep and host defense systems; our sleep is perceptively different when sick, and insufficient sleep may predispose to getting sick. These beliefs are not new. Indeed, Hippocrates, Aristotle, and many of our predecessors acknowledged such a relationship. But only within the past 30 years have modern science and medicine systematically investigated relationships between sleep and host defense systems. This chapter is organized around four main themes related to sleep and host defense. They are (1) the acute phase response and host defense; (2) infection-induced alterations in sleep; (3) effects of sleep loss on immune function; and (4) mechanisms linking sleep and immunity. Finally, in the Clinical Pearl box, we briefly present sleep as a recuperative process during sickness.

THE ACUTE PHASE RESPONSE AND HOST DEFENSE

Rapidly after infection or trauma or during some malignant conditions, a complex response involving many cell types and peripheral organs is evoked that is collectively referred to as the acute phase response (APR). Markers of the APR include changes in serum concentrations of acute phase proteins. Measurement of acute phase proteins, such as C-reactive protein (CRP), for example, is useful in clinical practice because they indicate inflammation. In addition to changes in serum concentrations of acute phase proteins, the APR includes physiologic changes such as fever and increased vascular permeability and other metabolic and pathologic changes. A major theme of this chapter is that altered sleep as a host defense also is part of the APR to inflammatory challenge. Altered sleep during inflammatory challenge is actively driven by multiple mediators and systems, many of which are shared with other facets of the APR.

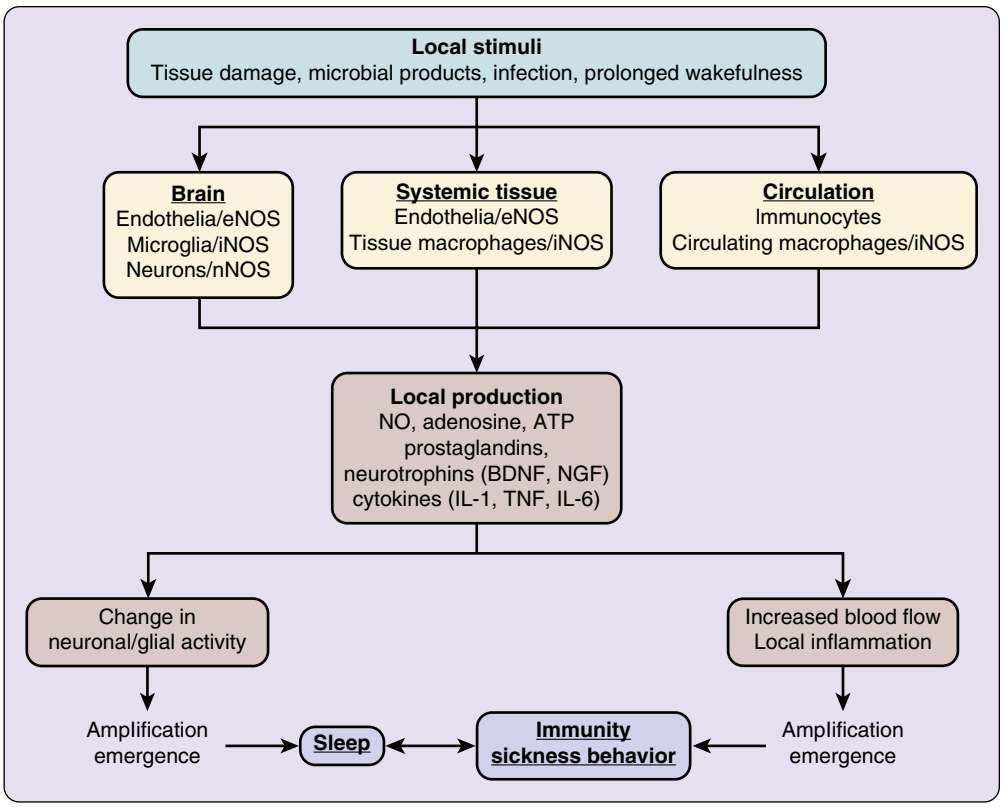

Figure 26.1 Multiple cell types from various tissue compartments (*yellow boxes*) contribute to sleep and host defense responses to microbial and tissue damage challenges (*green box*). The sleep and inflammatory responses are mediated by a common set of regulatory molecules whose production/release is modified in response to local stimuli, which enhance cell activity, for example, action potentials in neurons (*brown boxes*). These regulatory molecules are vasodilators and through that action contribute to local inflammation. These molecules are also sleep regulatory substances via their production and actions in brain. Local actions as they increase in number and merge and amplify higher order levels of tissue organization leading to emergent whole animal processes (e.g., sleep). Local actions provide some degree of compartmentalization of sleep and inflammatory actions. However, these responses remain influential upon each other (*lower blue boxes*). Such actions are likely responsible for the low-grade inflammation associated with certain sleep pathologies such as sleep apnea. ATP, Adenosine triphosphate; eNOS, endothelial nitricoxide synthase; IL, interleukin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; TNF, tumor necrosis factor.

Recent advances in our knowledge of central nervous system (CNS) innate immunity provide a framework for understanding many of the shared mechanisms underlying the APR in general, and the specific alterations in sleep that occur during immune challenge. The APR is a critical innate immune response[1] that follows any inflammatory challenge, such as an infection or traumatic injury. Inflammatory challenges that are localized (e.g., a minor cut or splinter) may activate a low-level APR that manifests as redness at the site of injury and may not be perceived by the subject. But with increased injury severity, or response to an infectious challenge, the full systemic APR develops. The APR to infection by invading pathogens develops within a matter of hours, and the subject feels sick. In the case of infections, the function of the APR is to alert the host to the invasion and mobilize systemic protective responses, isolate and destroy invading pathogens, and remove tissue debris. The systemic inflammatory response activates the brain, liver, and bone marrow to react in a stereotypic manner. The APR includes physiologic and behavioral responses (e.g., fever, excess sleep, anorexia), as well as biochemical responses (e.g., CRP, serum amyloid A, mannose binding protein). Increased secretion of a broad array of endocrine hormones, including the stress hormones, also occurs. This complex of responses leads to host protective behaviors (such as social withdrawal),[2] physiologic responses (such as fever, which can increase efficiency of the immune response and inhibit growth of some microorganisms),[3,4] and immune responses (such as mobilization of leukocytes and natural killer [NK] cells).[1] Hormonal changes (such as prolactin regulation of antimicrobial nitric oxide levels)[5] and biochemical changes (such as potentiation of microbial phagocytosis)[6] also contribute to host defense. Although physical barriers (skin, mucosa) are the first line of defense, the APR is the first responder of host defense and is the trigger for acquired immunity, mediated by specific antibodies, and cytotoxic T lymphocytes.[7]

A major class of proteins, cytokines, initiates the APR. Cytokines are generally associated with immune cells, but they are made by most cell types. More than 100 of these intercellular signaling molecules have been identified, and the complexity of their interactions rivals that of the CNS. Cytokines induce their own production and the production of other cytokines, and they form biochemical cascades characterized by much redundancy. Cytokines are classified into two major groups, type I cytokines that promote inflammation (proinflammatory) and type II cytokines that suppress it (antiinflammatory).[8] Three proinflammatory cytokines appear to be primary triggers of the APR. These early responder cytokines are interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6, each of which is implicated in the regulation/modulation of sleep. The class II cytokines include interferon (IFN)-α, IFN-β, IL-4, and IL-10. These cytokines damp the APR and may also modulate sleep responses; for example, IL-4 and IL-10 inhibit spontaneous non–rapid eye movement (NREM) sleep. Cytokines can act in an autocrine, juxtacrine, paracrine, or endocrine manner to activate numerous APRs via such effectors as nitric oxide, adenosine, and prostaglandins (Figure 26.1).

