Association between Sleep and Immune System Activation

Research Project

Submitted to the University of Salahaddin-Erbil Department of Biology in partial fulfillment of the requirements for the degree of Bachelor (BSc) in Biology

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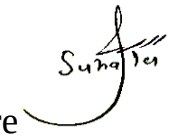
Certification

We certify that this study was prepared by a student (Barin Sherzad Ali) under our supervision at College of Education/ Salahaddin University- Erbil in partial fulfillment of the requirements for the degree of Bachelor in Biology.

Signature 

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Abstract

A joint function of tissues, organs, and cells for the protection of the body develops the immune system. The human immune response against various infections during sleep, its mechanism, neuroimmune interactions, the immune regulatory effect of sleep along with sleep deprivation, and the role of cytokines in sleep deprivation were addressed. It is revealed that the human immune system and sleep both are associated and influenced by each other. Sleep deprivation makes a living body susceptible to many infectious agents. As the result, the immune system of the human body is altered by releasing immunomodulatory in response to infections as reported by various researchers. The basic reasons and mechanisms of most of the poor sleep networks and the release of proinflammatory modulators are still uncertain. The current situation requires improved sleep habits to make the immune system efficient for a healthy life

1. Introduction

1.1 Definition

Sleep is an active physiological process necessary for life and normally occupies one-third of our lives, playing a fundamental role in physical, mental, and emotional health (Luyster et al., 2012). Sleep patterns and needs are influenced by a complex interplay between chronological age, maturation stage, and genetic, behavioral, environmental, and social factors (Grandner, 2017, Ohayon et al., 2004, Galland et al., 2012, Aricioglu and Cetin, 2020, Boulos et al., 2019).

The immune system is an organization of cells and molecules with specialized roles in defending against infection, Immune system response is regulated by three physiological events such as wakefulness, non-rapid eye movement which is NREM or slow sleep, and rapid eye movement which is REM sleep (Cardinali et al., 2004).

In the 1970s, the association between sleep and the immune system was first recognized when muramyl peptide acquired from bacterial peptidoglycan or Factor S from human urine was isolated chemically as a sleep-inducing factor (Krueger et al., 1984).

Sleep and the immune system have a bidirectional relationship. An immune response, like that caused by a viral infection, can affect sleep. At the same time, consistent sleep strengthens the immune system, allowing for balanced and effective immune function (Besedovsky et al., 2019b).

1.2 Sleep Function

Sleep is a common feature and need in almost all living things. It is a condition that occurs naturally in the brain and body, characterized by the altered state of consciousness, reduced response to external stimuli, and the absence of voluntary movements. Contrary to popular belief, sleep is not a state dominated by passive inactivity, it is a daily rhythm with complex functions(Zielinski et al., 2016).

Why must we sleep?

Pinpointing the essential and irreplaceable aspects of sleep remains one of the great challenges of mammalian biology. Still, much has been determined about the structures, processes, and pathways underlying the regulation of sleep and the relationship of sleep to daytime functioning and overall well-being(Mignot et al., 2011).

Sleep itself is not a homogenous process. There exist two fundamentally distinct types of sleep: rapid eye movement (REM) sleep, which is associated with active dreaming, and non–rapid eye movement (NREM) sleep. Switches between NREM and REM sleep appear to be controlled by reciprocal inhibition between monoaminergic neurons and a specific subset of cholinergic neurons within the brainstem. These “REM-on” cholinergic neurons exhibit reciprocal inhibitory connections to noradrenergic (LC) and serotonergic (raphe) neurons (8). When REM sleep is triggered, REM-on cholinergic neurons become maximally active, while noradrenergic and serotonergic neurons become virtually silent. The switching between activity and inhibition of these neurons results in a characteristic cycling between NREM and REM during the sleep period (Dunmyre et al., 2014).

There are many biologic functions associated with sleep, including those that lead to restoration of body, brain and neurocognition (Rechtschaffen, 1998). Nevertheless, it is quite evident that sleep is essential for many vital functions including development, energy conservation, brain waste clearance, modulation of immune responses, cognition, performance, vigilance, disease, and psychological state (Zielinski et al., 2016).Sleep is vital for health and well-being in children, adolescents, and adults. Healthy sleep is important for cognitive functioning, mood, mental health, and cardiovascular, cerebrovascular, and metabolic health. Adequate quantity and quality of sleep also play a role in reducing the risk of accidents and injuries caused by sleepiness and fatigue, including workplace accidents and motor vehicle crashes. Short-term sleep deprivation, long-term sleep restriction, circadian misalignment, and untreated sleep disorders can have a profound and detrimental impact on physical health, mental health, mood, and public safety. Chronic insufficient sleep is associated with an increased risk of mortality and contributes to both the individual risk and societal burden associated with several medical epidemics, including cardiovascular disease, diabetes, obesity, and cancer (Ramar et al., 2021).

