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Sleep, Immunity, and Circadian Clocks: A Mechanistic Model

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Sleep · Immune · Clock · Circadian · Rhythm · Diurnal · Synchrony

Abstract
The lack of sufficient amounts of sleep is a hallmark of modern living, and it is commonly perceived that in the long run this makes us sick. An increasing amount of scientific data indicate that sleep deprivation has detrimental effects on immune function. Conversely, immune responses feedback on sleep phase and architecture. Several studies have investigated the impact of short-term sleep deprivation on different immune parameters, whereas only a few studies have addressed the influence of sleep restriction on the immune system. In many cases, sleep deprivation and restriction impair immune responses by disrupting circadian rhythms at the level of immune cells, which might be a consequence of disrupted endocrine and physiological circadian rhythms. Little is known about the mechanisms underlying the circadian regulation of immunity, but recent studies have suggested that local as well as central circadian clocks drive the rhythms of immune function. In this review, we present a mechanistic model which proposes that sleep (through soluble factors and body temperature) primes immune cells on the one hand, and, on the other hand, provides a timing signal for hematopoietic circadian clocks. We hypothesize that chronic sleep disruption desynchronizes these clocks and, through this mechanism, deregulates immune responses.

Introduction

Over the last 25 years, the modern urban lifestyle has led to a constant decrease in average sleeping time [1], resulting in what has been called an 'epidemic of sleep restriction' (table 1). In the USA and Europe, approximately 15–20% of the population work at night [2], which frequently leads to reduced sleep [3]. An increasing body of evidence suggests detrimental effects of chronic sleep disruption on health and life expectancy. For example, Kripke et al. [4] showed in a study of 1.1 million men and women that both shortened and extended sleep times are associated with a significantly increased mortality hazard. Furthermore, the common perception that sleep loss makes us more susceptible to infections is supported by human and animal studies [5–7]. On the other hand, infections can also feedback to the regulation of sleep, most likely via proinflammatory cytokines [for a review, see 8]. Strikingly, a comparative analysis of mammalian sleep, immunity, and parasitism found a strong association be-

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tween longer sleep duration and reduced levels of parasitic infections [9].

Little is known about how sleep affects immune function, but we know from long-term sleep deprivation and restriction in experimental animal models and short-term sleep deprivation or restriction in human vaccination studies that sleep improves the immune response [6, 10, 11]. Furthermore, the analysis of several immune parameters has shown that sleep loss alters the normal circadian rhythm seen in many of these measures [8, 12–15]. Hence, sleep seems to influence the processes underlying the circadian immune rhythm. Such rhythms are generated by cell-autonomous molecular oscillators that control physiology via the orchestration of hundreds of clock-controlled genes [16]. Circadian clocks have been described in various types of immune cells and the network properties of the circadian timing system make it a prime candidate for communication between sleep and immune regulation. In this review, we summarize the current knowledge of the interaction between sleep, circadian clocks, and the immune system, and present a model of how sleep (loss) may affect immune function at different levels.

Table 1. Definitions of key terms used in this report

Circadian rhythm	an endogenous rhythm with a period of approximately 24 h that persists in the absence of external timing signals (zeitgeber) such as the light-dark cycle, temperature, or social rhythms
Diurnal rhythm	a 24-hour rhythm that is tied to an external zeitgeber; a diurnal rhythm is the representation of a circadian rhythm under synchronized (entrained) conditions
Sleep deprivation	experimental paradigm in which a subject is prevented from sleeping for an extended period of time; in this review, we use the term for experiments in which sleep was deprived for a least 24 h
Sleep restriction	a sleep time reduction below the physiologically required amount of sleep

For the sake of simplicity, we have not differentiated between 'circadian' and 'diurnal' rhythms, but have always used the term 'circadian' when referring to ~24 h rhythms under both free-running and entrained conditions.

Sleep-Immune Interactions

Two basic questions arise: do immune responses modulate sleep and does sleep, or the lack thereof, influence the course of an immune response? Several studies have shown that infections as well as low-dose lipopolysaccharide administration increase sleep in humans and mammals, most likely through induction of proinflammatory cytokines [for a review, see 8]. Additionally, it was demonstrated that neutralizing tumor necrosis factor-α (TNF-α), a key proinflammatory cytokine, causes substantially reduced sleepiness in obstructive sleep apnea patients [17]. By contrast, in humans, infections with rhinoviruses and, to a lesser extent, with *Trypanosoma brucei,* decrease sleeping times [18, 19]. However, rhinoviruses often cause respiratory problems which themselves can affect sleep. Moreover, *Trypanosoma brucei* infects the brain, which might mask the primary effects on sleep by the infection itself. Nevertheless, from these data it seems clear that infections affect sleep.

