Impact of Sleep, Sleep Loss and Recovery Sleep on Immunity

Uykunun, Uyku Yoksunluğunun ve Toparlanma Uykusunun Bağışıklık Üzerindeki Etkileri

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ABSTRACT

Sleep is a naturally, restorative process, characterized by altered consciousness. Normal sleep and circadian system act as important physiological regulator on immune functions, these regulation mediated by neurotransmitters, hormones and cytokines signals which support relation between the immune system and central nervous system. Various immune parameters in peripheral circulation show Diurnal changes over the day, these changes under effect of the 2 main stress systems, the sympathetic nervous system(SNS) and the hypothalamo pituitary adrenal (HPA) axis, changes occurring in immune parameters over the 24-h during the sleep–wake cycle categorized to nocturnal Proinflammatory and daytime anti-inflammatory activity. In addition to its effects on cognitive function, compelling evidence links sleep loss to alterations in the neuroendocrine, immune and inflammatory systems. sleep deprivation either in partial sleep deprivation or total sleep deprivation as a stressful status enhances the adrenergic tons that affects innate and adaptive immunity, with increasing susceptibility to infections and immune-related diseases. Several studies have shown negative effects of sleep deprivation on all functions of the body and its effect on the immune system this review aims to explain the changes occurring in immune parameters and inflammatory cytokines over the 24-h during the normal sleep–wake cycle and during sleep disturbance and benefit of sleep recovery(napping) to recede these physiological changes that resulting from sleep deprivation.

Key Words : Sleep, immunity sleep deprivation, napping, proinflammatory cytokines, anti-inflammatory cytokines

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ÖZET

Uyku değişen bilinç durumlarıyla karakterize onarıcı ve doğal bir süreçtir. Uyku ve sirkadiyen sistem bağışıklık sistemi fonksiyonları üzerinde güçlü bir düzenleyici etkiye sahiptir. Bu etki bağışıklık sistemi ve merkezi sinir sistemi arasındaki ilişkiyi destekleyen nörotransmitterler, hormonlar ve sitokinler aracılığıyla oluşturulur. Çeşitli bağışıklık sistemi parametreleri gün içerisinde kan dolaşımında diurnal değişiklikler göstermektedir. Bu değişiklikler hipotalamus-hipofiz-adrenal (HPA) aks ve sempatik sinir sisteminin (SNS) kontrolündedir. Gün boyunca uyku-uyanıklık döngüsünde, bağışıklık sistemi parametrelerinde gerçekleşen değişiklikler, gece pro-inflamatuar etki gündüz ise anti-inflamatuar etki olarak ortaya çıkmaktadır. Uyku eksikliği bilişsel işlev üzerindeki etkilerine ek olarak, nöroendokrin, bağışıklık ve inflamatuar sistemdeki değişikliklere de yol açmaktadır. Kısmi ya da tam uyku yoksunluğu stresli bir durum olarak sempatik tonusu arttırmasıyla doğal ve kazanılmış bağışıklığı etkilemektedir. Bu durum enfeksiyonlara yatkınlığa ve bağışıklık sistemiyle ilişkili hastalıklarda artışa sebep olmaktadır. Çeşitli araştırmalar, uyku yoksunluğunun vücudun tüm işlevleri üzerindeki olumsuz etkilerini ve bağışıklık sistemi üzerindeki etkilerini göstermiştir. Bu derleme gün içerisinde normal uyku-uyanıklık dönemi ya da uyku bozukluğu sırasında, bağışıklık sistemi parametreleri ve inflamatuar sitokinlerdeki değişiklikleri; uyku açığını kapatmak için yapılan toparlanma uykusunun, uyku yoksunluğunun sebep olduğu fizyolojik değişiklikleri geriletme üzerindeki faydalarını açıklamayı amaçlamaktadır.

Anahtar Sözcükler: Uyku, bağışıklık, uyku yoksunluğu, toparlanma uykusu, proinflamatuar sitokinler, anti-inflamatuar sitokinler

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INTRODUCTION

Sleep is a normal physiological condition, defined as a state of Unconsciousness, that is important for general health in humans (1). There are two important different mechanisms in regulation of normal sleep–wake cycle, the homeostatic drive for sleep and the circadian system. The Benefits of sleep in humans seems to have multiple functions, starting from metabolic to neurocognitive (2). Short or disturbed sleep associated with alteration in normal physiological function and effects by several ways for example, cardiovascular risk factor (3), increasing the risk of type 2 diabetes (4), upper respiratory tract infection(5), and all –cause mortality (6).

