DOI 10.1007/s11055-021-01113-2
Neuroscience and Behavioral Physiology, Vol. 51, No. 5, June, 2021

Sleep and Immunity

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Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 120, No. 9, Iss. 2, pp. 6–12, September, 2020. Original article received August 19, 2020; Accepted September 4, 2020.

This review presents data on changes in measures of innate and adaptive immunity associated with the state of sleep. The effects of restricted and prolonged sleep duration on measures of morbidity, mortality, and susceptibility to infectious diseases and the effects of vaccination are discussed. Measures of immunity in patients with insomnia and changes on the background of correction of sleep impairments are presented.

Keywords: sleep, immunity, cytokines, insomnia, hypnotics, melatonin.

Organization of the Immune System. The function of the body's immune system is to maintain its integrity and biological individuality by recognizing and eliminating foreign substances and cells. This system is mediated by the existence of protective barriers between the surrounding environment and the body's internal milieu, as well as special cellular and humoral mechanisms countering infections. The integrity of the skin and epithelium of the mucous membranes and the presence upon them of antimicrobial proteins and complement factors provide protection against penetration by foreign agents. If invasion into the body occurs, innate and adaptive immunity factors come into play. The innate immunity system includes granulocytes (neutrophils, eosinophils, basophils, monocytes/tissue macrophages, dendritic cells, and unspecialized lymphocytes, i.e., natural killer (NK) cells). Innate immunity cells can neutralize pathogens independently of type as defined by the most conserved properties – the presence of typical molecular structures (for example, lipopolysaccharides). On penetration of an antigen into tissues, its recognition by macrophages or dendritic cells is followed by induction of a nonspecific reaction, resulting in synthesis of NF-ϰB, which induces inflammation and the production of acute-phase cytokines, interferons, prostaglandins, and chemotactic factors attracting leukocytes. Antigen is destroyed both directly via phagocytosis by phagocytes (macrophages, neutrophils, monocytes) and via damage by cytokines and complement system proteins.

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Adaptive immunity cells include dendritic cells (myeloid- or lymphoid-type cells located in the tissues) and T and B lymphocytes. Adaptive immunity is supported by the ability of cells (dendritic cells) to extract antigenic features specific to the corresponding pathogen and present them to other cells (T helpers or CD4 cells), and then on to T killer cells (CD8 cells), which begin to "hunt" for agents with the same properties, or B cells, which synthesize enormous quantities of protein substances (antibodies) which tag the foreign body and disrupt its functioning.

Immunocompetent cells arise in the primary lymphoid organs – the thymus and red bone marrow. After contact with an antigen, dendritic cells migrate to secondary lymphoid organs(lymph nodes, spleen, locally associated lymphoid tissue in organs), where they transmit information to CD4 cells, training them – from the "naïve" state they become specialized – to detect a particular antigen. These cells assist macrophages, CD8 cells, and B cells to eliminate the pathogen.

Immune cells interact with each other using mediators, the most important of which are cytokines, and by direct contact via surface molecules. Cytokines released in the framework of an adaptive immune response also have the ability to produce direct damage to foreign agents and trigger the production of acute-phase proteins. After eliminating antigen, most specialized T and B cells die, the remainder providing "immune memory" – ready for repeat encounters with the antigen [1, 2].

Changes in Immunity during Sleep. The first attempts to answer the question of the possible influence of the state of sleep on immunity were made in studies evaluating