INFECTION-INDUCED ALTERATIONS IN SLEEP

The impact of infection on sleep has been determined for viral, bacterial, and fungal pathogens; prion-related diseases; and protozoan parasites. Most studies have used virus and bacteria as the infectious agent, and so in this chapter we focus primarily on altered sleep in response to these pathogens.

Viral Infections and Altered Sleep

Viral diseases that cause CNS lesions and/or systemic inflammation alter sleep.[9] In von Economo's seminal paper,[10] he related the postmortem location of brain lesions of patients suffering encephalitis lethargica to specific changes in sleep patterns. This work led to the concept that sleep was an active process, not simply resulting from the withdrawal of sensory stimuli, and to the idea that there was some degree of localization of neural networks regulating sleep. Although von Economo's encephalitis is commonly thought to have been caused by the 1918 influenza virus pandemic ("Spanish flu"), recent analyses reveal that the disease preceded the 1918 pandemic and was probably an autoimmune complication of streptococcal infections affecting the basal ganglia.[11,12] Despite the importance of von Economo's work, many years passed before the direct effects of viral infections on sleep were experimentally determined.

During the early stages of infection with human immunodeficiency virus (HIV) and before patients are symptomatic for acquired immunodeficiency syndrome (AIDS), sleep is altered such that excess stage 4 NREM sleep occurs during the latter half of the night.[13] Other CNS viral diseases, such as rabies[14] or viral encephalitis in rodents after vesicular stomatitis virus (VSV[15]) infection, also are associated with altered sleep. In these CNS infections, it is difficult to know whether sleep is altered by direct actions on sleep regulatory mechanisms or whether altered sleep results from virus-induced brain lesions. However, cytokine messenger ribonucleic acid (mRNA) translation and toll-like receptor (TLR) signaling pathways are altered before VSV neuroinvasion, suggesting that at least some viruses modulate sleep regulatory systems in the absence of overt pathology.[16]

One model that has been used frequently to determine effects of viral infections on sleep is influenza. Influenza virus localizes to the respiratory tract and the olfactory bulb during the early stage of disease and does not cause brain lesions. In addition, influenza infections pose tremendous public health burdens because of the hundreds of thousands of lives lost each year and the threat of pandemics. Smith and colleagues[17] report that low doses of influenza in humans increase sleep and cognitive dysfunction; these symptoms appear after low viral doses that fail to induce the better known characteristics of the APR, such as a fever. However, in that study indices of behavior, not polysomnography, were used. Drake and colleagues[18] demonstrated in healthy human volunteers that infection with rhinovirus 23 disrupts sleep and impairs cognitive performance. (Rhinoviruses are the predominant cause of the "common cold.") In naturally occurring respiratory infections, individuals had subjectively and objectively disturbed sleep during the symptomatic phase of the infection, while spending a longer time in bed and had increased total sleep time.[19] In rabbits, intravenous injections of influenza virus are also associated with large increases in NREM sleep and suppressed rapid eye movement (REM) sleep, even though the virus does not replicate in this species.[9] Studies in mice infected with influenza virus demonstrate profound changes in sleep through the course of disease progression.[20-22] Changes in sleep of mice during influenza infection share some features of sleep responses to bacterial infections (described later). As a preclinical model, influenza infection of mice is clinically relevant because mouse-adapted strains of this virus can be introduced into the respiratory tract and can fully replicate in the lungs, causing a severe APR. Mice challenged intranasally with influenza virus display profound increases in NREM sleep and inhibition of REM sleep, which last 3 or more days.[20] Macrophages appear to be the critical immune cell type driving increased NREM sleep, whereas NK cells, neutrophils, and T lymphocytes do not play a significant role.[23] There are strain differences in responses of mice to this challenge,[24] indicating a genetic component affecting the sleep response to influenza virus. Genetic regulation of the inflammatory response to influenza in mice and humans has been reviewed elsewhere.[25]

One generic viral pathogen-associated molecule pattern (PAMP) that increases NREM sleep and initiates other facets of the APR is virus-associated double-stranded (ds) RNA. All viruses examined produce virus-associated dsRNA, which is generally derived from the annealing of viral replication products rather than from the virus itself.[26] Virus-associated dsRNA, recognized by the pathogen recognition receptor (PRR) TLR3, induces numerous cytokines, including IL-1, IL-6, TNF, and IFN. Virus-associated dsRNA can be extracted from lungs of infected mice[27] and is capable of inducing an APR in naïve rabbits that is similar to that of live virus. Similarly, rabbits given short double-stranded (but not single-stranded) oligomers that correspond to a portion of influenza gene segment 3 also exhibit large increases in NREM sleep.[28] Synthetic dsRNA (polyriboinosinic:polyribocytidylic acid; poly I:C), when inoculated into the lungs of mice primed with IFN-α, induces an APR that is virtually identical to that after influenza virus.[26] Influenza virus is a single-stranded negative-sense RNA virus; during replication the positive-sense strand is synthesized, and double-stranded influenza RNA forms. In contrast, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), is a single-stranded positive-sense RNA virus[29]; during its intracellular replication, double-stranded viral RNA is also expected to form and be biologically active. It is not known, as of this writing, whether SARS-CoV-2 dsRNA in lungs and/or olfactory bulbs is responsible for potential sleep responses or anosmia. Regardless, these observations suggest that virus-associated dsRNA is sufficient to initiate the APR.

It is apparent that, in severe cases of COVID-19, plasma inflammatory mediators are elevated, including IL-1β, TNF-α, and IFN-γ, among others.[29] Based upon plasma concentrations in severe cases, TNF-α may be among mediators that contribute to, or indicate, disease severity.[30] One of the PRRs that coronaviruses activate is TLR7, which subsequently initiates a signaling cascade that upregulates type I IFN and other inflammatory cytokines.[29]

Interferons play a major role in viral symptoms. Knockout (KO) mice have been widely used to better understand the role of specific cytokines or hormones in host defense. Mice genetically deficient for the receptor that binds both IFN-α and IFN-β (the type I receptor) respond to poly I:C with altered sleep and a hypothermic response that is similar to that seen in infected wild-type mice. However, in influenza-infected IFN-receptor KO mice, the APR occurs earlier,[31] suggesting that type I IFNs may modulate the APR, presumably by regulating proinflammatory cytokine production. Influenza-infected IFN-receptor KO mice are less ill later in the infection and recover sooner.[31] Sleep-modulatory cytokines, in addition to IFNs, likely mediate the sleep responses to influenza virus. For

example, although the duration of altered NREM and REM sleep is the same in both strains after viral challenge, mice deficient in the 55-kD and 75-kD TNF receptors manifest reduced electroencephalogram (EEG) delta power, a measure of sleep intensity, whereas in wild-type control mice, delta power increases.[32] IL-1 signaling in brain requires a brain-specific receptor accessory protein.[33] Mice lacking the IL-1 receptor brain-specific accessory protein have higher morbidity and mortality after influenza inoculation, and they sleep less during the infection than do wild-type mice.

