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Sleep and Immune System; Best Weapon Against to Coronavirus

Uyku ve Bağışıklık Sistemi; Koronavirüse Karşı En İyi Silah

Ghsoon Ismael, Mustafa Saygın

Süleyman Demirel Üniversitesi, Tıp Fakültesi, Fizyoloji ABD, Isparta.

Öz

Koronavirüsler (CoV'ler), günümüzde çok çeşitli doğal konakçılara sahip olan en büyük pozitif - duyarlı RNA virüsü grubudur. Bağışıklık cevabı CoV enfeksiyonunu kontrol etmek ve sonlandırmak için esastır, ancak düzensiz bağışıklık cevapları immünopatolojiye ve ölümün önde gelen nedeni olan pulmoner gaz değişimlerinde bozulmaya yol açabilir. Uyku, bağışıklık hücrelerinin dağılımını ve enflamatuar sitokinlerin ekspresyonunu etkileyen fizyolojik sistemleri değiştirerek bağışıklık fonksiyonlarının düzenlenmesinde önemli bir role sahiptir. Uyku sırasında metabolik talep düşüktür. Bu nedenle uyku ertesi gün maruz kalınabilecek patojenlere ve enfeksiyonlara karşı vücudun bağışıklık sistemini hazırlama şansı verir. Örneğin; sirkadiyen faktörler vücudun geceleri enfeksiyonlara karşı savunmasını sağlayan uykudan önce artan IL-6 seviyesini arttırır. Uyku bozuklukları, efektör sistemlerde bağışıklık sisteminin düzenlenmesinden sorumlu olan değişikliklere yol açarak ve bu da enflamatuar yanıtta anormal artışlara neden olur. Güçlü inflamatuvar yanıt sonucunda görülen bağışıklık sisteminin aşırı aktivaasyonu, COVID-19 hastalığında en önemli ölüm sebeplerinden biri olarak kabul edilmektedir. Bu nedenle enfeksiyon ile mücadelede kaliteli uykunun önemi dikkat çekicidir. Uyku bozukluğu; enflamasyonun hücrelerde ve organ fonksiyonlarında olumsuz etkiye, şiddetin artışına, ölüme neden olabilecek olumsuz etkilere ve bağışıklık yanıtının yanlış ayarlarına yol açabilir. Bu nedenle, bu makalede, enfeksiyonlara karşı vücut bağışıklık yanıtlarının düzenlenmesinde ve optimize edilmesinde düzenli ve kaliteli uykunun önemi anlatılmak istendi.

Anahtar kelimeler: Uyku, İmmün sistem, Covid-19

Abstract

Coronaviruses (CoVs) are the biggest group of positive-sense RNA viruses those have a wide range of natural hosts have been known up today. The immune response is fundamental to control and terminate CoVs infection, although, dysregulated immune responses may lead to immunopathology and impairments in pulmonary gas exchanges which is the leading cause of death. Sleep has a fundamental role in regulation of immune functions by changing the physiological systems that affect the distribution of immune cells and the expression of inflammatory cytokines. The metabolic demand during sleep is low, so it gives a chance to prepare the body's immune system to fight the pathogens and infections that would expose to it the next day. As well as, circadian factors enhance the increasing IL-6 level before sleep that enables the body to defend against infections at night. The sleep disturbances lead to the alterations in the effector systems that responsible for the regulation of the immune system which in turn causes abnormal increments in the inflammatory response. As the over-activation of the immune system that occurs due to robust inflammatory response considered the most important cause of death in COVID-19 disease, we can speculate the importance of sufficient regular sleep in the war against this infection. Minimizing the adverse effect of inflammation on the body owning cells and organ functions since the disturbance of sleep may lead to negative effects and maladjustments of immune response that may lead to increase the severity of infections and subsequent death. So we focused in this article review on the importance of sleeping quality and regularity in the regulation and optimizing of the body immune responses against infections.