the numbers of basic immunocompetent cells in the states of sleep and waking and in conditions of sleep deprivation. Thus, for example, in 1997, Born et al. [3] reported studies of the effects of sleep or prolonged night-time waking in people on the total number of leukocytes and the composition of different lymphocyte populations. These authors observed that as compared with sleep deprivation, subsequent nocturnal sleep was accompanied by a decrease in the total number of leukocytes and the numbers of NK cells and various lymphocyte populations. Numerous studies reported by other authors [1] have demonstrated reductions in the total number of leukocytes during sleep as compared with sleep deprivation. This supports the theory that these changes are not due to circadian oscillations in the number of immunocompetent cells but are directly associated with sleep. The authors of this study explained the reduction in the number of leukocytes in peripheral blood not in terms of changes in leukocyte production during sleep, as some investigations found these effects 3 h after going to sleep or even earlier, but in terms of a redistribution of immunocompetent cells from the peripheral bloodstream to the internal organs and lymph nodes. Thus, Ruiz et al., [4] used a model of skin transplantation in mice (used to assess immune graft rejection reactions) and showed that the number of lymphocytes in the lymph nodes and spleen was greater in natural sleep than in sleep deprivation.

Nonetheless, just as many studies have failed to detect significant changes in leukocyte counts towards either increases or decreases. The results of all studies provide evidence at least supporting the notion that the state of sleep does not lead to increased numbers of leukocytes in the peripheral blood [1].

The same can be said about the influence of sleep on the total numbers of monocytes, lymphocytes, and their main subpopulations (B-lymphocytes, CD4 and CD8 T-lymphocytes, NK cells) [1].

The state of sleep has no effect on the number of basophils or eosinophils, and the number of neutrophils can decrease or remain unaltered (but cannot increase) [1].

It can be concluded that the total number of peripheral blood immunocompetent cells does not increase in association with the state of sleep. The observed reductions in some of their subpopulations may be due to migration from the bloodstream to secondary lymphoid organs, such as lymph nodes or the spleen, where animal studies have shown increases in numbers during sleep.

Assessment of the effects of sleep on the functional activity of immunocompetent cells is important. Studies reported by Irwin et al. [5] showed that NK cell activity increased during sleep but decreased on sleep deprivation. However, increases in the duration of sleep deprivation led to onset of recovery of NK cell activity, such that sleep is not an obligate factor for the operation of this branch of the immune system. These facts were obtained in relation to the effects of sleep deprivation on the ability of mononuclear cells (monocytes and lymphocytes) to proliferate – these values decreased in the morning after sleep deprivation, though after a number of such nights the ability to proliferate recovered [1].

Data on the influences of sleep on humoral immunity are also exclusively contradictory. The effects of sleep and its deprivation on the production of interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and IL-1 have received the most study.

IL-1 synthesis starts in response to the introduction of microorganisms or tissue damage. This cytokine is required for the development of local inflammation and mediates the entire set of protective reactions termed the acute-phase response. The acute-phase response includes metabolic rearrangement of the body's activity, with fever reactions, changes in the production of various proteins, and production of acute-phase reactant proteins (the complement system, C-reactive protein (CRP), and others). The main cells producing IL-1 in the body are monocytes and macrophages, as well as cells with a common origin with macrophages [6].

Most studies have shown that IL-1 production decreases during sleep, while during prolonged waking in conditions of sleep deprivation it increases. In prolonged waking, IL-1 receptor antagonist production increases, this evidently being a homeostatic response to the increased IL-1 concentration [1].

IL-6 is the main activator of the synthesis of most acute-phase proteins in the liver (including the best-known "large" acute-phase protein CRP); it also supports the proliferation of antigen-activated B-lymphocytes, with a corresponding increase in the production of antibodies, and increases in T-killer activity. It is synthesized by many cell types involved in initiating and regulating inflammation and the immune response: T-lymphocytes, monocytes/macrophages, fibroblasts, etc. [6].

Both during sleep and in prolonged waking, peripheral blood IL-6 levels, as shown in a number of studies, can change in either direction or remain completely unaltered, which probably speaks against sleep having any effect on its secretion. However, determination of IL-6 concentrations directly within lymphocytes in most investigations reveals reductions during sleep and increases during prolonged waking [1].

TNF-α is a proinflammatory cytokine which influences IL-1 and IL-6 production, inducing the death of cells with intracellular parasites and viruses and activating various types of T-lymphocytes. It is produced by macrophages and T- and B-lymphocytes [6].