Normal sleep associated with circadian system that regulate periodic changes in normal physiological function through 24 hours as energy metabolism, cognitive and behavioral parameters (7). The similarity between the immune system and the central nervous system is the ability to generate memory as response to external stimuli (8). Disturbance in the normal immune responses and stimulation of inflammatory cytokines one of the consequences of sleep disturbance (9), that leads to alterations of natural and cellular immune function (10). Some of the physiological changes resulting from sleep deprivation is simple and recede by sleep recovery (11).

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Relationship between regular sleep–wake cycle and changes in number and performance of immune cells

Sleep-wake cycle is important for normal physical and mental activity, as well as in regulation of cellular immune activation like leukocyte numbers, function and cytokine production(8). There is alteration in immune parameters over the 24h day in human blood. These fluctuations under effect of circadian system and sleep and achieved by hormonal signals that's very effective in inducing changes in leukocyte traffic. The circadian process driven by suprachiasmatic nuclei (SCN) in hypothalamus, that responsible for generation of endogenous clock pulses in several cells all over the body, depending on exogenous stimuli (12) according to that these changes can be categorized into two classes:

Changes in immune parameters over the 24-h of the day

Activity of the immune system under the control of hormones, neurotransmitters and neuropeptides. The influence of neuro-endocrine signals on proliferation of immune cells or the last effector mechanism as production of antibodies or the activity of cytotoxic cells were estimated in previous studies (13, 14), Each of the main stress system hypothalamo pituitary adrenal(HPA) axis and the sympathetic nervous system(SNS), during nocturnal sleep period their activity inhibited, associated with suppression in cortisol and catecholamines in circulation (13, 15), In normal nocturnal sleep cytokine production will support towards type1 dominance and therefore reinforce proinflammatory activity and showed that the nocturnal prevalence of type1 cytokines shifted towards type2 cytokines by acute experimental sleep deprivation that's mean sleep leads to direct suppression of IL-10 production as anti-inflammatory cytokines (16). The pituitary growth hormone (GH), prolactin and the pineal hormone melatonin that responsible about cell growth, differentiation and restoration that's during sleep show an increase in their blood levels (17), that promote activation of immune cells and enhance production of pro-inflammatory cytokines as interleukin IL-12,tumor necrotic factor alpha TNF- α (18-20). Where these proinflammatory cytokines found to be peak throughout nocturnal sleep (21, 22). Production of tumor necrotic factor and interleukin 12 dependent on sleep, but production of IL-6 not related to Sleep-wake cycle (12). The level of IL-6 reaches its highest rate after 2 hours of sleep onset (23). During slow wave sleep maximum pro-inflammatory and Th1 cytokines observed (24). Cytokine production throughout the rest time are often explained by shift toward raised release of hormones with Proinflammatory actions (15, 25, 26).

During sleep maximum differentiation of immune cells

Regulation of immune function by sleep mainly through fostering adaptive immune responses (12). In regular sleep-wake cycle leukocytes demonstrate strong daily rhythm, Reach the maximum during night or throughout the day, depending on the cell (27). Immune cells reaches peak rate of differentiation in blood and lymph nodes during the sleep period(8).There is evidence support that throughout nocturnal sleep lymphocytes assemble in the lymph nodes (28), accumulation of lymphocytes in lymph nodes, suggesting that there are a Compatibility and balance between lymphatic compartments and the peripheral circulation (29). Cortisol facilitates redistribution of Leukocytes to the bone marrow by upregulation of the chemokine receptor CXCR4 (30). Throughout the rest time(sleep) CXCR4+ lymphocyte sent out from the bone marrow to the lymph nodes when HPA and cortisol activity decreased wherever they will start adaptive immune reactions (8). In addition to increase blood levels of growth hormone GH and decrease activity of sympathetic nervous system SNS during sleep that lead to accumulation of lymphocytes in lymph nodes (26, 31).

During wake period Cytotoxic function of immune cells

There's a further increase in the stress hormones during awakening, These stress hormones inhibit the pro-inflammatory response induced throughout nocturnal sleep and have anti-inflammatory effect (15, 32).