Key word: Sleep, Immune system, Covid-19

Dr. Guhsoon Ismael
Süleyman Demirel Üniversitesi Tıp Fakültesi, Fizyoloji Anabilim Dalı Çünür, Isparta
Tel: 0246 211 33 10 E mail: guhsooni@gmail.com Fax: +90 246 2371165

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1. Introduction

In December 2019 in China's city called Wuhan, severe acute respiratory distress syndrome coronavirus (SARS-CoV) new generation was first identified and named as SARS-CoV-2 (1). This virus identified as a novel coronavirus (nCoV) and formaly named by world health organization as 2019 nCoV at 7 January 2020 (2).

2. What Is Coronaviruses?

Coronaviruses are non-segmented, enveloped, positive-sense single-stranded RNA virus genomes. It is largest known viral RNA genome because it's size about 26 - 32 kilo bases. The virion has a nucleocapsid contain genomic RNA and phosphorylated nucleocapsid (N) protein that located in phospholipid bilayers and coated by 2 different types of spike proteins, one of them the spike glycoprotein trimmer (S) that can be found in all CoVs, and the other hem-agglutinin esterase (HE) which present in some CoVs. The envelope (E) protein and the membrane (M) protein (a type III trans-membrane glycoprotein) are found among S proteins in viral coat.

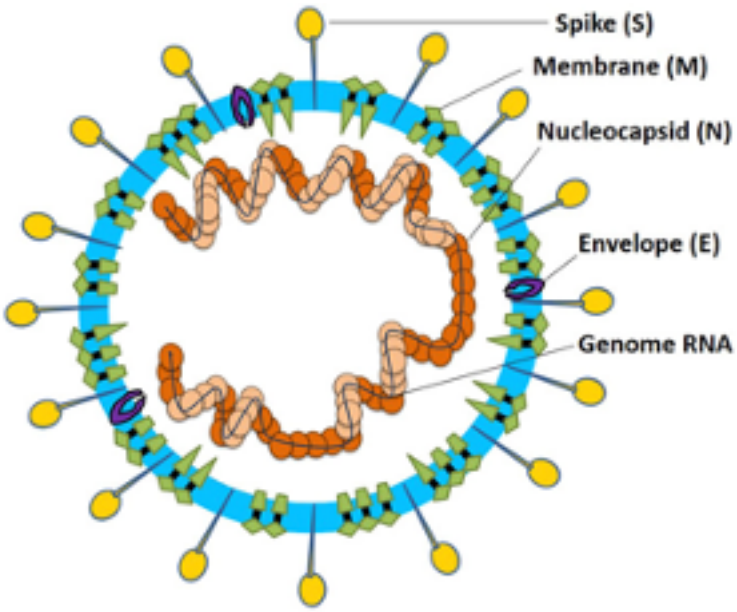

Fig.1. Schematic structure of the coronavirus (3).

Genotypically and serologically the coronavirus subfamily divided into 4 generations; α, β, ɣ, and δ CoVs. Human coronavirus infections are caused by α and β CoVs. The infections with these viruses are generally associated with upper respiratory tract infections, that leading to the signs and symptoms usually include headache, cough and fever; however, lower respiratory tract infections may also be occurred (3). Depending on the degree of infection and the body immune response of infected persons this infection can cause a disease range from mild asymptomatic to sever life threatening disease.

2. Effects of Sleep on Immune Response

Today it is clearly known that sleep is one of most important factor to maintain psychological and physiological health. Sufficient regular sleep is essential for continuation and potentiation the functions of different body organs and systems. Immune system is one of body systems that affected by sleeping regulated itself depending on circadian rhythm. Sleep has essential role in regulation of the immune functions by changing the physiological systems that affect the distribution of immune cells and the expression of inflammatory cytokines (4). The cells that contribute in the immune response are divided into nonspecific immune cells for example, neutrophils, monocytes, natural killer (NK) cells, and the specific immune cells for example, T and B lymphocytes. Under regular sleep-wake conditions, depending on the cell type, immune cells exhibit robust diurnal rhythms with the night or daytime maximum (5). Cortisol that causes up-regulation of the chemokine receptor CXCR4 regulates rhythms of white blood cells (WBC) with a peak count at night, like naive T helper (Th) cells, and as a result, enhance retention of these cells to the bone marrow (6). Furthermore, epinephrine that coordinate the rhythms of WBCs