Mice and rats with natural mutations of the growth hormone–releasing hormone (GHRH) receptor express a dwarf phenotype and altered spontaneous NREM sleep.[34] The GHRH receptor is a candidate protein for regulating NREM sleep increases in response to influenza virus.[35] Dwarf mice with nonfunctional GHRH receptors (called lit/lit mice) fail to respond to influenza virus with increased NREM sleep or EEG delta power.[36] Instead, infected lit/lit mice manifest a pathologic state with EEG slow waves, enhanced muscle tone, and increased mortality.[36] Such results indicate that single genes can substantially modify sleep responses to infectious challenge. Importantly, results from lit/lit mice also demonstrate that the sleep responses forming part of the APR correlate with survival.

Influenza virus is a frequently used model for APR studies, in part because it was assumed that the virus does not invade the brain or lead to the complications associated with the use of neurovirulent viruses. Recent studies, however, demonstrate that the strain of influenza most commonly employed in preclinical studies rapidly invades the olfactory bulb of the mouse brain after intranasal inoculation.[37] The virus activates microglia in the outer layer of the olfactory bulb and upregulates IL-1 and TNF at times that correspond to the postinfection time period when the systemic APR begins. The same mechanisms may be true for other viruses. For example, cytokine mRNA transcription is detected in mouse olfactory bulb within hours after intranasal inoculation with VSV.[16] Collectively, these studies suggest that cytokines made in the olfactory bulb impact the CNS components of the APR to some viruses, including sleep responses.

Bacterial Challenge

Altered sleep is also observed after bacterial infection. Indeed, results obtained after inoculating rabbits with the gram-positive bacteria *Staphylococcus aureus* were the first to suggest that NREM sleep responses were part of the APR.[38] In those experiments, rabbits were given *S. aureus* intravenously to induce septicemia; within a few hours of the inoculation NREM sleep was twice the amount as during comparable periods after control inoculation. Associated with the increase in NREM sleep were increases in amplitude of EEG slow waves. EEG slow wave (0.5 to 4.0 Hz) amplitudes are thought to indicate the intensity of NREM sleep. This initial phase of increased duration and intensity of NREM sleep lasted about 20 hours; it was followed by a more prolonged phase of decreased NREM sleep and decreased EEG slow wave amplitudes.[38] During both phases of the NREM sleep changes, REM sleep is inhibited and animals are febrile. Other changes characteristic of the APR (e.g., fibrinogenemia and neutrophilia) occurred concurrently with the changes in sleep.[38] In subsequent studies in which gram-negative bacteria and other routes of administration were used, a similar general pattern of biphasic NREM sleep responses and REM sleep inhibition was observed.[39] However, the timing of sleep responses depends upon the bacterial species and the route of administration. For example, after intravenous administration of *Escherichia coli*, NREM sleep responses are rapid in onset, but increased NREM sleep lasts only 4 to 6 hours. The subsequent phase of reduced NREM sleep and reduced amplitude of EEG slow waves is sustained for relatively long periods. In contrast, if the gram-negative bacterium *Pasteurella multocida* (a natural respiratory pathogen in rabbits) is given intranasally, a different time course of sleep responses is observed. In this case, the increased NREM sleep responses occur after a longer latency, and the magnitude of the increases in NREM sleep is less than the effects of this pathogen given by other routes of administration.

The intestinal lumen of mammals contains large amounts of many different bacteria species. Bacteria translocate into the intestinal lymphatics under normal conditions. Of importance to this discussion, intestinal permeability is altered after sleep deprivation, resulting in increased release of bacterial products into the lymphatics. Local lymph node macrophages phagocytose and digest these bacterial products,[40] releasing PAMPs that can trigger sleep responses. This mechanism operates at a low basal rate under normal conditions and is amplified during systemic inflammation. The phagocytosis by macrophages of bacterial products is also likely to be involved in sleep responses induced by sleep deprivation and excess food intake. A role for gut bacteria in sleep modulation is also evidenced by observations that reducing bacterial populations in the intestine is associated with reduced sleep.[41]

Another bacterial product that is involved in sleep responses to gram-negative bacteria is the lipopolysaccharide (LPS) component of cell wall endotoxin. LPS is the dominant PAMP associated with endotoxin, and it binds to TLR4. LPS has been intensively studied in animal models[42] and humans volunteers[43] with respect to effects on sleep. LPS alters sleep in humans and nonhuman animals.[44,45] Healthy human volunteers injected with LPS manifest sleep changes, fever, cytokine expression, and hormonal changes[43] somewhat similar to those seen in animals. However, the impact of LPS on the human EEG differs from those observed in rabbits or rats, and in humans it requires a higher LPS dose to increase NREM sleep than it does to suppress REM sleep.

Most experimental studies of bacterial infections and sleep have used inoculation of a single pathogen species as the infectious challenge. The gut microbiome, however, is polymicrobial, and many infections result from invasion by multiple pathogen species. Such is true in sepsis, during which polymicrobial infections routinely occur. Clinical studies demonstrate EEG anomalies in patients who become septic.[46] The etiology of sepsis is complex, and sepsis may result from many different kinds of insult. As a consequence, several preclinical models have been developed to study sepsis. Although each model used has strengths and limitations, the model currently considered to be the gold standard is cecal ligation and puncture (CLP[47]). CLP produces a polymicrobial infection that is considered clinically relevant because of its time course, because it reproduces the dynamic changes in cardiac function observed in human patients, and because there is a progressive release of inflammatory mediators. The severity of the ensuing infection is readily titrated in this model. Sleep is altered during the acute phase of CLP sepsis in rats, which occurs from 1 to 4

days after sepsis induction.[48] During this period, NREM and REM sleep of rats increases during the dark period (the normal active period for nocturnal rodents), whereas these sleep phases are reduced during the light period (the inactive period for nocturnal rodents). These changes in sleep coincide with increased cytokine mRNA and protein in brain.[49] Of interest, effects of sepsis on body temperature and activity rhythms persist long after the animal has recovered and is no longer at risk of dying.[49] These observations suggest that sepsis alters brain function and are in agreement with observations that patients surviving sepsis often suffer severe and debilitating cognitive impairment.