A master circadian pacemaker is located in the hypothalamus, the suprachiasmatic nucleus which increases production of the hormone melatonin in order to trigger sleep is important for matching the body's circadian rhythm to the external cycle of light and darkness through pineal gland. In communication with the brain stem, especially the pons and medulla, thalamus, cerebral cortex, basal forebrain and midbrain regulates sleep, wakefulness, clock genes and immune system (Figure 1)(Harper, 2014).

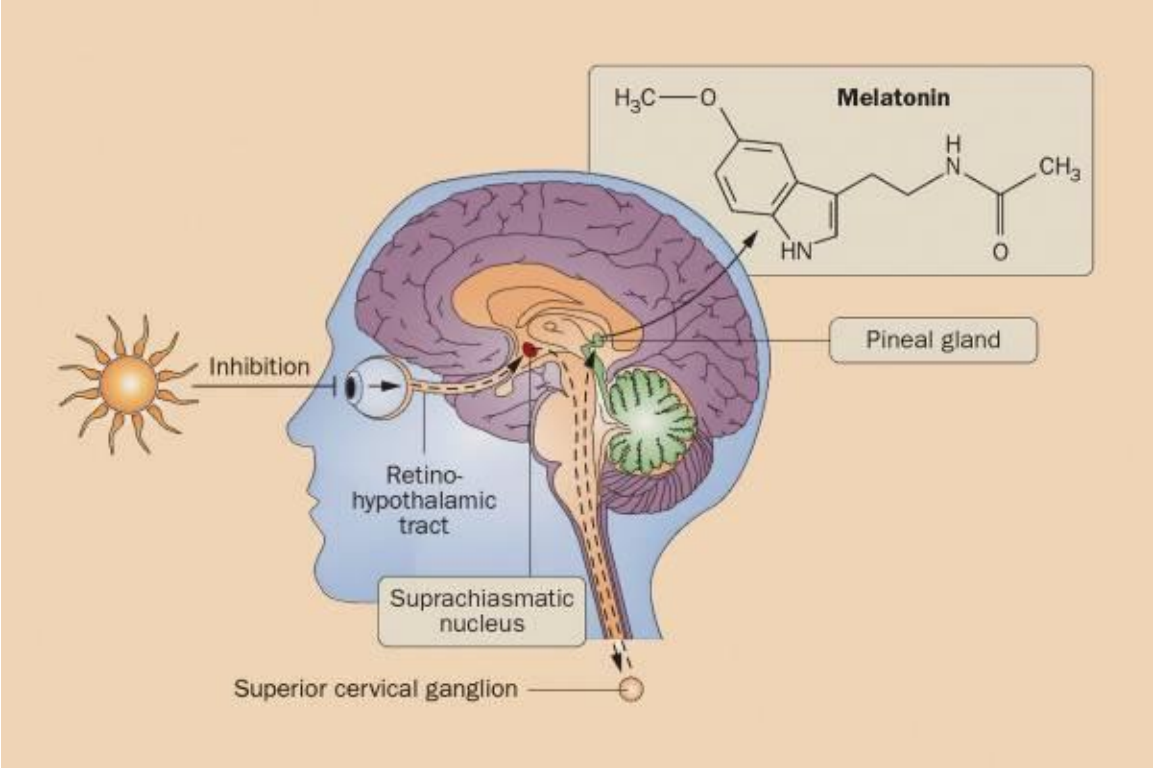

Figure 1. Biological clock, sleep regulation and immune system.

1.3 Immune System

Numerous components contribute to the complexity of the immune system. An important component of our immune system are leukocytes or white blood cells. The leukocyte's job is to identify, attack, and remove foreign pathogens from our bodies. Our immune system reacts to pathogens in an immediate (innate) and learned (adaptive) way, which allows us to safely interact with our environment every day. The results of studies conducted for more than twenty years reveal the relationship between sleep and the immune system. These studies have also shown the existence of bi-directional communication between the sleep regulating networks in the central nervous system and the cells of the immune system (Aricioglu and Cetin, 2020).