with a peak count during the daytime, like cytotoxic NK cells, will promote releasing of these cells from marginal pool by prompt inhibition of adhesive fractalkine receptors (CX3CR1) signaling (6, 7). The redistributions of naive and central memory T cells to the bone marrow that controlled by cortisol during the day was interpreted as a mechanism to pause adaptive immune responses and to prevent cortisols apoptotic effects on these cells during stress. On other hand, during daytime the adrenaline act to increase circulating cytotoxic effector cells that in turn thought to support immediate effector immune defense against tissue damage and infections which mostly happens during the active period (8). By maintaining a stable rhythm for epinephrine and cortisol, sleep can strengthen these counteract leukocyte rhythms. On top of the circadian rhythm, it's shown that during night sleep, lymphocytes, monocytes, and NK-cell counts are markedly decrease (5, 9). The reductions in cell count of monocytes, lymphocytes, and NK cells mostly due to enhancing effects of sleep on "silence period" in catecholamine release which likely to contribute to enhancing the margination of these cells during sleep. Some studies show that circadian T-cell count in the circulation run in parallel with the lymph nodes contents of these cells with a peak count at rest period (10, 11). Several animal and human data show that during nocturnal sleep low level of lymphocyte count in efferent lymphatic vessels (in comparison with their level during daytime waking) was associated with an aggregation of lymphocytes in lymph nodes during this period (12, 13). So, we can speculate that the nocturnal sleep-associated low cortisol levels may constitute the primary cause of releasing of naive Th cells from bone marrow, and thereby, normal sleep can ultimately assist the aggregation of these cells in lymph nodes and as a result, facilitate the meeting of antigen-presenting cells (APC) and antigens (7), so the sleep facilitates the initiation of adaptive immune responses. Cortisol is a hormone that secreted from adrenal gland and has a fundamental role in the coordination of immune responses. It's found that it reduce or prevent releasing of substances that cause inflammation in the body , .As it inhibit production of interleukin (IL)-12, interferon (IFN)-gamma, IFN-alpha, and tumor-necrosis-factor (TNF)-alpha by APCs and Th1 cells, on the other hand cortisol up regulates IL-13, IL-10, and IL-4 by Th2 cells. This results in a shift toward a Th2 immune response rather than general immunosuppression. The induction of the stress system that occurs in case of infection will lead to an increase in cortisol level this will serve as a protective mechanism that prevent the over activation of the inflammatory responses (14). Although the regularity and quantity of sleep is essential to maintain general health it is important to refer that sleep quality also affects our physiological and psychological functions. Sleep, as determined by electroencephalogram, is composed of two phases; non rapid eye movement (NREM) and rapid eye movement (REM). Sleep in the past also divided into; N1, N2, and N3 or slow-wave sleep (SWS) (4), which is predominant in the early stage of sleep and is responsible for getting restfulness during sleep. It is found that getting deep sleep (N3 sleep) is very important to restore many body functions as detoxification of brain, physical recovery, maintain the metabolic balance and energizing of the immune system (15). Some studies suggest that different sleep stages may influence the activities of cytokines, so during early stage of sleep when SWS is predominant there is increasing in inflammatory cytokines while there is a high level of IL-6 and its receptor during later stages of sleep with the dominance of REM sleep. In addition, the amount of REM sleep would affect the level of a toll like receptor 4 - stimulated monocyte production of IL-6 in the morning (16). Interestingly, the amount and depth of SWS have a substantial role in the initiating adaptive immune response and memory T cells, thereby it assist eradication of different pathogens (17). From previously mentioned we can suggest that sleep might serve to support the organized and

balanced adaptation of our bodies to the immunological challenges and prepare our immune systems to optimize its function to get rid of pathogens and tumor cells. This enables us to evaluate the importance of sleep quality, quantity, and regularity in supporting our balanced immune defense, since the COVID 19 disease-associated complications and threatening occurs due to under or over- activation of the immune system. In addition to the importance of natural immunity in defensing against SARS CoV-2 infection to avoid respiratory and other multiple organ long- term complications that occur due to extreme inflammatory system activation named cytokine storm.