In summary, infectious challenge is associated with profound changes in sleep. As mentioned in the overview of the APR, PRRs such as the TLR and NLR receptor families detect the various PAMPs capable of altering sleep. Detection of PAMPS by the innate immune system explains, in part, why diverse microbial pathogens activate stereotypic host defense responses such as fever, anorexia, and altered sleep. Microbe-induced alterations in sleep, like the other components of the APR, are adaptive.[50]

EFFECTS OF SLEEP LOSS ON IMMUNE FUNCTION

Sleep is altered during immune challenge, yet whether sleep loss alters immune function has been more difficult to demonstrate. There are multiple systems associated with immunity, each with a myriad of mediators and modulators. There are positive and negative feedback control mechanisms that interact in complex ways. This complexity of the immune system makes it difficult to determine what measurement(s) one should use to assess immune function. From a functional perspective, the most important question is whether sleep loss renders the animal or human more vulnerable to infection, tumor formation, or systemic inflammatory diseases. (We already know that sleep loss renders an individual more vulnerable to accidental injury.) Although few studies have been conducted within the context of sleep, some suggest relationships between sleep and functional immune outcomes. For example, among 12 mammalian species sampled, those with longer daily sleep times have the greatest number of white blood cells and are least susceptible to parasites.[51] Susceptibility to infection has been used as an end point in some studies of human subjects.

Results from studies of laboratory animal subjected to short-term sleep deprivation are consistent with most human studies. Toth and colleagues[52] challenged rabbits with *E. coli* before or after 4 hours of sleep deprivation. They concluded that sleep deprivation failed to exacerbate *E. coli*–induced clinical illness, although the combination of sleep deprivation and bacterial infection altered some facets of sleep responses as compared with either manipulation alone.[52] Furthermore, mice immunized against influenza virus and then re-challenged with influenza just before sleep deprivation fail to clear the virus from their lungs.[53] However, in a similar study,[54] sleep loss failed to alter preexisting mucosal and humoral immunity in either young or senescent mice. The variation in the effects of sleep loss on outcomes in mice subjected to influenza virus is likely due to differences in the sleep deprivation protocols, end points analyzed, and influenza models employed. Little research has focused on sleep deprivation and clinical responses to bacteria, but mortality is greater in mice in which sleep is disrupted after they are made septic by CLP.[55] Collectively, these studies suggest that acute sleep loss impairs or alters host defense.

The effects of long-term sleep loss on host defense in laboratory rodents are more striking. If rats obtain only about 20% of their normal sleep when deprived by the disk-over-water method,[56] they die after a period of 2 to 3 weeks.[57] Yoked control rats, which manage to maintain about 80% of their normal sleep during the protocol period, survive. The experimental rats, but not the yoked controls, develop septicemia.[57] Bacteria cultured from the blood are primarily facultative anaerobes indigenous to the host and environment. These results demonstrate that, using this method, innate host defenses in the rat are compromised by long-term sleep loss. These results suggest that prolonged sleep loss likely amplifies the normally occurring process of gut permeability to bacteria and bacterial products.

Sleep disruption may induce low-grade inflammation or may render the animal more susceptible to inflammatory challenge. We recently demonstrated that disrupting daytime sleep of mice for prolonged periods (9 days) exacerbates febrile responses to LPS.[58] The exacerbated febrile response to LPS under the conditions of this study may be due to sleep disruption per se, because no other parameters measured (corticosterone, food or water intake, body weight) differed substantially from either home cage control animals or animals housed on the sleep disruption device but allowed ad libitum sleep.

In contrast to animal studies, experiments using in vivo challenges with bacteria or viruses are rare in humans. Investigations mainly focus on sleep loss–induced changes of leukocyte numbers in blood (e.g., monocytes, neutrophils, T cells), immune cell activity and proliferation (e.g., NK cells, lymphocyte proliferation, T regulatory function), and cytokine and cytokine receptor levels in blood or production by stimulated immune cells (see the comprehensive review by Besedovsky and colleagues[59]). With respect to cytokine responses, for example, acute total sleep deprivation increased levels of IL-1b and IL-1ra in the blood circulation of healthy volunteers.[60] In studies using models mimicking common patterns of sleep restriction (generally restricted to 4 hours of sleep/night), IL-1b and IL-6 production by stimulated peripheral blood mononuclear cells,[61] expression of TNF, and IL-6 by stimulated monocytes[62] and in the blood circulation[63] increased. Furthermore, the IL-2/IL-4 ratio was reduced by several days of sleep restriction, indicating a shift toward a Th2 cytokine balance.[64] In a recent study using a model that mimics common patterns of recurrent sleep restriction with intermittent recovery sleep over 3 weeks, monocytic expression of IL-6 progressively increased with ongoing exposure to sleep restriction[65] and did not fully recover after a night of full sleep. Although these immune measures do not directly indicate an impact on host defense, cytokines, such as IFN, IL-1, and TNF, are well known for their role as immunomodulators, and their perturbation deteriorates tumor and pathogen defense in the long term (see the review by Frasca and colleagues[66]).

There are several reports that show in healthy volunteers that plasma levels of cytokines are related to the sleep-wake cycle. Such relationships were first described by demonstrating that plasma IL-1–like activity was related to the onset of slow wave sleep.[67] Plasma concentrations of TNF vary in phase with EEG slow wave amplitudes.[68] There is also a temporal relationship between sleep of healthy human volunteers

and IL-1 activity.[69] Several clinical conditions associated with sleepiness, such as sleep apnea, chronic fatigue syndrome, chronic insomnia, preeclampsia, postdialysis fatigue, psychoses, rheumatoid arthritis (RA), and AIDS, are associated with enhanced plasma levels of TNF and other cytokines.[70] Only those sleep apnea patients showing elevated TNF activity experience fatigue.[71]

Other facets of the immune response are also linked to sleep. About 40 years ago, altered antigen uptake after sleep deprivation was reported.[72] Studies carried out in the 1970s also showed a decrease in lymphocyte DNA synthesis after 48 hours of sleep deprivation and a decrease in phagocytosis after 72 hours of sleep deprivation.[73,74] Sleep deprivation also induces changes in mitogen responses. Circulating immune complexes fall during sleep and rise again just before an individual gets out of bed. In mice sleep deprivation reduces IgG catabolism, resulting in elevated IgG levels. In contrast, one study failed to show an effect of sleep deprivation on spleen cell counts, lymphocyte proliferation, or plaque-forming cell responses to antigens in rats.[55,75] In a comprehensive study of human volunteers, 64 hours of sleep deprivation reduced CD4, CD16, CD56, and CD57 lymphocytes after 1 night of sleep loss, although the number of CD56 and CD57 lymphocytes increased after 2 nights of sleep loss.[76] Another group also showed that a night of sustained wakefulness reduced counts of all lymphocyte subsets measured.[77]

Sleep and sleep loss are associated with changes in NK cell activity. NK cell activity is reduced in patients with insomnia[78] and decreases after partial night sleep restriction.[79,80] In contrast, NK cell activity increases after 64-hour total sleep deprivation.[76] Circulating NK cell activity, as well as NK cell activity in a variety of tissue compartments, may be sensitive to sleep, although the exact nature of relationships between NK cell activity and sleep likely depends upon the specific experimental conditions used to elucidate them.