Toth et al. [20] demonstrated that the morbidity and the mortality of experimentally infected rabbits are decreased with a longer sleep duration after the infective challenge. Furthermore, it was shown that long-term sleep deprivation as well as restriction in animals leads to septicemia and can even be fatal [6, 7]. Hence, sleep has a protective role. Conflicting data have been published on the impact of sleep on experimental influenza infection in mice: while some authors found benefits of sleep on the immune response, other authors observed the opposite or no effect [21–23].

In humans, it has been shown that one night of sleep deprivation after a hepatitis A vaccination results in decreased antibody responses [10], and that 4 days of sleep restriction prior to influenza vaccination also substantially decreased antibody responses [11]. Furthermore, it was shown in a correlational study by Cohen et al. [24] that reduced sleep increases the risk of acquiring a common cold. From this experimental evidence, it seems clear that sleep has beneficial effects in most infections or vaccination responses.

Several studies have reported immunological alterations related to sleep by using sleep deprivation or restriction paradigms, but the underlying mechanisms remain elusive. One limitation of human studies is that immune cells or cytokines in the peripheral blood have been analyzed, and these might not reflect the changes taking place in the spleen and lymph nodes. Unfortunately, there is no good alternative in humans. Most studies have addressed the influence of sleep on the changes in absolute and relative leukocyte counts in the blood and the rate of cytokine-producing cells after polyclonal stimulation [13–15; for a review, see 8]. These studies have elegantly

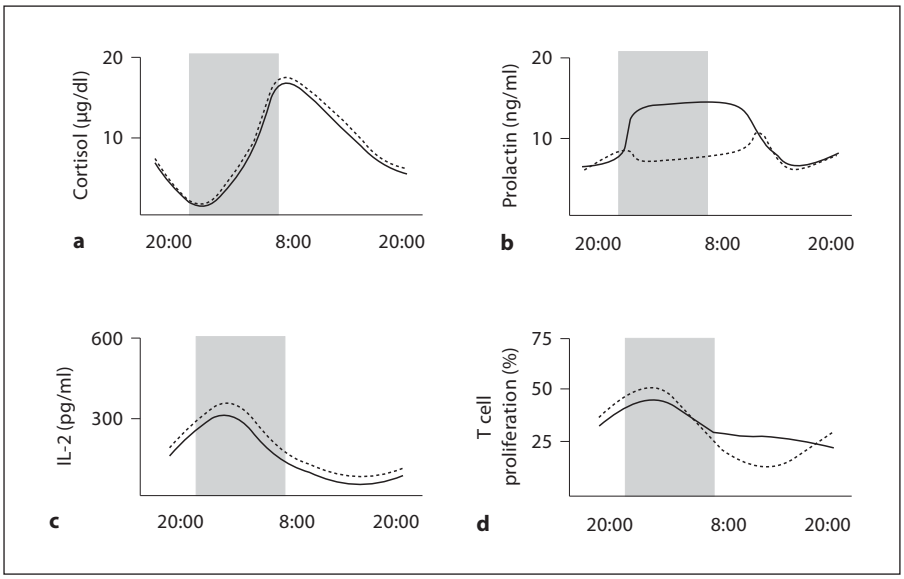

Fig. 1. Influence of sleep on rhythmic hormonal and immune parameters. Peripheral blood was drawn from 7 healthy young men who either slept normally (solid line) or were sleep deprived for 1 day (dashed line). Average circadian serum profiles of cortisol (**a**) and prolactin (**b**) under both conditions are shown. The secretion of IL-2 (**c**) and the proliferation (**d**) of polyclonally stimulated CD4+CD25– T cells is depicted (modified from Bollinger et al. [13]).