3. Sleep regulatory effect on anti and Pro-inflammatory mechanisms

By the coordination of distribution of immune cells in the human body and by promoting the production of antiviral cytokines, regular nocturnal sleep, jointly with circadian factors, consolidate the adaptive immune responses to viral infections. During nighttime sleep, T cells and APCs move from the circulation and aggregate in lymphoid tissue (9). Increasingly, sleep activate T cells to produce more IL-2 and IFN-γ that in turn provocate activation of this cell type, and dendritic cells and monocytes to produce more IL-12 which has a critical role in enhancing Th1 cell-type immune responses (7, 18). At nighttime sleep, there is shifting to Th1 cell-type immune responses, and this shifting thought to be related to sleep which occurs due to down-regulation of anti-inflammatory cytokine IL-10 expression in monocytes at the same time up-regulation of IFN-γ expression in T cells (18, 19). Interestingly, later studies revealed that during sleep the mechanisms of immune defense are clearly improved (16). By the potential and synchronized aggregation and maturation of APCs in lymphoid tissues, the variability of T cell receptors that are available to participate in immune responses thought to be enhanced by sleep (19, 20). Moreover, decreased levels of catecholamines and cortisol, in addition to increased levels of prolactin and growth hormone are possibly responsible for the suppressing and augmenting effects of sleep on anti- and pro-inflammatory cytokines, respectively (21, 22). This particular endocrine effects mainly happen through the early stage of night sleep simultaneously with (SWS) this referred to the importance of SWS in the coordination of immune function. Furthermore, as previously mentioned, the sleep by its enhancing effect on IL-12 expression and the fundamental role of APC-derived IL-12 in the activation of T cell's type-1 cytokine profile, this can suggest the association between SWS and the shifting of type-1/type-2 cytokine balance toward type-1 activity (23, 24).

In summary, when destabilizing influences (immune-suppressants, stress) reach a minimum at night, nocturnal sleep together with circadian rhythm enhances starting the adaptive immune responses regionally in the peripheral lymphatic tissues, this occur by promoting homing the Th cells and releasing the endogenous adjuvants which are mostly pro-inflammatory and potentially damaging. So strong anti-inflammatory signals limit these processes to specific periods and suppress it during daytime waking. In contrast, along wakening in the day, activity and stress enhance cytotoxic effector functions immediately against tumor cells and invading pathogens (25, 26). This systemic organization of immune defense in time and space represents the physiological basis for the commonly held belief that sleep consolidate the immune defenses (27). A recent study shows that the persons who slept for short periods for weeks are more susceptible to the common cold after exposing to rhinovirus infection (28).

4. Immune Response to Coronaviruses

After entry of viral particles to the upper respiratory tract through the nose, eyes or mouth, breathing will carry some particles into the lower parts of the lungs where the coronavirus spike proteins are found. These proteins acting as a key lock into epithelial cells those line the airways and alveoli. SARS-CoV2 had the ability to remain undiagnosed for the long

