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Sleep in Relation to the Body's Immunity

Jirathan Pongchababnapa*

*[1]Anglo Singapore International School, Bangkok, Thailand 10260

Email: tonklar_p_2020@anglosingapore.ac.th

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Abstract:

Human body's immunity is strongly affected by sleep and the circadian cycle. This influence is expressed by the bilateral relationship between the central nervous system (CNS) and the immune system, with various cytokines, neurotransmitters, and various hormones acting as signaling keys between the components. Though it is difficult to gauge the extent to which the circadian rhythm affects the immunological processes, comparisons of cytokine and hormonal activity between the wake period and the sleep period over the 24-h clock are made. It is hypothesized that the various cellular stresses causes the build-up of pro-inflammatory cytokines, creating a positive feedback loop that initiates the adaptive immunity during the sleep period. It is during this time that undifferentiated immune cells such as T cells are more dominant and suppressed by nTreg. In addition, Slow-wave sleep helps the body release hormones such as prolactin and GH while cortisol and catecholamine are suppressed. With the right condition of hormonal stimulation, sleep supports (1) maintenance of the secretion of IL-6 at the right period of the day (2) increase in nTreg and Il-2 concentration at 02:00am (3) increase in proliferation of tumor necrosis factor (TNF) during nocturnal sleep. Though it is to note that many intracellular signals (such as: cytokines and hormones) are interchangeable in many mechanisms and one type of signal can function as the other in different systems.

Keywords **—Homeostasis, immunity, sleep-wake cycle**

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I. INTRODUCTION

The rise of research in neuroimmunology has verified, with strong evidence, the common belief of 'sleep helps healing', and vice versa applies as well. In other words, the link communication between the networks of the central nervous system and the cells and tissues of the immune system is bidirectional in nature (1). For example: improved sleep during infection has been shown to reduce infection risk; promote inflammatory homeostasis through the release of mediators that have synergistic properties with the immune system such as Th1 cytokines, or hormones such as melatonin, GH, prolactin, and leptin; and act as an excellent adjuvant, enhancing the adaptive immune response after vaccination (1-5). This theory is supported by findings that show that the disturbance of sleep can activation of chronic inflammation which is associated with various diseases that is affected by the inflammatory response such as diabetes due to development of insulin resistance, atherosclerosis, and Alzheimer (6-8). On the other hand, the inflammation triggered by the immune system can lead to an increase in the duration and the intensity of sleep. However, it can also lead to an increase in disruption of sleep as well. The aim of this review is to outline the bilateral relationship between sleep (and lack of) and the immune response and the involved mechanisms.

II. SLEEP-WAKE CYCLE

Sleep is governed by interactions between the two mechanisms which are sleep-wake dependent homeostasis (Process S) and the circadian pacemaker (Process C) (9). Process C is a complex

molecular loop that is composed of three components: the suprachiasmatic nucleus (SCN) afferent pathways of photic and non-photic stimuli, and the nervous outputs produced by the SCN (10-12). Regarding the second component, the hypothalamus receives non-photic information through three pathways: emotional input from the limbic system; cognitive input from the insular, prelimbic, and infralimbic cortex; and visceral input from the parabrachial nucleus. Meanwhile, the SCN receives photic information via the retinohypothalamic tract, regulated by the activation of both NMDA and Non-NMDA glutamate receptors (13-15).

Onto the third component: the SCN modulates the circadian rhythm of body functions and behavior, mainly known to be responsible for controlling the sleep-wake rhythm but also other various functions. The SCN generates signals to nearby parts of the brain (which will in turn stimulate other effector organs) in a transcriptional-translational molecular loop (16, 17).

Studies show that the circadian system is indistinguishably linked to sleep. Because these two processes generally work synchronically to meet the changing requirements of the solar day (24 hours) and differentiate conflicting bodily functions, it is customary to speak of them as working in concert (18-20). Thus, significant changes occur during the normal sleep-wake cycle in terms of physical and mental activity, hunger drive, cardiovascular function, and temperature regulation, and immune parameters such as leukocyte numbers, function, proliferation, and the production of cytokine and other related signaling proteins (20). Most of these changes exists in tandem with the innate sleep-wake cycle regardless of whether such organisms are diurnal animals which have active phase during day time (such as humans or elephants) or if they are nocturnal animals which have active phase during night time (such as racoons or aye-aye). Thus, in humans which are diurnal creatures, changes in the immune parameter that occurring in the sleep-wake cycle can be categorized in two ways based on the time that the activity of the changes peaked: rhythms of change that peak during 'rest period', which is during night time for humans; and rhythms of change that peak during 'active period', which for humans is during the day time. Before delving into the specific role of immunity in relation to sleep, this section will dive deeper into the immune cell counts and functions typically associated with regular sleep-wake cycle (18, 21, 22).