demonstrated circadian rhythms for counts of several leukocyte subpopulations, including neutrophils, monocytes, dendritic cells, natural killer (NK) cells, B cells, T cells, and regulatory T cells which are (T cells, B cells, NK cells, dendritic cells, monocytes) or are not (neutrophils, regulatory T cells) modulated by sleep. In most of these cases, sleep loss flattens existing circadian rhythms. This clearly demonstrates that the analysis of sleep-dependent changes requires sequential measurements for a period of at least 24 h. Therefore, studies which investigated sleep and immune parameters are only cited in this review if such time-course measurements were performed. However, one limiting factor remains: the blood only contains 2–3% of all leucocytes. Hence, it is questionable whether changes in leukocyte counts in the blood faithfully mimic functional processes at single cell level or rather changes in leukocyte distribution. In order to investigate whether a defined immune cell population is functionally altered by sleep, it would be necessary to analyze the function of purified immune cell populations or, as an example, the measurement of function on single cell level in non-separated leukocytes in sleep deprivation/restriction experiments. We have demonstrated that purified and polyclonally stimulated T helper cells (CD4+CD25–) proliferate more and that the rhythmic activity of regulatory T cells, which suppress detrimental immune responses, was only observed in the condition of normal sleep compared to sleep deprivation [13], whereas cytokine secretion by T cells follows a circadian rhythm, which was not altered by sleep [Bollinger T., unpublished work]. Figure 1 shows that the circadian rhythms of prolactin and T cell proliferation are significantly influenced by sleep, whereas the circadian rhythms of IL-2 and cortisol are not. Additionally, in human experiments with sleep restriction for several days, it has been shown that proinflammatory substances like IL-6 and TNF-α are increased [12]. Hence, sleep seems to be an important regulator of immunological homeostasis.

Most of the above-mentioned studies demonstrated circadian rhythms in the analyzed immune parameters which were modified by sleep. The overall finding is that sleep improves immune responses and that most immune cells, with the exception of NK cells, have their peak proinflammatory activity at night. Therefore, in order to understand the influence of sleep on immune responses, it is essential to understand the basis of circadian rhythms of immune functions. Moreover, to distinguish between systemically driven (e.g. circadian rhythms of hormones) and cellular rhythms (cellular circadian clock), future studies should address the analysis of circadian and sleep-dependent immune functions in distinct and purified cell populations or at the single cell level.

Interestingly, immunological changes seen in sleep loss and those observed in aged humans bear several similarities, such as attenuated T cell immunity, increased innate immune activation, and reduced adaptive immune responses after vaccination [25]. Furthermore, it is known that the circadian timing system (explained later) changes with age, resulting in phase advances of the sleep-wake cycle and attenuated rhythms of hormones

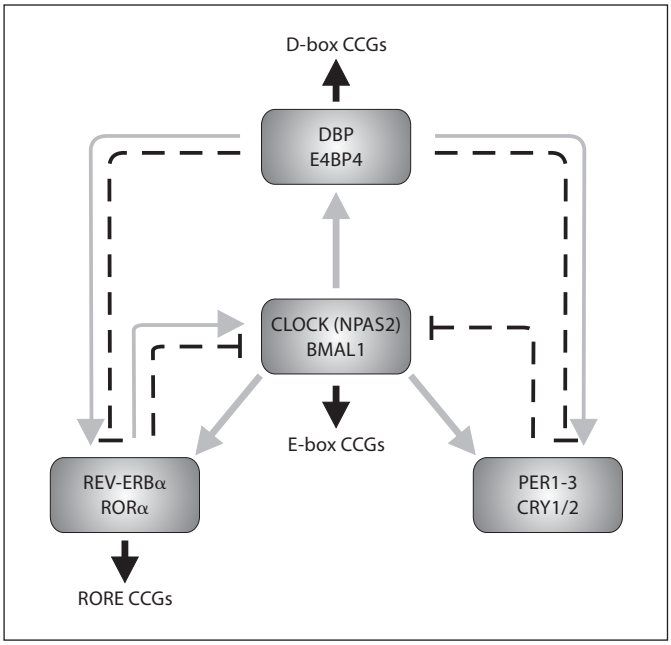

Fig. 2. Molecular model of the circadian clock. Cellular oscillations of circadian clocks are driven by a set of transcriptional/translational feedback loops. At the positive limb, CLOCK (or in some tissues: NPAS2) and BMAL1 activate transcription of *Per* and *Cry* genes. PER/CRY protein complexes negatively feedback on CLOCK/BMAL1 (negative limb). This core oscillator is stabilized by ancillary loops including *Rev-erbα*/*Rora* and *E4bp4*/*Dbp*. Timing signals from core and ancillary loops are translated into physiological signals via transcriptional regulation of clock-controlled genes (CCGs) via E-box, D-box and RORE promoter elements. Dashed lines = Inhibitory signals; gray arrows = activating signals. This model of the circadian clock was modified from Hastings et al. [42].

such as cortisol and growth hormone [25]. Even though there is no mechanistic link between the immunological changes brought about by sleep loss or aging, it seems remarkable that both processes deregulate circadian timing and circadian endocrine rhythms. Therefore, the principles of the proposed model might also be true for at least some of the age-related changes of the immune system.