In summary, determination of sleep deprivation effects on immune function may be confounded by stress and other coincident physiologic responses in animals. Concurrent physiologic changes (other than stress) also complicate sleep deprivation studies in humans. Sleep deprivation protocols are not standardized in animal or human studies, making comparison of results across studies difficult. The lack of standardized sleep deprivation protocols is just one among many factors contributing to the often disparate results reported.

MECHANISMS LINKING SLEEP AND IMMUNITY

Substantial evidence now suggests that IL-1 and TNF are involved in physiologic sleep regulation.[70,81] Furthermore, IL-1 and TNF mRNA and protein change during pathologies characterized by altered sleep. Sleep deprivation is associated with enhanced sleepiness, sleep rebound, sensitivity to kindling and pain stimuli, cognitive and memory impairments, performance impairments, depression, and fatigue. Exogenous administration of IL-1 or TNF induces these sleep loss–associated symptoms.[42,70] Further, chronic sleep loss–associated pathologies such as metabolic syndrome, chronic inflammation, and cardiovascular disease are also characterized by changes in IL-1 and TNF activity,[42,70] and in some cases these pathologies are attenuated if these cytokines are inhibited.[82-84] Clinically available inhibitors of either IL-1 (e.g., the IL-1–receptor antagonist, anakinra) or TNF (e.g., the TNF-α soluble receptor, etanercept) alleviate fatigue and excess sleepiness in humans with pathologies such as sleep apnea or RA.[82,83,85] The IL-1–receptor antagonist and TNF soluble receptor are normal gene products found in blood and brain, and their concentrations are altered by sleep.[42]

In addition to being immunocyte products, whose production is amplified by viral and bacterial components, IL-1 and TNF are also found in the normal brain.[42,70] IL-1 and TNF mRNA have diurnal rhythms in brain with the highest values being associated with periods of maximum sleep. TNF protein also has a sleep-associated diurnal rhythm in several brain areas, and IL-1 in cerebrospinal fluid varies with the sleep-wake cycle.[86] Cortical expression of TNF is enhanced by afferent nerve activity,[87] and IL-1 and TNF expression are enhanced in culture when neurons are stimulated,[88] which may be part of the process that is responsible for local use-dependent sleep.[42]

Administration of either IL-1 or TNF promotes NREM sleep.[42,44,70] The increase in NREM sleep after either IL-1 or TNF administration is physiologic in the sense that sleep remains episodic and readily reversible if animals are disturbed. Further, IL-1 or TNF enhances NREM sleep intensity, as measured by the amplitude of EEG delta waves. The effects of IL-1 on sleep depend upon dose and the time of day it is given.[89,90] IL-1 and TNF inhibit the binding of the BMAL/CLOCK complex in the suprachiasmatic nucleus[91]; this action may be responsible for the differential effects of these cytokines at different times of the day. Finally, knockout strains of mice that lack the type I IL-1 receptor,[92] the 55 kD TNF receptor,[93] or both of these receptors[94] sleep less than control strains.

NREM sleep increases after sleep deprivation, excessive food intake, or acute mild increases in ambient temperature. The somnogenic actions of each of these manipulations are associated with enhanced production of either IL-1 or TNF. After sleep deprivation, circulating IL-1 increases, brain levels of IL-1 mRNA increase, and the NREM sleep rebound that would normally occur after sleep deprivation is greatly attenuated if either IL-1 or TNF is blocked using antibodies or soluble receptors.[95]

IL-1 and TNF act within a biochemical network (Figure 26.2). For example, IL-1 and TNF stimulate nuclear factor kappa B (NFκB) production. NFκB is a DNA-binding protein involved in transcription. Other sleep-altering cytokines, such as acidic fibroblast growth factor, epidermal growth factor, and nerve growth factor also stimulate NFκB production. NFκB promotes IL-1 and TNF production and thus forms a positive feedback loop. Sleep deprivation is associated with the activation of NFκB in the cerebral cortex, basal forebrain cholinergic neurons, and the lateral hypothalamus. Activation of NFκB also promotes IL-2, IL-6, IL-8, IL-15, and IL-18 production, each of which promotes sleep in rats.[42,44,70]

The mechanisms by which sleep regulatory substances (SRSs) are regulated and induce sleep are beginning to be understood. TNF and IL-1 neuronal expression is enhanced in response to afferent nerve activity. For instance, excessive stimulation of rat facial whiskers for 2 hours enhances IL-1 and TNF immunoreactivity in the cortical layers of the somatosensory cortical columns that receive the enhanced afferent input.[87]

What is it about neuronal activity or wakefulness that causes the enhanced SRS activity? Neuronal activity manifests

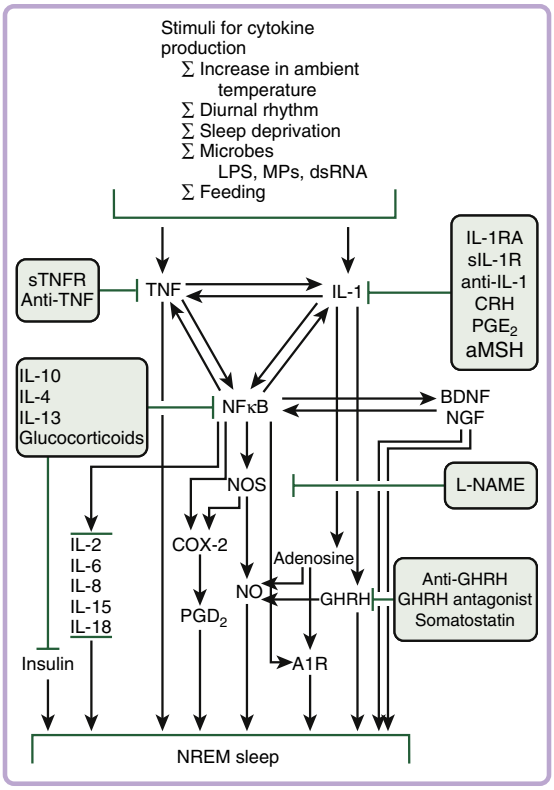

Figure 26.2 Interleukin (IL)-1β and tumor necrosis factor (TNF)-α are part of a brain biochemical network that regulates physiologic sleep and links multiple facets of innate immunity to sleep regulation. Much is known about mechanisms by which IL-1 and TNF directly or indirectly regulate/modulate non–rapid eye movement (NREM) sleep. Less is known about mechanisms of action for the rapid eye movement (REM) sleep–suppressing effects of immune challenge. Current knowledge of the biochemical network that translates information about environmental perturbation into host responses that actively drive changes in sleep-wake behavior is much more complicated than depicted, and sites of action are not indicated (but see the work by Imeri and Opp[50]). This biochemical cascade included cytokines, chemokines (not included), growth factors, transcription factors, neurotransmitters, enzymes, and their receptors. Because the network is redundant and parallel, inhibition of any single component does not result in complete sleep loss, nor does it block altered sleep in response to immune challenge. Such redundant pathways provide stability to the sleep regulatory system and alternative mechanisms by which sleep-promoting or sleep-inhibitory stimuli may affect sleep. Substances in boxes inhibit NREM sleep and inhibit either the production of, or the actions of, substances in downstream pathways. The receptor and intracellular signaling systems for all these substances are found in neurons. Also not depicted in this schema are interactions of components of this biochemical network with glial cells. Gliotransmission is implicated in the modulation of physiologic sleep and is likely to play a critical role in brain responses to immune challenge that result in altered sleep-wake behavior (see the work by Ingiosi and colleagues[97] and Porkka-Heiskanen). → indicates stimulation or upregulation; ⊥ indicates inhibition or downregulation. BDNF, brain-derived neurotrophic factor; CRH, corticotropin-releasing hormone; GHRH, growht hormone-releasint hormone; MSH, melanocyte stimulating hormone; NGF, nerve growth factor; PGD, prostaglandin.