Over the last fifteen years, research following a systems approach of neuroimmunology has accumulated surprisingly strong evidence that sleep enhances immune defense, in agreement with the popular wisdom that ‘sleep helps healing’. Although the communication between sleep regulatory networks in the central nervous system and the cells and tissues of the immune system is basically bidirectional (Besedovsky et al., 2012).

Sleep profoundly affects endocrine, metabolic, and immune pathways, whose dysfunctions play a determinant role in the development and progression of chronic diseases. Specifically, in many chronic diseases, a deregulated/exacerbated immune response shifts from repair/regulation towards unresolved inflammatory response (Hand et al., 2016).

Regular sleep is crucial for maintaining immune function integrity and favoring a homeostatic immune defense to microbial or inflammatory insults. Sleep deprivation may result in deregulated immune responses with increased pro-inflammatory signaling, thus contributing to increase the risk for the onset and/or worsening of infection, as well as inflammation-related chronic diseases (Irwin and Opp, 2017).

1.4 Sleep and Immunity

Assessing the influence of sleep on the production of these three proinflammatory cytokines leads to the conclusion that the state of normal sleep promotes reductions in the levels of their secretion. This allows sleep to be regarded as an anti-inflammatory state. IL-2 is an important mediator of adaptive immunity, participating in forming responses to vaccination. It stimulates the growth, differentiation, and proliferation of T- and B-

lymphocytes, monocytes, and macrophages and has direct cytotoxic effects. It is produced by T-lymphocytes in response to antigenic and mitogenic stimulation. Basal IL-2 production does not respond to sleep or its deprivation, though stimulated production (for example, on vaccination) increases during sleep. Prolonged waking leads to suppression of this response (Besedovsky et al., 2019a). The main function of IL-10 is to suppress the release of proinflammatory cytokines and the antigen-presenting function of macrophages and dendritic cells. IL-10, operating via the Th2-cell activation system (T-helper type), stimulates the proliferation and differentiation of B-lymphocytes, which are involved in protection from intestinal parasites, neutralization of bacterial toxins, and the local protection of mucous membranes. It is produced mainly by monocytes and Th2 cells. IL-4 is similar to IL-10 in terms of its anti-inflammatory action. This cytokine regulates the transition of T-helpers from the Th0 to the Th2 state, as well as the growth and differentiation of B-lymphocytes, and antibody biosynthesis and secretion. It suppresses the proinflammatory activity of macrophages and their secretion of IL-1, TNF-α, and IL-6. It is produced by Th2 lymphocytes, basophils, eosinophils, and mast cells (Skripchenko et al., 2015) .

d mast cells. Experiments quantifying these two anti-inflammatory cytokines in plasma during sleep and on the background of prolonged waking did not reveal any significant differences in their contents. However, stimulated IL-10 and IL-4 production in humans during sleep decreased, indicating a decrease in anti-inflammatory activity during sleep. Some studies have evaluated the proinflammatory/anti-inflammatory cytokine ratio during sleep and on the background of sleep deprivation. Dimitrov et al. found an increase in the TNF/IL-4 ratio in the first half of sleep, changing to the opposite in the

second half. The change in the IL-2/IL-4 ratio in the proinflammatory direction during prolonged partial sleep deprivation on evaluation of blood tests in the waking period after sleep deprivation(Zhang et al., 2020).

Which hormones affect sleep?

The levels of several hormones fluctuate according to the light and dark cycle and are also affected by sleep, feeding, and general behavior. The regulation and metabolism of several hormones are influenced by interactions between the effects of sleep and the intrinsic circadian system; growth hormone, melatonin, cortisol, leptin, and ghrelin levels are highly correlated with sleep and circadian rhythmicity (Kim et al., 2015).

Role of cytokines in sleep regulation

There is substantial evidence implicating the brain cytokine network in sleep regulation, this network seems to be intimately involved in the regulation of daily psychological sleep as well as sleep responses perturbations such as sleep loss and infectious challenge {Krueger, 2008}.

During sleep, your body releases cytokines, which are essential for the regulation of the immune system. Cytokines are required in increased amounts when you are attacked by a pathogen or are under stress. The level of cytokines increases during sleep, and therefore lack of sleep hinders the body's ability to fight infections, this is also a reason why the body tends to sleep more while suffering from any infection (Irwin and Opp, 2017). Immunoregulatory cytokine, i.e. interleukin (IL)-1, a key player in sleep regulation has levels associated with sleep propensity in the brain induced by muramyl dipeptide and Factor S related peptidoglycans. So, it is expedient

that sleep regulated cytokines effect the immune system, our bodies also produce T-cells during sleep, which are white blood cells that play a critical role in our body's immune response to an infectious disease {Krueger, 2008}.