Circadian Clock and Immune Responses

Circadian rhythms are an external manifestation of an internal clock that measures daytime [26]. Circadian clocks are found in most species and allow the organism to anticipate reoccurring daily variations in environmental conditions. They regulate a wide range of biological functions from behavior (such as the sleep/wake cycle [27–30]) down to molecular processes including chromatin modifications and DNA repair. The latter and the circadian influence on immune function are important factors in the regulation of cellular homeostasis and, hence, of development and aging [26]. Mutations in clock genes can lead to sleep disorders [27]. Hence, the circadian clock, together with a homeostatic component of unknown origin, directly regulates sleep/wake patterns and, therefore, sleep can be seen as an integral manifestation of the circadian timing system.

In mammals, a master circadian pacemaker is located in the hypothalamic suprachiasmatic nuclei (SCN). The SCN synchronizes semi-autonomous peripheral clocks found in most central and peripheral tissues [28] with the external light/dark cycle. The means of this synchronization are not yet fully understood, but likely involve SCN regulation of hormone release (e.g. melatonin, glucocorticoids), body temperature rhythms [29, 30], and signaling via the autonomic nervous system [30]. Conversely, behavioral and physiological signals may feedback to the brain and ultimately the SCN, resetting clock phase by so-called non-photic cues [28]. At the molecular level, circadian clocks are based on cellular oscillators built from a set of interlocked transcriptional/translational autoregulatory feedback loops in which the protein products of particular clock genes negatively feedback on their own transcription, resulting in mRNA and protein rhythms with a period length of approximately 24 h [26] (fig. 2). Hundreds of clock-controlled genes that are regulated in a similar fashion, but have no feedback function, translate time information into a physiologically meaningful signal [28].

Interestingly, it has been demonstrated that rat NK cells, mouse macrophages, and human leukocytes show rhythmic expression of clock genes, with the latter shown to be associated with sleep-wake patterns [31–33]. In rats, NK-cell inhibition of the clock gene *Per2* (Period2, negative limb; fig. 2) leads to a decrease in expression of the immune effectors granzyme-B and perforin, whereas inhibition of the clock gene *Bmal1* (*Arntl*, positive limb; fig. 2) has the opposite effect [32]. Surprisingly, the knockdown of *Per2* in NK cells only marginally alters the rhythm of interferon-γ (IFN-γ), an important cytokine for the cellular adaptive immune response. In contrast, in *Per2*-deficient mice, the rhythm of IFN-γ is severely blunted [34], indicating that the rhythmic expression of IFN-γ might be driven by systemic circadian signals such as hormones or core body temperature. The fact that

rhythmically secreted hormones, e.g. glucocorticoids or melatonin, or autonomic activation can modulate immune functions has been previously demonstrated [35–38]. *Per2* mutant mice respond less severely to lipopolysaccharide-induced septic shock than wild-type animals [39]. Furthermore, deletion of *Bmal1* causes impaired B cell development [40]. Together, these data strongly indicate that circadian clocks are key regulators of immune functions. Because of the tight entanglement of circadian rhythms, sleep, and the mutual effect of both factors on immunity, it seems likely that the 3 processes are causally linked and interact with each other.

