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Review Article
Human immune system during sleep

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

Keywords: Sleep, innate immunity, cytokines, infectious agents, circadian rhythms

Introduction

Sleep is a physiological process that shows recuperative and regulatory characteristics [1, 2]. Immune system response is regulated by three physiological events such as wakefulness, non-rapid eye movement that is NREM or slow sleep, and rapid eye movement that is REM sleep [3]. Various pathogens constantly attack living organisms, and the immune system which is composed of complicated networks of physical and biochemical components keep the organism existent [4].

In the 1970's, 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 sleep inducing factor [5]. 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 [6]. So, it is expedient that sleep regulated cytokines effect the immune system [7].

In a similar manner, inflammatory mediators increase due to constant sleep loss that alter CNS processes and behavior during immune feedback to infection, including sleep [8]. Thus, during the intense phase response to infection or in chronic inflammation regulatory molecules cytokines are shared by sleep and the immune system involve in both physiological and disturbed sleep phase [9]. In my present study, I will discuss the human immune response against various infections during sleep, immunoregulatory effect of sleep along with sleep deprivation and role of cytokines in sleep regulation.

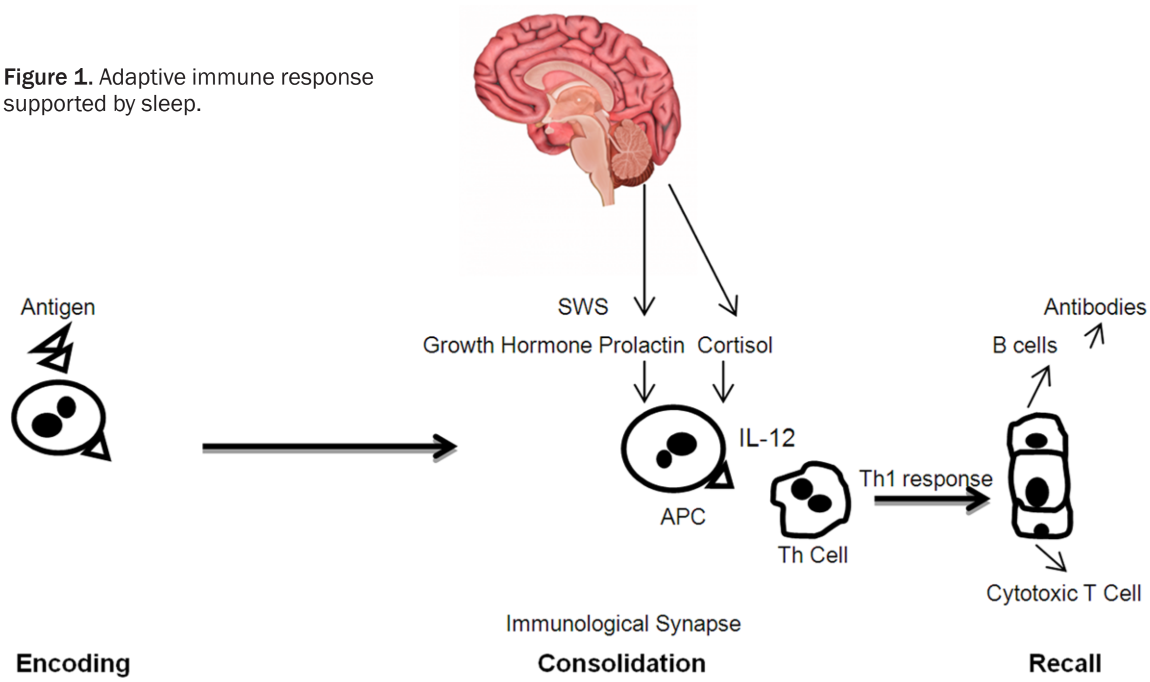
Mechanism of adaptive immune response supported by sleep

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 [10] as shown in **Figure 1**.

Neuroimmune interactions

Particular anatomical and physiological conditions are based upon neuroimmune interac-

Figure 1. Adaptive immune response supported by sleep.



tions whereas chemokines and modulators, cytokines and neurotransmitters, hormones are intercellular signals that may be shared by immune cells, neurons and glia cells [11, 12]. In both directions, blood-brain barrier can be crossed by some of the shared signals [13, 14]. In cerebrospinal fluid, nerve endings and at meningeal borders immune cells come in their close contact and flow in all directions throughout the body [15, 16].

Somehow, sensory nerve fibers, sympathetic and peptidergic may also create connections between primary lymphatic tissues that are bone marrow and thymus and secondary lymphatic tissues such as lymph nodes and spleen [17, 18]. Immune functions not only regulated by autonomous and endocrine nervous system through hormones and neural innervations but also through lymph flow, blood pressure and blood flow [18, 19], oxygen, fatty acids and via supply of substrates like glucose [20-22].

Poor sleep and health

Downturn in activity and vigilance is not only indicated by sleep deprivation but it is an integral process that restrains many physiological functions [23, 24].