Many studies assessing the level of this cytokine have noted decreases in its concentration during sleep and increases during prolonged waking. This applies both to the TNF-α concentration in plasma and that in intracellular fluid, and well as to the level of expression of this protein in the tissues [1].

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 [6].

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 [1].

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 [6].

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 [6].

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 [1].

Some studies have evaluated the proinflammatory/anti-inflammatory cytokine ratio during sleep and on the background of sleep deprivation. Dimitrov et al. [7] found an increase in the TNF/IL-4 ratio in the first half of sleep, changing to the opposite in the second half. Axelsson et al. [8] found a 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.

Thus, assessments of levels of anti-inflammatory cytokines in the state of sleep and the ratio of proinflammatory/anti-inflammatory cytokines demonstrated opposite trends – the level of defense from inflammation was essentially decreased during sleep. Alternatively, there was a pattern of inflammatory/anti-inflammatory activity during sleep: the first half of the night was characterized by dominance of inflammatory and the second by anti-inflammatory changes in the humoral compartment of immunity.

In relation to the influence of sleep on other measures of humoral immunity, such as the level of antibody secretion and the protein concentration in the complement system, data are entirely contradictory [1] and it is even more difficult to draw any definitive conclusions.

Overall, the processes occurring in the immune system during sleep can be represented as follows. The number of cellular elements in the immune response in the bloodstream decreases, evidently reflecting migration of immunocompetent cells to secondary lymphoid organs. This can probably hinder an effective immune response, as the first encounter with antigen occurs in the vascular system. Along with decreases in the total number of immunocompetent cells, their activity (at least that of NK cells and mononuclear cells) in sleep increases. As regards humoral mediators (cytokines), despite the decreases in inflammatory mediator contents during sleep, there is also a decrease in the production of anti-inflammatory cytokines at this time, which leads to a change in the ratio between them towards inflammatory cytokines. This is understandable at least in relation to the first half of sleep. The second half is characterized, conversely, by an anti-inflammatory pattern. In attempting to put these experimental data in practice, it can be suggested that sleep facilitates the development of inflammatory reactions arising in the framework of the immune response.

Measures of Immunity and Sleep Duration. Considering that sleep overall has a restorative function in relation to the immune system, we might expect a reduction in the usual duration of sleep to lead to immune impairments in real conditions, giving excessively low or, conversely, elevated measures of inflammation as compared with the waking state. Population studies have repeatedly demonstrated that insufficient (<6 h) or excessive (>9 h) sleep is associated with an increased risk of cardiovascular events and mortality. Some of these studies evaluated measures of humoral and cellular immunity. A study involving 2500 elderly people over seven years showed that contraction of sleep time to <5 h was associated with a complex increase in the content of proinflammatory substances such as CRP, IL-6, and TNF-α, which the authors believed explained the increased mortality in this subgroup [9]. In another population study following 3000 elderly people for nine years, inflammation markers (IL-6, TNF-α, and CRP), lifestyle, and state of health provided the best explanation of the link between reduced sleep duration and increased mortality [10].

As regards measures of cellular immunity, population studies in short-sleeping (<8 h) adolescents revealed increased numbers of leukocytes, neutrophils, and monocytes, along with increases in certain T-lymphocyte subpopulations [11]. Women with short sleep durations (<7 h) also showed decreased numbers of NK cells [12]. A decrease in telomere length in immunocompetent cells was regarded as a sign of aging of immunity. Studies reported by Jackowska et al. [13] in men sleeping less than 5 h found that telomere length was 6% shorter than in those sleeping 7 h or more.

Similar changes were seen even in a child population, regardless of sex. However, the influence of reduced sleep duration on telomere length might be indirect, as proinflammatory cytokines may themselves have this effect.

There is evidently a relationship between measures of humoral and cellular immunity on the one hand and sleep duration on the other in the general population. Reduction in the usual sleep duration is accompanied by increases in the contents of proinflammatory cytokines and CRP, which in turn increases the risk of developing cardiovascular diseases and mortality.