as presynaptic and postsynaptic events that act in both the short and long term. Neuronal activity in presynaptic neurons results in the release of transmitters and adenosine triphosphate (ATP).[96] In turn, some of that ATP is converted to adenosine and some ATP acts on purine P2X7 receptors on glia to release TNF and IL-1.[42,97] ATP also acts to release cytokines in immunocytes.[98] The extracellular adenosine derived from ATP interacts with neurons via the adenosine A_1 receptor (A1AR). The TNF released in response to ATP activates NFκB in postsynaptic and presynaptic neurons.[42] NFκB enhances the A1AR, thereby rendering the cell more sensitive to adenosine. NFκB also enhances production of a subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor gluR1 mRNA. The time courses of enhanced mRNA for receptors or ligands are much slower than the direct actions of adenosine or TNF; the subsequent production of protein offers a way for the brain to keep track of prior neuronal network activity and translate that activity into a greater sleep propensity. The various time courses of action of the neurotransmitters (milliseconds), the conversions of ATP to adenosine and its actions (seconds), and the actions of ATP-induced release of cytokines and their subsequent effects on gene expression (minutes to hours) provide a mechanism for activity-dependent oscillations of neuronal assembly sleep.[99]

There is a growing literature demonstrating direct effects of IL-1 and TNF on neural substrates implicated in the regulation of sleep. Some of these mechanisms include interactions with classical neurotransmitters such as glutamate, serotonin, acetylcholine, gamma-aminobutyric acid, histamine, and dopamine.[100] For example, IL-1 increases serotonergic activity in brain regions implicated in sleep regulation,[101] and an intact serotonergic system is required for the full effects of IL-1 on sleep to manifest.[102,103] IL-1 inhibits discharge rates of serotonergic[104,105] and cholinergic[106] neurons in the brainstem. Within the hypothalamus, IL-1 increases c-Fos[107] and inhibits wake-active neurons.[108] TNF promotes sleep if microinjected into the anterior hypothalamus, while injection of a soluble TNF receptor into this area reduces sleep.[109] TNF also alters sleep if injected into the locus coeruleus,[110] effects likely related to interactions with alpha$_2$-adrenergic receptive mechanisms and norepinephrine release.[111] Interestingly, TNF or IL-1, if applied locally onto the surface of the cerebral cortex unilaterally, enhances EEG delta activity on the side to which it is applied but not the contralateral side.[112,113] Conversely, application of the TNF soluble receptor unilaterally onto the cortex of sleep-deprived rats attenuates sleep loss–induced EEG delta activity on the side injected but not on the opposite side. Further, unilateral application of a TNF siRNA (inhibits TNF) reduces spontaneous cortical TNF expression and EEG slow wave activity on the ipsilateral side.[114] These latter studies suggest that TNF acts locally within the cortex (in addition to its somnogenic actions in the hypothalamus) to enhance EEG synchronization and possibly sleep intensity. In fact, application of TNF directly to the cortex of intact mice[87] or to co-cultures of neurons and glia[88] increases the probability that a sleep-like state will manifest in local circuits.

CLINICAL ASPECTS AND IMPLICATIONS

Effects of Sleep on Infection Risk and Vaccination Responses

In controlled experimental settings, acute short and/or disturbed sleep affects a wide array of immune cells, mediators, and functions.[115] Such immune changes also occur in more chronic forms of short or disturbed sleep, such as observed in insomnia disorder or shift work. It is thought that these changes increase infection and other disease risks over time, but the exact mechanisms remain unknown. Some studies investigated the effects of sleep on more clinical outcomes, such as infection risk or vaccination responses, which is discussed in the following sections.

Sleep and Infection Risk

In rodents, sleep can affect the outcome of bacterial or parasitic infections, such that the survival rates decrease or increase

with reducing or prolonging sleep duration, respectively.[116,117] Human studies focus on the association between sleep and infection risk, rather than infection outcome (i.e., survival). Using an experimental model of upper respiratory infection induced by a rhinovirus, participants who reported to sleep less than 7 hours/night the week before the experimental infection were almost three times more likely to develop a clinical cold.[118] This finding was replicated in a study that objectively measured sleep duration using actigraphy.[119] With respect to naturally occurring infections, pneumonia risk in a large cohort of nurses increased by almost 40% (adjusted odds ratio [OR] of 1.39) in women sleeping less than 5 hours.[120] Respiratory infection risk, including influenza and pneumonia, increased by about 50% (adjusted OR of 1.51) in a large cohort of adults sleeping less than 5 hours compared with those sleeping 7 hours.[121] A recent study focused on the effect of sleep disturbances, rather than sleep duration, found that self-reported insomnia symptoms in an adult population were prospectively associated with respiratory tract infections as assessed through daily infection diaries.[122] Influenza and pneumonia are among the top 10 leading causes of death in the United States[123] (https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm), and current research findings suggest that adequate sleep can help to prevent airway and other infections, possibly including infections with SARS-CoV-2. Although not yet documented, the lack of sleep in emergency and critical care health providers is expected to aggravate respiratory distress and other symptoms associated with COVID-19.

Sleep and Vaccination Responses

Vaccinations are effective only when the antigenic challenge (the vaccination) induces a sufficient antibody response (acquired immunity) such that, upon subsequent exposure to the same or similar pathogen, there is an effective immune memory. Some individuals do not respond to vaccination with an antibody response sufficient to confer protection, and factors contributing to "nonresponders" are not well understood. The effects of sleep duration on subsequent antibody responses to vaccines in humans are experimentally studied. Total sleep deprivation of a single night or sleep restriction over several nights before or after vaccinations against hepatitis A, hepatitis B, or influenza strains reduces antibody responses.[124-127] Across studies, antibody responses are on average reduced by half, and the duration of the sleep deprivation–induced reduction in the antibody response varies across studies. In some studies, the effect disappeared at 4 weeks after vaccination, while in another study, the effect was still present at 1 year after the initial vaccination (see the review by Bsedovsky and colleagues[115]). One study investigated the effects of habitual sleep duration on the magnitude of the antibody response after a standard three-vaccination series against hepatitis B.[128] Shorter sleep duration (as assessed objectively with actigraphy) in the days surrounding the first vaccination is associated with lower secondary antibody levels. When sleep duration was categorized into less than 6 hours, 6 to 7 hours, and greater than 7 hours of sleep/night, each hour of less sleep is associated with a reduction of the antibody response by about 50%. Of importance, sleeping less than 6 hours translated into a significant risk of being unprotected against the virus, as assessed 6 months after the final vaccination. The mechanisms underlying the beneficial effect of sleep on infection risk or vaccination responses is not understood, but elevations of inflammatory mediators, as frequently observed in response to short or disturbed sleep, is associated with a decreased ability to mount adaptive immune responses.[129] Collectively, these aforementioned studies suggest that adequate sleep can help to prevent and/or lower the risk of airway and other infections and support optimal antibody responses to vaccinations.