The natural killer (NK) cell of innate immunity considered as simple homogeneous and undiscriminating in comparison with the B and T cells of adaptive immunity. They participate in the early defense against intracellular pathogens and tumor cells (33). These cells increase in blood throughout daytime and have high expression of beta 2 –adrenoceptor (34). They have ability to rapidly eliminate infected, mutated or cancerous cells (35). When epinephrine Stimulate beta 2-adrenergic receptor in natural killer cells will increase their enumeration in circulation by enhancement their release from many compartments (36). Sympathetic nervous system has influence on neutrophils, pro-inflammatory monocytes that causes mobilization of these cells into the circulation. These rhythms continuous even after conditions of 24-h wakefulness. Rather, effects of sleep on immune cells change their activity and their level in blood, sleep as compared with continuous wakefulness shown to decrease number of cells in blood during the night where throughout next daytime this reduction is recompense by elevated cell numbers for most of the lymphocyte subsets (37). This is for T helper(Th) cells, cytotoxic T lymphocytes CTL, activated T cells as well as NK cells and monocyte.While there is no evidence of compensation in B lymphocyte numbers throughout the subsequent day. Sleep selectively lead to alteration in some leukocyte but not all, specifically decrease certain some of the monocytes subtype and natural killer cells(8). Releasing and redistribution of the immune cells to various compartments throughout regular sleep leads to attenuation in leukocyte numbers (38, 39). That's why many studies depend on cytokine production and cell proliferation rather than cell count to evaluate functional aspects of immune cells.

Sleep deprivation a general state of stress associated with increase the adrenergic tons. The hypothalamic pituitary adrenal axis(HPA axis)(glucocorticoids - GC) and sympathetic nervous system (adrenaline and noradrenalin) the main stress mediator effects on immunoinflammatory system (40). Stimulation of α- and β- adrenergic receptors of Immune cells by adrenergic and noradrenergic innervation hormones enhanced during sleep deprivation (41, 42). Natural killer cells at first will raise their count in peripheral circulation when beta 2-adrenergic receptor stimulated their release from many compartments (36), followed by decreasing of their cytotoxic effect against tumor cells (43) as well as increase release of neutrophils, pro-inflammatory monocytes into the circulation by the sympathetic nervous system. So sleep deprivation as stressful state that coordinate activity of the innate system like natural killer and natural killer T cells by upregulate of blood levels of glucocorticoids and adrenaline (8).

Relation between sleep and immunological memory

The immune system as well as the neurobehavioral system responds to external stimuli and confers these to a memory (44). The similarities between immune and the central nervous system they each when exposed to exogenous stimuli produce memory in a very multiple process (45). The stages of immunologic memory include, the encoding part, that explained by the uptake of the antigen by antigen presenting cell APC, consolidation part characterized by generation of the immune related connection between T cell and antigen presenting cell (46), and the recall part that defined as the expedited immune reaction upon re-encounter of the antigen, Since sleep mainly have role in reinforcing the consolidation of immunological memory formation because encoding and recall phases occurs throughout waking time (47).

Studies about consequence of sleep deprivation in humans include protocol of total sleep deprivation for one or 2 days, acute sleep restriction 25%–50% of a normal sleep 8 h during a single night, 50%–75% of a normal 8 h night's sleep for several successive nights considered as chronic sleep restriction SR (11).

Effects of partial sleep deprivation on immunological function

Partial sleep deprivation is more common than total sleep deprivation(TSD), the evidence demonstrated that decreased NK cell activity as well as a decreased ratio of NK cells in blood during sleep deprivation of the late-night and early night PSD, in addition, decreased production of IL-2 by T-lymphocyte, and decreased activity of IL-2-induced lymphokine activated killer cells (48). On the first day after sleep deprivation, they proved significant changes in HLA-DR and the mitogen proliferation assay (49). HLA-DR present on monocytes and B cells as antigen-presenting cells as an antigen presentation molecule, the alteration in HLA-DR expression leading to induction of anti-inflammatory or immunosuppressive signals and decrease capability of monocytes to stimulate T-cell proliferation (50), In partial sleep deprivation there were transiently impaired mitogen proliferation, decreased major histocompatibility complex class II molecule(HLA-DR), variations in CD4 and CD8 and the upregulate CD14, that increase tendency to respiratory tract infections (49), There are data show that natural immune reactions that measured by natural killer activity and T cell cytokine production decreased even after modest disturbance of sleep associated with inhibition in a stimulated IL-2 production (10).

Effects of sleep restriction (SR) on immunity

There were evidences of an increase in blood leukocytes, after one night of sleep restriction to 2 h, In the next day after recovery sleep white blood cells mainly neutrophil counts remained at a similar high grade (51). During chronic sleep restriction, where they allowed 4 h of sleep, additionally resulted in enhanced number of leukocyte in the next day after nights of sleep restriction (52).

Total sleep deprivation(TSD) and immunity

Elimination of normal sleep for 24 hours in humans considered as Total sleep deprivation (TSD), after TSD there were evidence reported that no important changes within the variety of leukocytes, monocytes, or B-lymphocytes, The increase was mainly observed in interferon production per lymphocyte (48). TSD associated with a decrease in blood lymphocyte DNA synthesis in-vitro, that's suggested that TSD could reduced cell-mediated immunity and alter some parts of host defense (53). In study of total sleep deprivation, they significantly showed raised counts of leukocytes, NK cells, NK cell activity and monocytes, and reduction in number of CD4, and CD57 lymphocytes after 1 night of total sleep deprivation, No statistically important changes in B-lymphocytes, T-lymphocytes, suppressor cells (CD8), inducer helper cells, inducer suppressor cells, activated T-cells (54). These changes in WBC during TSD are transitory and come back to normal levels after a night of recovery sleep.