Sufficient sleep duration can determine susceptibility to infectious diseases. Studies reported by Patel et al. [14] showed that short (<5 h) nocturnal sleep was associated with an elevated (1.7-fold) risk of pneumonia in the next two years or the next few months. Another experiment involving healthy volunteers assessed the probability of contracting acute respiratory viral diseases (ARVD), depending on sleep duration. Young people sleeping <7 h (assessed subjectively) fell ill 2.9 times more frequently than those sleeping ≥8 h [15]. This experiment was subsequently repeated using actigraphy as a method for objective assessment of sleep duration. This yielded less dramatic results – despite the fact that subjects sleeping <5 h fell ill 4.2 times more frequently than those sleeping >7 h, sleep duration in the range 6–7 h was not accompanied by any significant increase in the risk of illness [16]. A relationship between the incidence of infectious diseases (ARVD, influenza, gastritis) and sleep duration was also seen in adolescents.

A model for studies of the effects of sleep on measures of adaptive immunity may be provided by experiments with vaccination of healthy volunteers with different sleep durations. The first study of this type addressed the effects of sleep deprivation on the formation of specific antibodies to influenza virus H1N1. Spiegel et al. [17] found that patients with normal (7–8 h) sleep plots had antibody titers 2.5 times higher than those able to sleep only 4 h for six nights. Further studies showed that even one night of sleep deprivation led to decreases in the titers of antibodies to hepatitis A and B and swine flu respectively [1]. The positive influence of sleep on the formation of acquired immunity is linked with the effects of increases in the proinflammatory cytokine and/or effector cell population discussed above.

In the long term and in larger contingents of patients, increases in sleep duration also constitute a winning strategy in increasing the efficacy of vaccination. Thus, a study reported by Prathner et al. [18] in a group of patients undergoing three hepatitis B immunizations found a relationship between vaccination efficacy and the usual duration of sleep. The proportion of people attaining adequate protection as a result of vaccination (defined as a level of anti-HB_s IgG ≥ 10 mIU/ml) was 3.5 times higher in the group of people sleeping >7 h than in those sleeping <6 h.

Researchers have explained better immunization associated with sleep primarily in terms of the anabolic effects of prolactin and somatotropic hormone. Furthermore, an important role in supporting better responses is evidently played by the "proinflammatory" tuning of the cytokine system during sleep. Besedovsky et al. [1] took the view that the existence of large numbers of antigen-presenting cells and T-cells in secondary lymphoid organs during sleep will provide better exchange of information on the incoming antigen. This involves a process analogous to memory consolidation in the brain – which operates better in sleep because the right conditions for it are created (detachment from external stimuli and a special mode of neuronal electrical activity in the form of slow-wave oscillations). In this case, the conditions involve a high probability of close contact of immunocompetent cells in secondary lymphoid organs, a proinflammatory cytokine trend, and a favorable (anabolic) hormonal background. The positive effect of this particular hormonal-neuronal "tuning" of the body during sleep was supported by data reported by Besedovsky et al. [19] from studies producing an artificial increase in slow-wave activity in the slow-wave sleep phase, in which a decrease in the circulating cortisol concentration and a reduction in the number of lymphocytes (interpreted by the authors as result of their migration to secondary lymphoid organs) were seen.

Other approaches to the use of sleep as an immunomodulator included an attempt to evaluate the effects of an increased duration of nocturnal sleep in humans on measures of cellular and humoral immunity, and also studies of the effects of short daytime naps on these measures. In studies reported by Chennaoui et al. [20], sleep duration in healthy young people was increased by 1.5 h for six nights, confirmed by polysomnography data. However, there were no significant changes in the numbers of peripheral blood lymphocytes, monocytes, and neutrophils during daytime sleep. A pilot study reported by Haack et al. [21] in which sleep duration was assessed by actigraphy, where an increase in initially reduced (to 6 h per night) sleep duration led to minor reductions in the lymphocyte count, CRP, and IL-6.