Sleep is important because it is integral to most issues in neurobiology and neuropathology. Further, sleep and sleep pathologies are of direct importance to the quality of our life. Although our understanding of sleep remains limited much has been accomplished over the past 20 years especially within the context of cytokine regulation of sleep and related physiological and pathophysiological processes {Kapsimalis, 2005}. Many laboratories have developed what is now overwhelming evidence linking sleep deprivation-enhanced inter-leukin-1 beta (IL1), and the related cytokine tumor necrosis factor alpha (TNF), to symptoms associated with sleep deprivation, such as sensitivity to kindling {Yi, 2004} and pain stimuli{Kundermann,2008}{Kawasaki,2008},cognitive{Baune,2008},memory{Banks, 2007},and performance impairments, depression, sleepiness, and fatigue.

Further, chronic sleep loss is associated with pathologies such as metabolic syndrome, chronic inflammation, and cardiovascular disease. All of these sleep deprivation-associated symptoms can be induced by injection of exogenous IL1 and/or TNF, or in some cases blocked if these cytokines are inhibited {Larsen, 2007}.

Two substances, the cytokines interleukin-1 beta (IL1β) and tumor necrosis factor alpha (TNFα), known for their many physiological roles, for example, cognition, synaptic plasticity, and immune function, are also well characterized in their actions of sleep regulation. These substances promote

non-rapid eye movement sleep and can induce symptoms associated with sleep loss such as sleepiness, fatigue, and poor cognition. IL1β and TNFα are released from glia in response to extracellular ATP. They bind to their receptors on neurons resulting in neuromodulator and neurotransmitter receptor up/downregulation (e.g., adenosine and glutamate receptors) leading to altered neuronal excitability and function, that is, a state change in the local network. Synchronization of state between local networks leads to emergent whole brain oscillations, such as sleep/wake cycles {Jewett, 2012}.{Tanaka, 2014}

Role of melatonin in sleep regulation

Melatonin is the hormone best known to important physiological sleep regulator in diurnal species including humans, being low during the daytime but rising once darkness sets in, leading to sleep.

The sharp increase in sleep propensity at night usually occurs 2 h after the onset of endogenous melatonin production in humans

Melatonin displays high lipid and water solubility, which allows it to diffuse easily through most cell membranes, including the blood-brain barrier. Its half-life is about 30 minutes, and it is cleared mostly through the liver and subsequently excreted in the urine as urinary 6-sulfatoxymelatonin {Arendt, 2005}.

In humans and most diurnal mammals, melatonin is secreted at night with a robust circadian rhythm and maximum plasma levels that occur around 3 to 4 AM. The daily rise of melatonin secretion correlates with a subsequent increase in sleep propensity about 2 hours before the person's regular bedtime.

The time before this secretion is the least likely for sleep to occur, and when it starts, the propensity for sleep increases greatly as the “sleep gate” opens. The rhythmic release of melatonin is regulated by the central circadian rhythm generator-the suprachiasmatic nucleus (SCN) of the anterior hypothalamus {Maldonado, 2009}.

2.3 Melatonin and the circadian rhythm of the sleep-awake cycle

The daily sleep-wake cycle is influenced by 2 factors: process C (circadian), an endogenous “clock” that drives the rhythm of the sleep-wake cycle; and process S (sleep), a homeostatic “sleep propensity” that determines the recent amount of sleep and wakefulness accumulated. The SCN interacts with both processes, and it is where the main component of process C is located. Excitatory signals from the SCN and subsequent melatonin suppression are thought to promote wakefulness during the day in response to light and the suppression of melatonin inhibition of the SCN. This inhibition is released in the dark phase and leads to melatonin synthesis/release with consequent sleep promotion and the sleep-wake cycle is only one of many circadian rhythm3.

The central role of circadian rhythms, representing biological oscillation around 24 h, is increasingly acknowledged in human health in the field of clinical psychiatry, abnormalities of sleep and circadian rhythms are more a rule than exception, the abnormalities of circadian rhythms are related to negative outcomes such as symptom aggravation and recurrence in psychiatric disorders.

Accumulating evidence suggests that correction of abnormal sleep and circadian rhythms beyond psychiatric symptoms to improve outcome in psychiatric disorders is warranted.