III. PROINFLAMATORY STATE OF RESTING PERIOD

During night-time sleep, the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis are significantly downregulated, decreasing the levels of stress hormones cortisol epinephrine, and noradrenaline in the bloodstream, among other things. The pineal hormone melatonin (in people who are awake) and the pituitary growth hormone (GH) (which promotes cell growth, differentiation, and restoration) show a noticeable increase in their blood levels while people are asleep(23, 24). On the other hand, it is assumed that adipocytes release leptin, thus diminishing feelings of hunger and restlessness during sleep. Melatonin, prolactin, leptin, and GH all show surprisingly collaborative effects on the immune system despite being drawn from different cellular sources(23, 25, 26). Cytokines such as TNF-α and IFN-γ both help promote immune cell activation, proliferation, differentiation, and production of other cytokines such as IL-1, IL-12, TNF-α, and IFN-γ, all of which promote inflammation(27, 28). Though, it is to note that most of the inflammatory aspects are generally suppressed by catecholamines and cortisol, these signals support a few immune aspects. While the outcomes caused by these hormones are dependent on timing and dosage, they are only relevant in the context of acute actions within the physiological range. Numerous experiment have found evidences of the connection between the pattern of secretion of hormones by endocrine glands and the immune rhythm, which can be seen to occur on a cycle involving an "inflammatory peak" occurring in the hours before nightfall, where wakefulness is found to feature predominant anti-inflammatory properties (23, 25, 26, 29). Spikes in Th1 cytokines and have been observed during the period of slow-wave sleep (SWS) in various tissues such as the lymph node, serum/plasma, and the brain, in animals regardless of whether they are stimulated or not (30, 31). As previously mentioned, the change in the pattern producing more hormones with pro-inflammatory

effects during rest periods can be used to explain the increase in cytokine production induced by stimulation during rest periods (32, 33). However, the question remains as to why spontaneous release of cytokines follows a similar rhythmic release during many rest periods. According to preliminary explanations, many various cellular stresses that have accumulated during the active wake period such as synaptic transmission, physical exercise, metabolism, and cell invagination can act as exogenous danger signals that trigger the release of pro-inflammatory cytokines. A positive feedback loop is created by pro-inflammatory cytokines, which act as danger signals and, as a result, help to promote the initiation of adaptive immune responses (34, 35).

The immune system is regulated by cellular clocks, which have been found in macrophages and Th cells, and is capable of maintaining secretion of pro-inflammatory cytokine many days in vitro after extraction (36). When it comes to immune cells, clock genes are responsible for up to 8 percent of the transcriptome. This includes antigen presentation, phagocytosis as well as heat shock protein (HSP), lipoprotein signal peptidase (LPS), and NF-kBsignaling(37-40). Numerous other indicators of immune responses, including T cell activity, phagocytosis, and spontaneous immune cell proliferation have been shown to exhibit a diurnal pattern, peaking during the rest period (41, 42). Interestingly, it found that there is a positive correlation between the concentration of prolactin and GH in blood with both Interferon (IFN0 production and mitogenic response in rat lymph nodes, implying that these pro-inflammatory hormones contribute actively to the rhythm of immune responses (43).

In combination, neuroendocrine rhythms characterised by the predominant secretion of pro-inflammatory hormones and the suppression of anti-inflammatory during the parts of sleep rich in SWS, as well as the combination of endogenous and exogenous danger signals as products of cellular stresses during active wake period have a synergistic effect on immune and non-immune responses (22). Sleep's pro-inflammatory effect can be beneficial (44). Thus, sleep following vaccination can act as an adjuvant, enhancing the following immune response. On the other hand, inflammation induced by hormones and cytokine during the rest period can be injurious to the immune response, as evidenced by the increased mortality rate of mice injected with LPS during sleep period (83%) compared to active period (10%). This pattern is also detected in septic patients (45-47).

IV. RECIPROCAL REGULATION OF SLEEP AND INNATE IMMUNITY

Since both Process C and Process S are involved in regulating inflammatory processes while sleeping, it is crucial to evaluate the influence of both processes when studying the changes of the immune response during rest periods (48). To accomplish this experimental goal and clearly distinguish the effects of circadian oscillator and sleep on immune functions, studies of immune parameters between a normal sleep-wake cycle and 24-hours of continued sleep deprivation are needed. Additionally, such studies must take into account various zeitgebers, maintain static circumstances throughout the course of the experiment, and enrol subjects who are able to maintain a sleep-wake activity schedule (48). Some studies are conducted involving 24 hours sleep deprivation, and many others have surmounted these methodological hurdles and discovered differences across a standard 24-hour period, though the effects of sleep and Process C to some of these alterations has not been dissociated (49).