Inflammatory marker during sleep deprivation

Acute exposure to fatigue, exhaustion, tissue damage or infection will result to release inflammatory cytokines, and this reaction is adaptive; while chronic disturbance in inflammatory markers causing health problems as cardiovascular and endocrine diseases (55),There were multiple studies used to evaluate the consequences of prolonged sleep loss, They reported that a rise in IL-6 and also the soluble TNF-α receptor result from 4 days without sleep (56),and after sleep restriction for 10 days Plasma concentrations of IL-6 were additionally increased (57). While during total SD there were evidences of increase expression of pro-inflammatory cytokines, like IL-1β and IL-6, throughout the day following TSD (58), and elevated blood level of C-reactive protein CRP (59). After acute sleep restriction SR of one night and after chronic SR, many studies have reported that there were alterations in blood inflammatory cytokine,tumor necrotic factor alpha TNF-α and interleukin IL-6 showed significant increase in the subsequent day immediately after SR (60). When sleep allowed throughout only the second part of the night, normal nocturnal increase in IL-6 levels delayed until sleep onset (61). Reinforcement of adaptive immune responses and support their cytokine production could be during SWS, whereas responses of innate immunity and enhancement of pro-inflammatory signals without effectively counter-regulated by anti-inflammatory agents are resulting from prolonged sleep loss, because after prolonged sleep loss there is transient and simple elevation in the anti-inflammatory hormone cortisol, and differs from that elicited throughout healthy slow wave sleep SWS (14), that's why sleep loss is a state of increase the pro-inflammatory signals, There were studies showed that after 6 days of restricted sleep normal immune activity that generated after vaccination against influenza virus decreased (62), that is mean chronic sleep loss in addition to causing augmentation in inflammatory markers also promote immunodeficiency state and increased susceptibility to infections (63).
In addition when normal nocturnal sleep makes an inhibiting effect on leukocyte subsets by decreasing catecholamine and cortisol release, during PSD stress system mediators over-expressed resulting in increase in leukocyte mobilization to the circadian influences (11), While TSD leading to increase cortisol levels in the evening, that in normal condition cortisol at its nadir (64).

Benefits of napping after recovery from sleep deprivation

Napping is an important for enhancing performance (65, 66). The changes in natural and cellular immune function after sleep deprivation are transient and come back to basal levels following a night of recovery sleep, rebound increases of slow wave sleep underlie recovery of immunity (10), after sleep deprivation there are alteration in the immune and inflammatory signal which increase risk of cardiovascular diseases (11), after recovery from total sleep deprivation or acute sleep restriction these signal remained significantly more than normal levels (51), Polysomnography analysis indicated that a short episode of SWS during a nap can decrease the homeostatic pressure of sleep deprivation (64, 67), Neutrophil count which reflect the leukocyte count in healthy humans, Its importance even without an acute medical event. High number of leukocytes more than normal considered as biomarker of inflammatory processes and associated with increases risk of all-cause mortality (68). Midday nap before recovery sleep amended alertness and regress of leukocyte mainly neutrophil to normal levels (51),increases cortisol release stimulate bone marrow production, and demarginating of neutrophils (69), Epinephrine also mobilizes neutrophils from the marginal pool more faster than cortisol (69, 70), During nap, SWS could inhibit the hypothalamic pituitary adrenal axis activity that elevated as result from sleep deprivation (58, 71, 72), In previous study to evaluate consequences of sleep deprivation on inflammatory markers during total sleep deprivation, then followed by 2 h sleep during a midday, with 1h of SWS resulting in retreat the impact of 1 night of total SD on pro-inflammatory cytokine IL-6 (58).

In summary interactions between the central nervous system and neuroendocrine reflecting on immune functions leads to increases in neutrophils levels in blood and IL-6 as results from sleep loss. These alterations might reflect increases receptivity for sleep,and balanced by napping strategies.

CONCLUSION

Sleep is important for supporting the immune system, and beside circadian system considered as regulator for immune function, and disturbance in this physiological process leads to general state of stress result in immunodeficiency with an increase susceptibility to infections, as well as increase in inflammatory markers that contribute to health problems including cardiovascular diseases, These changes retreated after the short episode of SWS during a nap.

Conflict of interest

No conflict of interest was declared by the authors.

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