Melatonin is a key hormone regulating both sleep and circadian rhythms, A recent systematic review and meta-analysis reported positive effects of exogenous melatonin on sleep quality in adults with metabolic disorders, respiratory diseases, and primary sleep disorders, while no statistically significant findings were reported for individuals with mental disorders and neurodegenerative diseases {Bendz, 2010}.

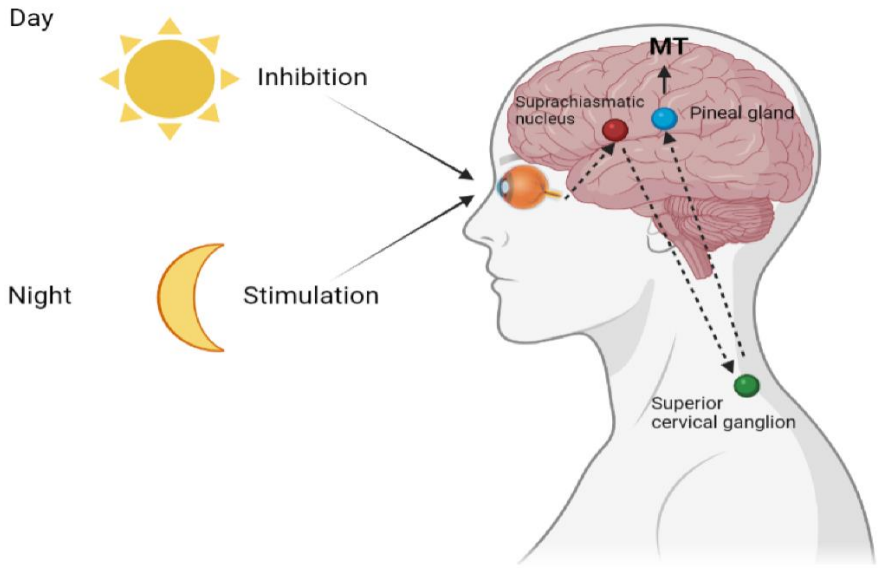

Figure 2. Melatonin is the main regulator of the circadian rhythm in all living organisms. Light information from the rods and cones of the retina through the ganglion cells and directly from the light-sensitive ganglion cells enters the paired suprachiasmatic nucleus (SCN) of the hypothalamus. These signals then travel to the cervical spinal cord, from where they travel back to the brain and reach the pineal gland. During sleep in the dark, when most of the SCN neurons are inactive, the nerve endings release norepinephrine, which activates the synthesis of melatonin in the pinealocytes. Bright light blocks the synthesis, while in constant darkness, the rhythmic production, maintained by the periodic activity of the SCN, is preserved.

Sleep stages

The human body cycles through two phases of sleep, (1) rapid eye movement (REM) and (2) non-rapid eye movement (NREM) sleep, which is further divided into three stages, N1-N3. Each phase and stage of sleep includes variations in muscle tone, brain wave patterns, and eye movements. The body cycles through all of these stages approximately 4 to 6 times each night, averaging 90 minutes for each cycle {Memar, 2017}.

How Much Sleep Do We Really Need?

Healthy adults need at least seven hours National Library of Medicine, Biotech Information The National Center for Biotechnology Information advances science and health by providing access to biomedical and genomic information of sleep per night. Babies, young children, and teens need even more sleep to enable their growth and development {Panel, 2015}.

Recommended Sleep Times by Age Group

- Infant 4-12 months (12-16 hours of sleep per 24 hours)
- Toddler 1-2 years (11-14 hours of sleep per 24 hours)
- Preschool 3-5 years (10-13 hours of sleep per 24 hours)
- School age 6-12 years (9-12 hours of sleep per 24 hours)
- Teen 13-18 years (8-10 hours of sleep per day)
- Adult 18 years and older (7 hours or more)

Sleep recommendations for newborns are not available because sleep needs in this age group vary widely and can range from as few as 11 hours to as many as 19 hours per 24-hour period {Paruthi, 2016}.