Sleep Disturbances in Chronic Infectious and Inflammatory Diseases: Effects of Pharmacologic and Nonpharmacologic Interventions

Sleep disturbances are increasingly common in the general population, with 30% of the population reporting symptoms of insomnia (e.g., difficulties falling or staying asleep) and 6% meeting diagnostic criteria for insomnia disorder (see the review by Ohayon[130]). Insomnia or symptoms of insomnia are even more common in medical populations with chronic infectious or inflammatory diseases. These include patients infected with the human immunodeficiency virus,[131] hepatitis C virus,[132] or Epstein-Barr virus,[133] and patients with inflammatory diseases, such as inflammatory bowel diseases (IBD),[134] RA,[135] systemic lupus erythematosus,[136] Sjögren syndrome,[137] and other chronic diseases with an inflammatory involvement, such as osteoarthritis or migraines (see the review by Bjurstrom and colleagues[138]). The high comorbidity between chronic infectious or inflammatory diseases with sleep disturbances is not surprising given the bidirectional sleep-immune relationship. Consequently, physiologic sleep regulation will likely fail when inflammatory mediators are constantly dysregulated, and, in turn, sleep disturbances may negatively affect the underlying immunopathologic process, thus feeding into a vicious circle. Interventions that target either immune dysregulation or sleep disturbances are likely to have a beneficial outcome on both sleep and the immunopathologic process.

Pharmacologic Interventions Targeting Inflammation

Antiinflammatory therapies are often used to treat several chronic inflammatory diseases, including RA or IBD. In RA, about 50% of patients experience sleep disturbances,[135] and PSG-derived sleep is characterized by indices of disturbed sleep, such as increased alpha-EEG intrusions, increased nocturnal wake time, or frequent sleep stage transitions (see the review by Bjurstrom and colleagues[138]). The immunopathology of RA is reasonably well understood and involves inappropriate production of various cytokines, in particular TNF, which was one of the first cytokines validated as a therapeutic target for RA.[139] Downregulation of increased TNF production may also have direct effects on sleep given TNF's sleep-regulatory properties (see the review by Rockstrom and colleagues[140]). Indeed, anti-TNF therapy improves subjective and objective measures of sleep in RA patients; anti-TNF infusion treatment in patients with active disease reduced sleep-onset latency, increased sleep efficiency,[141] and reduced wake time at night.[142] These sleep improvements were not associated with a reduction in joint pain in the morning after infusion treatment, suggesting that the effect on sleep may independently result from the inhibition of TNF actions in the CNS.[87] Similarly, treatment of RA patients with active disease with an IL-6 receptor inhibitor (tocilizumab) improves self-reported sleep quality and daytime sleepiness. The observed sleep improvement could not be explained by a reduction in disease activity, again suggesting a direct effect of cytokines on sleep regulation that is independent of disease activity.[143] Administration of the antiinflammatory

agents anti-integrin (vedolizumab) or anti-TNF (infliximab or adalimumab) also improved sleep quality in patients with IBD within 6 weeks of therapy initiation.[144] These limited findings suggest that pharmacologically reducing TNF production or blocking IL-6 actions in rheumatic diseases or IBD may have a direct effect on sleep regulation, rather than just being the result of improved disease activity, such as pain.

Nonpharmacologic Sleep Interventions

Sleep hygiene (i.e., good sleep habits), mindfulness, and relaxation training are effective strategies to improve sleep quality in populations reporting poor sleep health (see review by Murawski and colleagues[145]). In clinical populations meeting diagnostic criteria for insomnia disorder, cognitive behavioral therapy for insomnia (CBT-I) is the first-line treatment[146] and outperforms pharmacologic treatment with respect to long-term benefits.[147] A few studies have assessed the immunologic effects of CBT-I. In adults diagnosed with insomnia disorder, CBT-I has been shown to lower systemic levels of the acute phase protein CRP. This reduction was associated with the remission of insomnia and sustained at 16 months posttreatment.[148] CBT-I additionally reduced cellular expression levels of TNF and IL-6 by monocytes, downregulated gene transcripts involved in inflammation (e.g., TNF, IL-6, IL-1β), while upregulating genes involved in interferon and antibody responses (e.g., CD19, MX-1).[149] These immune effects suggest that CBT-I in adults suffering from insomnia disorder reduce both insomnia symptoms and inflammation. There is very little knowledge on the effects of CBT-I in medical populations with chronic infectious or inflammatory conditions, although insomnia symptoms are very common in these populations. In adults with osteoarthritis comorbid with insomnia, CBT-I is reported to improve sleep and disease activity[150,151] and results in less serum IL-6 reactivity to a physiologic challenge (cold pressor test) in adults showing an improvement in sleep compared with those without.[152]

Although more research is needed in this area, findings suggest an avenue by which improving either sleep or immunopathologic processes can have a beneficial effect on both sleep and immune outcomes.

Sleep and Postsurgical Outcomes

Sleep patterns in postoperative periods can be severely disrupted with a suppression of both slow wave and REM sleep.[153] Sleep quantity and quality after surgery are influenced by a multitude of factors, including hospital-related environmental factors (e.g., noise, light), interruptions in sleep resulting from nurse checks or other medical interventions, the extent of surgical tissue injury, the magnitude of the surgical stress response (i.e., autonomic, neuroendocrine and inflammatory responses to surgical trauma), the effectiveness of the analgesics, and pain, which is one of the cardinal signs of an inflammatory response to infection or tissue injury.[154] Sleep disturbances induce hyperalgesia and thereby have the potential to amplify pain in the postsurgical phase.[155] A recent meta-analytical review on the effects of pharmacologic sleep interventions (zolpidem or melatonin) administered in the perioperative phase reported an improvement of pain control in the postoperative period, as indicated by a decrease in pain reports and the use of analgesics.[156] It is currently unknown whether pharmacologically induced sleep improvements mediate the beneficial effect on pain control, or whether pharmacologic agents exert a direct effect on pain control mechanisms, independent of their sleep-promoting effect.