More encouraging results were obtained by assessment of short daytime naps on measures of immunity. Population studies have shown that the occurrence of short daytime naps (self-reported) was associated with increased CRP and IL-6 levels, i.e., proinflammatory substances [1]. However, the experimental conditions did not allow evaluation of the direction of the causality. It is entirely likely that the existence of the health-burdening states accompanying increases in the levels of these substances promoted increases in the need for sleep, given that administration of IL-6 in experimental models in animals led to increases in the duration of slow-wave sleep [1].

Daytime naps in controlled conditions were found to have positive influences on measures of immunity when initially decreased on the background of sleep deprivation. For example, studies reported by Vgontzas et al. [22] showed that 2-h postprandial sleep led to a decrease in elevated IL-6

and cortisol concentrations. In two further studies, daytime naps after significant (up to 2 h) contraction of nocturnal sleep duration were accompanied by decreases in IL-6 levels and neutrophil counts [1].

Sleep Disorders and Immunity. The occurrence of sleep disorders is accompanied not only by decreases in sleep duration, but also by impairment to its quality. Studies reported by Donners et al. [23] in Dutch students used the sleep disorder questionnaire SLEEP-50 and self-assessed health status. Students evaluated themselves as "frequently ill" had worse self-assessments of sleep and higher scores in questionnaire sections addressing sleep disorders such as insomnia, obstructive sleep apnea syndrome, and circadian rhythm sleep disorder.

Insomnia is a common sleep disorder, which in its chronic form affects at least 6% of the general population. The annual incidence of acute (short-term) forms of insomnia is 20% [24]. The structure of insomnia includes various impairments to the process of sleep or its perception (difficulty going to sleep after going to bed in the evening or after nocturnal waking, frequent nocturnal waking, feelings of shallow sleep, early morning waking, unsatisfactory sleep).

Consideration of the role of sleep in ensuring the normal operation of the body's immune system raises the question of whether patients ininsomnia have abnormalities with innate or adaptive immunity. Apart from the Dutch study [23] noted above, which provided a very indirect assessment of immune system functioning, we found one study evaluating the role of insomnia in forming specific immunity on vaccination against influenza with a trivalent vaccine. Immunized students with insomnia had lower postvaccination antibody titers than those without sleep disorders [25].

The treatment of choice for insomnia is cognitive behavioral therapy (CBT-I). This is a multicomponent method directed at teaching patients the basic concepts of the mechanisms of their own sleep and the causes of its impairment, and then conducting behavioral experiments based on the resulting knowledge. Ultimately, this avoids dysfunctional beliefs and improves sleep quality. Standard CBT-I programs consist of 6–8 weekly sessions with a qualified specialist. Studies reported by Irwin et al. [26] included CBT-I and measurement of changes in IL-6, TNF-α, and CRP levels. Correction of sleep impairments using this method was accompanied by decreases in all inflammation markers over a follow-up period of two months, the only improvement persisting to 16 months being CRP. Transcriptome studies showed decreases in the expression of the genes for these proinflammatory humoral substances during treatment, while the expression of genes involved in producing interferons and antibodies increased. In another study, CBT-I in women with breast tumors was accompanied by increases in lipopolysaccharide-induced IL-1 and interferon production. In two other observations, improvements in sleep during CBT-I were accompanied by decreases in circulating IL-1, CRP, and IL-18 (a proinflammatory cytokine of the IL-1 family) levels [1].

Another direction in the treatment of chronic insomnia with a high level of evidential support is use of medications. Leaders in this area are benzodiazepines and nonbenzodiazepine $GABA_A$ receptor complex agonists. Binding with the specific (α1) protein subunits of the complex, these substances strengthen the hypnotic actions of GABA by binding to another domain of the complex. Benzodiazepine hypnotics (diazepam, lorazepam, temazepam, clonazepam), despite evidenced efficacy, are not recommended for use in chronic insomnia because they produce a range of undesirable side effects resulting from binding to other isoforms of $GABA_A$ receptor α protein, generating additional anxiolytic, amnestic, myorelaxant, anticonvulsant, and other effects. Nonbenzodiazepine agonists of this receptor complex such as zopiclone, zolpidem, zaleplon (the so-called Z drugs) have high affinity for α1 subunits, which are maximally represented in cerebral structures responsible for inducing sleep (primarily the ventrolateral preoptic nucleus of the hypothalamus). This results in a hypnotic effect with a minimal likelihood of developing undesirable side effects [24].