The proliferation of naive T cells and the concentration of IL-2 and this is the highest during night-time sleep, with peak at 02:00 am as a response to the beginning of adaptive immunity (50). In maintenance of immunological homeostasis, the suppressive action of nTreg regulates the excess proliferation of T cells, IL-2, and the total lymphocyte count, thus lessening unnecessary inflammations that would go on to cause symptoms such as allergies (1). In normal sleep conditions, nTreg is shown to have the highest suppressive ability during 02:00am and least during 07:00am. However, under the condition of sleep deprivation, there is no such rhythm of suppressive action across the time scale, indicating that the dampening of overactive immune system is dependent on sleep or the lack of sleep deprivation (51-54).

Because the central nervous system (CNS) and IL-6 respond dynamically to sleep at night, they may have reciprocal regulatory effects on neural functions (55). IL-6 receptor (IL-6R) is absent in neural tissues, meaning that the activity of IL-6 on the non-immune tissue and the brain is dependent on the presence of IL-6R, which has to be released for these tissues to be activated. Additionally, IL-6 production increases with nighttime, along with the notable increase in circulating levels of IL-6R (55,

56). Supporting the posit that the level of IL-6 are elevated throughout the night, including the later parts of the night, and the rise in IL-6 was most prominent in the last half of the night (57, 58).

The mechanisms surrounding the night-time elevation of pro-inflammatory cytokines are unknown. According to Besedovsky et al (2012), the increased production of pro-inflammatory proteins that is accumulated throughout the course of the wake period, which will act as cytokines that that initiates the adaptive immune response, is caused by 'danger signals' that that are present during the wake period such as heat-shock immunological stimulants, reactive oxygen species, and nucleotides (22). On the other hand, the release of pro-inflammatory cytokines is correlated with the release of GH and prolactin during the SWS portion of sleep since both of these hormones stimulate the activity of type 1 cytokines (1, 22). There is compelling evidence of the inextricable link between the body's innate immunity and the central nervous system (59, 60). As a result of this neural-immune signalling, it is possible for there to be a homeostatic feedback loop between cellular inflammation and sleep. Rheumatoid arthritis (RA) patients showed contrasting cytokine release and sleep maintenance patterns, as well as levels of sleep depth, according to a study recently conducted by Bjurström et al (2016) (61). At 2300 hours, for example, increased TLR-4 stimulation of monocytic TNF production was associated with a decrease in timeo of waking post sleep onset and increase in sleep efficiency. At 0800 however, the synthesis of TNF is shown to be inversely correlated to the maintenance of sleep. In addition, higher levels of IL-6 synthesis at 0230 has been shown to increase the amount of SWS and enhance the production of IL-6 during the subsequent NREM period of sleep (62-64)

CONCLUSIONS

Immunological processes are strongly influenced by sleep and the circadian rhythm. This influence can be characterised by reference to the bidirectional communication between the CNS and the immune system, with various hormones, neurotransmitters, and cytokines playing key roles. The autonomic nervous system directly innervates the immune system. During the diurnal wake period, many cellular stresses such as synaptic transmission, cell invagination, and respiration lead to adaptive immunity during the nocturnal period. The rhythmicity in immune function closely reflects the natural 24-hour sleep-wake cycle, as sleep and the circadian system contribute to these activities. During the sleep period when the adaptive immune system starts, undifferentiated immune cells such as naive T cells are more dominant due to proliferation in the function of the adaptive immunity but are suppressed by nTreg. It is well known that good sleep at night, especially SWS sleep, helps the body release growth hormone and prolactin, while cortisol and catecholamines are at their lowest levels. Early sleep is characterized by an endocrine environment that supports (1) the stability of concentration of IL-6, (2) regulation of T cell proliferation and IL-2 concentration (3) an increase in proliferation of TNF. In this way, an early night's endocrine milieu favours the initiation of Th1 immune responses, which subsequently helps establish long-term immune memory. The disruption of sleep can lead to (1) 'flat lining' of the level of Il-2, causing sleepiness during the day and poor sleep during the night (2) suppression of T cells production, which could lead to allergies (3) decreased in stimulation of pro-inflammatory cytokines such as Il-1 and Il-12. Hence, it could be concluded that healthy sleep is extremely crucial in maintenance of the immunological homeostasis, as to prevent compromised or overactive immune response.

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