Sleep disturbances are also an issue in the presurgical period. Presurgical short or disturbed sleep contribute to poorer postsurgical outcomes. In patients with coronary artery bypass graft surgery, self-reported sleep complaints in the month before surgery were associated with greater physical symptoms and sensory pain in the 2 months after surgery, indicative of a poorer physical recovery.[157] In breast cancer patients receiving mastectomy surgery, poor sleep quality before surgery predicted higher incidence of severe postoperative pain and fever and higher demands of analgesics in the first postoperative 24 hours.[158] Using a surgical incision model in rats, acute sleep deprivation the night before surgery caused a marked increase in mechanical hypersensitivity after surgery and prolonged postoperative recovery time.[159] Increasing sleep time before surgery has clinical benefit on postsurgical outcomes. Thus habitually short-sleeping patients scheduled to undergo joint replacement surgery were asked to extend their time in bed by 2 hours the week before surgery. This bed time extension resulted in an increase of actigraphy-monitored sleep time by 1 hour per night in the preoperative period, which resulted in less daily pain and less opiate use in the postoperative period compared with patients who stayed on their habitual bed time.[160] With respect to mechanisms underlying the association between preoperative sleep disturbances and poorer postsurgical pain control, dysregulation of inflammatory pathways have been suggested, including mediators involved in both sleep and pain control, such as IL-1, IL-6, and TNF.[156] Whether sleep disturbance–induced inflammatory dysregulations could potentially affect the magnitude of the surgical stress response to tissue damage, which is associated with a host of postoperative outcomes,[161] warrants further investigations. In summary, obtaining good quantity and quality sleep the night *before* surgery may serve as an interventional target in the management of surgical pain.

Contrary to the detrimental effects of short or disturbed sleep on postsurgical outcomes, there is limited evidence suggesting that sleep deprivation can also have a beneficial influence in certain clinical models. Using a skin allotransplant model, a prolonged allograft survival has been reported after acute sleep deprivation and chronic sleep restriction in rats, which was accompanied by a reduced number of graft-infiltrating CD4 T cells.[162] Using an ischemic stroke model, several studies have shown that sleep deprivation before stroke improves outcomes (e.g., less ischemic brain damage), whereas sleep deprivation after stroke is harmful (see the review by Pincherle and colleagues[163]). One explanation is that if sleep loss occurs before stroke, increased entry of microbial products (e.g., peptidoglycans) from blood into the brain site of stroke damage is priming the brain as such products do in the immune system. Overall, much research is needed to investigate whether there are certain clinical situations in which controlled sleep deprivation outweighs the overall detrimental consequences of short or disturbed sleep.

To conclude, sleep can affect infection risk, vaccination outcomes, chronic infectious or inflammatory pathologies, postsurgical outcomes, as well as many other immune-related pathologies that have not been discussed here, such as allergic diseases or tumor-related immune responses.[164,165] These findings indicate a beneficial effect of sleep improving interventions in numerous clinical settings.

CLINICAL PEARL

Although physicians routinely prescribe bed rest to aid in recuperation from infections and other maladies, as yet there is little direct evidence that sleep aids in recuperation. Such studies are difficult to perform because the recovery from an infection, for instance, is influenced by the baseline severity of the infection (i.e., differences in exposure or innate resistance that determine the replication level and clearance of the invading microbe) as well as by what the patient does during the infection. Physicians will continue to prescribe bed rest, and often this is just what the patient wishes to do. It seems likely that such advice is beneficial, as enhanced sleep is part of the adaptive APR. The only evidence of which we are aware that is relevant to this issue is consistent with the concept that sleep aids in recuperation; after infectious challenge, animals that have robust NREM sleep responses have a higher probability of survival than animals that fail to exhibit NREM sleep responses.[166] Although strictly correlative, these data suggest that sleep does indeed facilitate recovery. Perhaps our grandmothers' folk wisdom pertaining to the preventative and curative attributes of sleep and sickness is correct, although much additional research is needed before we know whether this admonishment has a biologic basis.

SUMMARY

Sleepiness, like fever, is commonly experienced at the onset of an infection or other cause of systemic inflammation. Changes in sleep in response to microbes appear to be one facet of the APR. Typically, soon after infectious challenge, time spent in NREM sleep increases and REM sleep is suppressed. The exact time course of sleep responses depends upon the infectious agent, the route of administration, and the time of day the infectious challenge is given.

There is a common perception that sleep loss renders one vulnerable to infection. Some studies demonstrate that sleep loss impairs acquired immunity, and many studies have shown that sleep deprivation alters selected aspects of the innate immune response. A few studies have combined sleep deprivation with infectious challenge. After mild sleep deprivation, several immune system parameters (such as NK cell activity) change, and resistance to a viral challenge is decreased in individuals who spontaneously sleep less. Studies have not yet been done to determine the effects of sleep deprivation on recovery from an infection.

The molecular mechanisms responsible for the changes in sleep associated with infection appear to be an amplification of a physiologic sleep regulatory biochemical cascade. Sleep regulatory mechanisms and the immune system share regulatory molecules. The best characterized are IL-1 and TNF, which are involved in physiologic NREM sleep regulation. IL-1 and TNF are key players in the development of the APR induced by infectious agents. During the initial response to infectious challenge, these proinflammatory cytokines are upregulated, leading to the acute phase sleep response. *This chain of events includes well-known immune response modifiers such as prostaglandins, nitric oxide, and adenosine. Each of these substances, and their receptors, is a normal constituent of the brain, and each is involved in physiologic sleep regulation.*

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REVIEW QUESTIONS

1. SARS-CoV-2 is the virus that causes COVID-19. Which of the following statements characterizes SARS-CoV-2?
   A. SARS-CoV-2 is a single-stranded RNA virus.
   B. SARS-CoV-2 is an adenovirus.
   C. SARS-CoV-2 is a double-stranded RNA virus.
   D. SARS-CoV-2 is a DNA virus.

2. Studies suggest a link between sleep duration and acquired immunity. Which of the following statements best describes the effects of sleep loss on acquired immune responses of human volunteers to vaccination?
   A. Sleep loss has no effect on antibody production after vaccination.
   B. Effects of sleep loss on antibody production after vaccination last only a few days.
   C. Sleep loss is associated with reduced antibody production after vaccination.
   D. Antibody production after vaccination is increased after sleep loss.

3. Cytokines are important mediators of innate immunity, and many preclinical studies demonstrate that interleukin-1β (IL-1β) and tumor necrosis factor (TNF)-α are involved in sleep regulation. Which of the following statements is not supported by empirical evidence?
   A. IL-1 and TNF are present in normal brain where they exhibit diurnal variation.
   B. Clinical inhibitors of IL-1 or TNF alleviate fatigue in patients with sleep apnea and rheumatoid arthritis.
   C. Clinical inhibitors of TNF improve sleep quality in patients with irritable bowel syndrome.
   D. Inhibition of plasma IL-1 reduces symptoms and improves sleep quality in patients with restless legs syndrome.

4. Which of the following best describes double-stranded RNA?
   A. Pathogen-associated molecular pattern
   B. Damage-associated molecular pattern
   C. Acute phase response
   D. Pathogen recognition receptor

ANSWERS

1. **A**

2. **C**

3. **D**

4. **A**