time more than those of many coronaviruses and its spike proteins can enter to lung cells by unlocking its ACE2 proteins. As they enter these cells the coronaviruses steal the cell's machinery, multiply, replicate and infect adjacent cells. On the surface of the viruses, there is a tell-tale signature called antigens, these antigens are responsible for activation of the immune systems with the enhancing of certain types of leukocytes to release cytokines and subsequent production of antibodies that all together lead to destroying viral particles (29). From the cytokines that have the most potent antiviral defense are type I/III-IFNs as well as TNF-α, IL-18, IL-6, and IL-1 also have the role in enhancing antiviral program in the target cells and potentiation of the adaptive immune responses. Early and proper localization of IFN-I can effectively restrict CoV infections (30, 31). In vitro, some evidence showing that SARS-CoV2 is sensitive to IFN-I/ III pretreatment (32, 33). Anyway, the specific IFN-stimulated genes (ISGs) that responsible for mediating these protective actions are till now under discussion. Some studies show that the lymphocyte antigen-6 complex locus-E interferes with membrane fusions those mediated by SARS-CoV2 spike (S) proteins (34, 35). Possibly, the IFN-induced trans-membrane family proteins also prevents entrance of SARS-CoV2 (36). Altogether, as a part of innate immunity NK cell also had an important protective roles against SARS-CoV2. The activations of CD56 CD16+ NK cells may induced when these cells recognize the Fc receptors of immunoglobulin1 (IgG1) and IgG3 antibodies that released and bind to the infected cells surface antigens or to extracellular virions during infections with SARS-CoV-2 (37, 38). This interaction will lead to lysis of infected cell through antibody-mediated cellular cytotoxicity and induce the NK cells to produce cytokines (39). The cytotoxicity of NK cells can be regulated by their expression of activating and inhibitory receptors and activation of these cells during SARS-CoV2 infection although it is very important in limiting the infections but also may lead to cytokine storm in acute respiratory distress syndrome (37). T-cells have a very important role in the war against virus infections since CD4 T-cells support the B-cells to produce immunoglobulins and coordinate other immune cells responsiveness, while CD8 T-cells minimize the virus load by lysing the virus-infected cells. Some evidences show that, in moderate and severe cases of COVID 19, there is a reduction in circulating lymphocyte count with markedly dropped CD4 and CD8 T-cells counts (40- 43). The extent of this reduction in lymphocyte count found to be more evident in CD8 T-cells in intensive care units patients and correlate with the severity and mortality associated with COVID-19 disease (44- 47). In contrast in mild COVID 19 cases, there is a normal or slight increase T lymphocyte count (48). There are many mechanisms that explain these findings, one of them; the circulating lymphocyte level is shown to be affected by the inflammatory cytokine environment. İn fact, the reduction in lymphocyte counts appeared related to IL-10, IL-6, and TNF-α levels whereas patients during convalescence period show restoring its normal lymphocyte counts along with reducing pro-inflammatory cytokine levels (49, 50). Some cytokines like TNF-α and IFN-I may enhance redistribution of T cells to the lymphoid tissue and increase their attachments to endothelium as a result, decreasing their circulating levels (51). In addition, over activation of T cells in severe cases of COVID-19, probably make their to be exhausted as they are continuously express inhibitory markers and generally their functions and cytotoxicity have been reduced. While the convalescent patients found to have increased level of follicular helper CD4 T cells and the effector molecules (such as granzyme A, granzyme B, and perforin) level also elevated (52). Despite the important effects of T-cells, maladjusted T-cell responses may lead to immunopathology (40, 53- 57). The humoral immune responses are essential for eradication of viral infections and constitutes an important portion of a memory response. SARS, CoV-2 trigger strong B-cell responses that proved by identifying

virus-specific IgA, IgG, IgM, and neutralizing IgG antibodies within a few days after infection (58). During the acute and convalescent phases of COVID 19 disease plasma cells form and continuously release immunoglobulins even after subsiding of infection and thereby establishing the serological memory. Longterm protection against reinfection has been achieved when long-lived memory B cells generate new high-affinity plasma cells (37). The extent of memory responses not yet be known but some studies emphasize that IgG specific to COVID 19 trimeric spike protein can be identified up to 2 months from the appearing of symptoms after that its titer begun to decrease (59).

In general, during viral infections, host factors trigger the immune responses against these viruses and when this immune response becomes out of control, it may lead to damaging of lung tissue, impair its function, and reduce its capacity. Chemotactic factors are fundamental in propagation of immune response against viral infection, given their regulatory effects in vasodilatations and migration of WBCs in the affected lungs. For this, spectral changes in chemotactic factors may result in maladjustment of immune response. Immune insufficiency or misdirection may provocate virus replication and cause tissue damage. on the other hand, overactive immune responses will lead to immunopathology (29).

Conclusion

Memory T cells, constitute an important component of the immune system, provide immune memory and, consequently, protection against infections is permanent. The formation of memory cells will be the most important tool of immunity in COVID19, which is new to our lives, and because the SARS-CoV-2 outbreak has recently emerged it is not yet possible to identify the extent and nature of long-term memory response. For this, a strong immune system is needed when the virus is taken into the body. In addition to the importance of organized, balanced immune response that can eradicate this infection even without appearing of symptoms to avoid the complications arise due to under or over activation of the immune response. So one of the most important tools to consolidate and coordinate our immune systems whether in terms of timing or determining the type and strength of its responses is sleep. Therefore, in this article, we focused on the role of healthy, regular, sufficient sleep in addition to the role of sleep quality in organizing and optimizing the immune function that enables the patients to recover from this infection without any long-term complications.

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