Figure 3 Recommended Sleep Times by Age Group

Mechanism of adaptive immune response supported by sleep

Fragments of antigen are presented to T helper (Th) cells along with the two types of cells which are involved in the formation of immunological synapse by APC that are antigen presenting cells that may pick and process invading antigen. Th1 response is induced by natural release of interleukin (IL)-12 APC and the function of antigen specific cytotoxic T cells along the production of antibodies by B-cells is supported by it as shown in Figure 4 (Besedovsky et al., 2012)

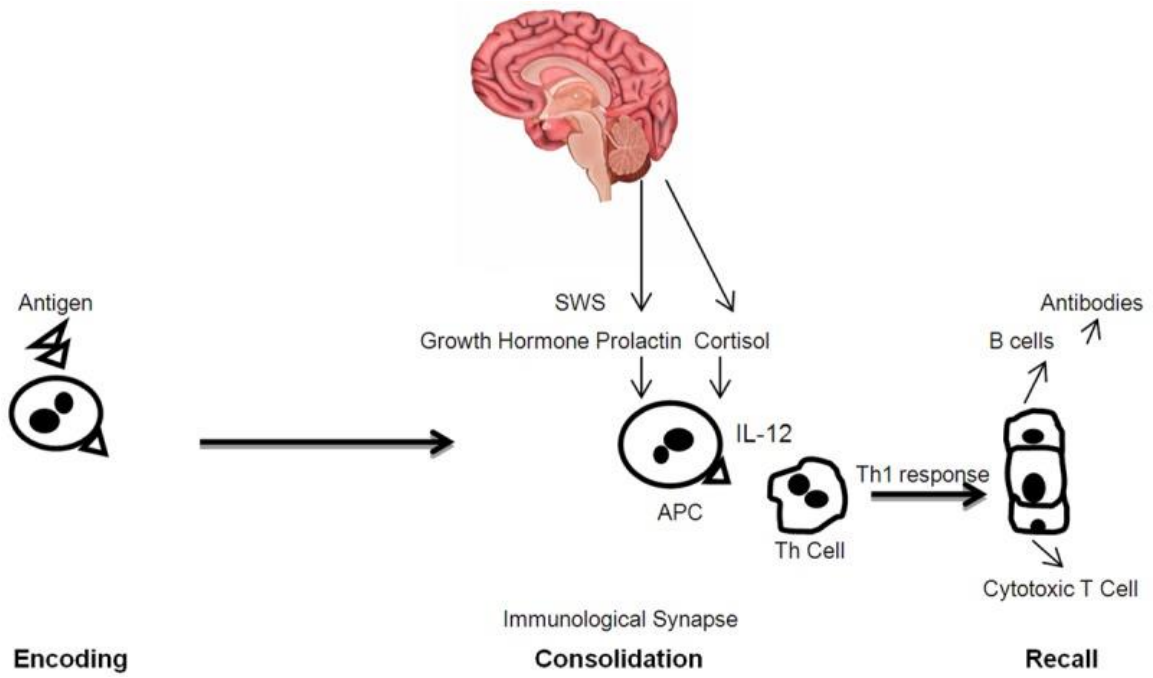

Figure 4 Adaptive immune response supported by sleep.

Conclusion

Sleep and the circadian system are strong regulators of immunological processes. The basis of this influence is a bidirectional communication between the central nervous and immune system which is mediated by shared signals (neurotransmitters, hormones and cytokines) and direct innervations of the immune system by the autonomic nervous system. Many immune functions display prominent rhythms in synchrony with the regular 24-h sleep–wake cycle, reflecting the synergistic actions of sleep and the circadian system on these parameters. Differentiated immune cells with immediate effect or functions, like cytotoxic NK cells and terminally differentiated CTL, peak during the wake period thus allowing an efficient and fast combat of intruding antigens and reparation of tissue damage, which are more likely to occur during the active phase of the organism. In contrast, undifferentiated or

less differentiated cells like naïve and central memory T cells peak during the night, when the more slowly evolving adaptive immune response is initiated. Nocturnal sleep, and especially SWS prevalent during the early night, promotes the release of GH and prolactin, while anti-inflammatory actions of cortisol and catecholamines are at the lowest levels. The endocrine milieu during early sleep critically supports (1) the interaction between APC and T cells, as evidenced by an enhanced production of IL-12, (2) a shift of the Th1/Th2 cytokine balance towards Th1 cytokines and (3) an increase in Th cell proliferation and (4) probably also facilitates the migration of naïve T cells to lymph nodes. Thereby, the endocrine milieu during early sleep likely promotes the initiation of Th1 immune responses that eventually supports the formation of long-lasting immunological
memories. Prolonged sleep curtailment and the accompanying stress response invoke a persistent unspecific production of pro-inflammatory cytokines, best described as
chronic low-grade inflammation, and also produce immunodeficiency, which both have detrimental effects on health.

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