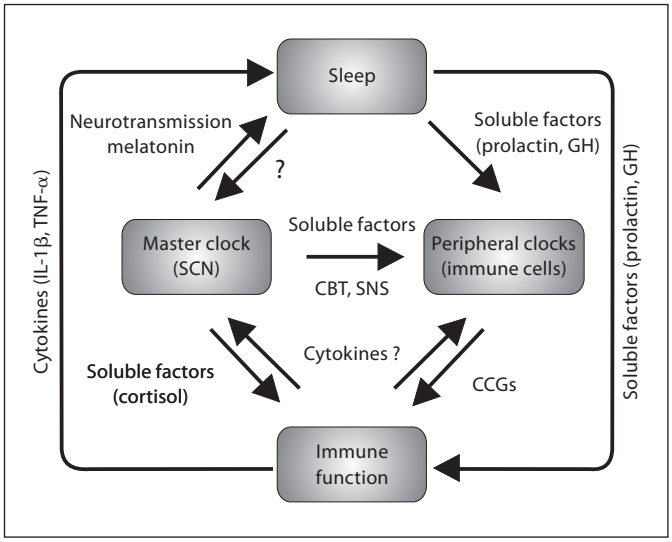

Fig. 3. Clock-sleep-immune model. The SCN is a key regulator of sleep and synchronizes peripheral clocks all over the body, including the cellular oscillators of immune cells. Sleep might feedback to the circadian timing system – most likely by neuronal and humoral factors and by modulation of core body temperature – thereby stabilizing the SCN as well as the peripheral clocks of immune cells. Furthermore, sleep and the SCN together modulate the function of immune cells through soluble factors (hormonal priming). Immune cells, on the other hand, affect sleep via the secretion of cytokines, such as IL-1β, IL-6, and TNF-α. The secretion of cytokines might further modulate SCN and peripheral clock rhythms. CBT = Core body temperature; SNS = sympathetic nerve system; CCGs = clock-controlled genes.

Hypothesis: Circadian Clocks – Master Regulators of Immune Rhythms

The circadian rhythm of immune responses is driven by the interplay of master (SCN) and peripheral clocks (immune cells). The SCN drives the release of rhythmic soluble factors (hormones) which affect immune cell function (hormonal priming) as well as the circadian clock of immune cells [Bollinger T., unpublished work]. Furthermore, the SCN may affect immune cells through the sympathetic nervous system as well as core body temperature. We suggest a model (fig. 3) in which factors released in relationship to the circadian rhythm – which are (e.g. prolactin, growth hormone) or are not (e.g. cortisol and melatonin) modulated by sleep – regulate the hormonal priming of immune cells and subsequently their immune function. Furthermore, we predict that such factors, the sympathetic nervous system, and core body temperature synchronize the peripheral circadian clocks of immune cells and thereby drive the functional rhythm of immunity at the cellular level. Conversely, immune cells are able to modulate sleep and circadian clocks [8, 41]. Our model predicts that immune cells would be able to sustain a rhythm, but need signals from the master clock (SCN) in order to stay synchronized to other peripheral clocks and to maintain clock synchrony within the leukocyte subpopulations. We further predict that immune cell cultures would gradually lose their synchrony in vitro due to the lack of such synchronizing factors. Adding these synchronizing factors should re-synchronize these cultures in a similar way to what has been shown for fibroblasts and other cell lines [29]. Since the circadian clock is redundantly stabilized, short-term sleep deprivation/restriction will have only minor effects on leukocyte clock synchrony, but it will affect the circadian immune rhythm through sleep-modulated circadian signals such as prolactin and growth hormone (hormonal priming of immune cells). Furthermore, we speculate that long-term sleep deprivation/restriction will disrupt the synchrony amongst different leukocyte clocks, leading to a desynchronization of immune functions and, ultimately, deregulated immune responses. Clock desynchrony has already been shown to be detrimental for metabolic homeostasis, for example [42]. If our assumption is right, then the effects of acute sleep loss on circadian immune rhythms should be reversible through the mimicry of circadian rhythms of prolactin and growth hormone serum levels, e.g. by timed infusion of these hormones. The disruption of circadian synchrony by long-term sleep deprivation/restriction can most likely be experimentally amended by enforcing a normal sleep/wake cycle or by timed exposure to circadian synchronizers such as light. A good model to monitor clock changes at tissue levels are circadian clock reporter mice [43]. We speculate that clock desynchrony in the leukocyte subpopulations due

to chronic sleep disturbances will promote immune-related diseases such as autoimmunity, allergy, and tumors. If this is true, then sleep-loss-induced clock desynchrony could be seen as a learned response and, hence, represent a form of peripheral memory of sleep loss.

In summary, it has become clear that sleep is essential for immune homeostasis and that the deprivation/restriction of sleep leads to altered immune functions. Our model proposes that the circadian timing system is the underlying mechanism which simultaneously regulates the sleep/wake cycle and, in consequence, the synchrony of circadian immune rhythms and thereby immune homeostasis. We speculate that long-term sleep deprivation/restriction deregulates the circadian timing system and subsequently disrupts immune homeostasis.

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