Our capacity to remain healthy is badly effected by loss of sleep and sense of comfort, physiological framework accompanied by health is badly influenced by poor sleep [25]. Our demand for sleep is also increased in most of the ailments as observed [26]. Perceptivity to infectious diseases and deterioration of systemic circulation of leukocytes is increased by petty alterations due to lack of sleep [27]. However, there is a huge complexity in both the immune system and sleep [28, 29].

Infections, infectious diseases and immune system response

CNS is tainted by infectious diseases related to sleep disorders under the immune response against the infection whereas other systems like respiratory and endocrine systems are also affected by sleep disruption [30].

Virus as infectious agent

Immunodeficiency virus that is HIV and influenza are caused by viruses [31]. Despite of declining body temperature, rapid eye movement sleep (REM), is decreased and non-rapid eye movement sleep (NREM) is increased by influenza virus leading towards fever, fatigue and sleep disturbances [32]. Thus, temperature such as fever is increased in response to an infection to kill the cells causing the sickness as defense tool of body [33].

Bacteria as infectious agent

The whole functioning of the body is extremely altered in response to bacteria that cause diseases [34]. In humans waking and REM sleep along with greater non-REM sleep is declined by *Salmonella abortus* endotoxin considerably [35]. Thus, waking and sleep discontinuation with daytime drowsiness is enhanced by reducing the total duration of NREM by *Salmonella abortus* endotoxin [36].

Parasite as infectious agent

Sleep patterns and transformations of some behaviors are changed to promote parasitic infection and complete their life cycle [37]. Transformation from wakefulness to REM sleep is baptized as sleeping sickness by Human African Trypanosomiasis HAT that effects sleep framework and nervous system to cause circadian rhythm dysfunction [38]. Whereas a long time sleep leads to the less extent of parasitic infection and the sleep is developed to secure humans from parasitic infections [39].

Sleep deprivation and immunoregulatory effect of sleep

In case of severe and persistent loss of sleep such as insomnia, alcoholism, stress and during the period of aging, balance of cytokine is shifted from type 1 to type 2 leading towards type 2 function [40]. In all these groups proinflammatory cytokines are enhanced constantly [41, 42].

Ascetic alcoholics and people with less deprivation of sleep have high levels of TNF-α and IL-6 whereas tumor necrosis factor cytokine (TNF-α) levels are compared to control in sleep narcoleptics and apneics [41]. T-helper (CD3+, CD4+), T-cytotoxic (CD8+) cell numbers and decreased natural killer (NK) cell activity is reduced in insomniacs along with elevated levels of inflammatory cytokines [43]. Whereas daily framework of cellular and immune events cause to decrease overall immune functions in normal adults by experimentally induced sleep loss [44-46].

There is an inhibitory effect on hypothalamic pituitary adrenal HPA axis due to deep sleep in comparison to the HPA axis activation or organization of glucocorticoids which leads to arousal and sleeplessness [47]. So, 24-hours increment in corticotropin and cortisol secretion, most frequent disorder insomnia along with a CNS hyperarousal disorder is caused [48].

Glucocorticoid and catecholamine plasma levels are increased for HPA axis activation clearly associated with lack of sleep due to removal of parasympathetic constituent of NREM sleep [49]. So, in the morning after a night of sleep loss, fluctuated level of activation and normal level of cortisol becomes noticeable [50].

Role of cytokines in sleep regulation

A benchmark to be accomplished for a supposed sleep regulatory molecule is inducing physiological sleep along with its receptors in the living entity that fluctuate with the circadian rhythm or inactivation of the substance or its receptor cause to reduce voluntary sleep [6].

This criterion is fulfilled by cytokines as immune mediators as they are versatile proteins and they are involved in different physiological and pathological mechanisms in the CNS along with immune response [51, 52].

Sleep proneness is associated with IL-1 levels in the brain, being highest at sleep onset, along cytokines such as IL-2, IL-6, IL-8, IL-15 and IL-18 are reported to increase NREM sleep whereas some proinflammatory cytokines manage physiologic body temperature and inclination [53]. Best established cytokines are IL-4 and IL-10 and cytokines that cause discontinuity in NREM sleep are less observed and the production of IL-1 and TNF-α is restricted by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF κB) activation by the activity of these cytokines [6].

Conclusion and recommendations

Communication network between the neuroendocrine and immune systems allows the body to maintain homeostasis, especially when it has to respond to a stimulus, such as an infection. The metabolic functions of the body to eradicate the pathogen are transformed during an infection. However, the brain mechanisms of sleep and the immune response are not completely figured out.

Generally, the effects of immune modulators cytokines, the sleep mechanisms, the resulting changes in the sleep-wake cycle and the effect of neurotransmitters in regulating sleep during an immune response are the processes which are associated. Subsequent studies reported that sleep deprivation decreases lymphocyte blastogenesis, NK cell activity and upregulates IL-1 and IL-2.

Furthermore, extensive surveys, search of literature and research on sleep patterns and their alterness during illness including novel approach to the mechanisms of cytokines, their receptors and role in immune system of human body is required.

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