Suppression of the activatory brain systems also promotes improvements in sleep. This is approached by blockers of central histamine H1 receptors such as diphenylhydramine and doxylamine, though the current international consensus does not recommend them for use in chronic insomnia because of a dubious benefit/risk ratio [27–29]. This is linked in particular with the unwanted cholinolytic effects of these substances and the weak intrinsic hypnotic action. Another approach to sleep induction via blockade of the activatory brain centers consists of the use of orexin receptor antagonists. The orexin system of the hypothalamus has a powerful activatory influence on the cerebral cortex, and also on other important activatory centers (the "activator of activators"). Suvorexant, a blocker of both types of orexin receptor, is included in the guidelines for the treatment of insomnia of the American Sleep Medicine Association, though it is not included in the European guidelines as it is not available in Europe.

A third approach to correcting sleep disorders in insomnia consists of the use of melatonin receptor antagonists. The pineal hormone melatonin has a weak GABAergic action, seen only in experiments on knockout (lacking a specific gene) animals. Its main effect is to alter the internal clock by acting on specific receptors (MT1 and MT2) in the suprachiasmatic nuclei of the hypothalamus. One melatonin formulation currently available in Russia is Sonnovan (Canonpharma Production). The effects of melatonin in relation to the time of going to sleep, sleep duration, and subjective sleep quality were greater than those of placebo and were most apparent in people of the older age groups [30, 31]. Thus, international guidelines for the treatment of chronic insomnia take different positions on this. The American and European guidelines do not include melatonin formulations for the treatment of chronic insomnia [27, 28]. The guidelines of the British Association for Psychopharmacology recommend mela-

tonin for sleep disorders in people over age 55 years [29]. The melatonin receptor agonist ramelteon is included in the American guidelines for the treatment of chronic insomnia, though it is not included in the European guidelines for the same reason as suvorexant.

The use of melatonin receptor agonists for the treatment of chronic insomnia is accompanied by reductions in CRP levels. This was demonstrated in studies of the efficacy of ramelteon reported by Shimizu et al. [32]. These authors explained the positive effect of ramelteon on inflammatory biomarkers not so much in terms of improvement in patients' sleep quality as immunomodulatory, anti-inflammatory and antioxidant effects arising as a result of stimulation of melatonin receptors. These effects of melatonin are mediated predominantly at the molecular (direct uptake of free radicals – studies have shown that one melatonin molecule can seize up to 10 free radical species) and cellular levels. Melatonin has a role in inhibiting the production of proinflammatory cytokines and inflammatory prostaglandins and the synthesis of adhesion molecules, as well as in decreasing cyclooxygenase-2 expression in macrophages. Melatonin has been found to have a role in T-lymphocyte proliferation. Data from a meta-analysis by Zarezadeh et al. [33] indicate that use of melatonin as a food supplement at doses of 3–25 mg for several months is accompanied by decreases in the levels of proinflammatory cytokines TNF-α and IL-6, and in some cases CRP. The authors of this meta-analysis concluded that melatonin is useful for decreasing the severity of low-grade inflammation. The melatonin formulations most frequently used in clinical practice generally contain 3 mg of active ingredient.

Attention to the immunomodulatory properties of melatonin has sharpened on the background of the COVID-19 epidemic – an illness caused by coronavirus SARS-CoV-2. A serious and potentially lethal complication of COVID-19 is development of a "cytokine storm" – a reaction of the innate immunity system in the form of an uncontrolled and excessive release of proinflammatory cytokines, particularly TNF-α and interferon-γ. The occurrence of a "cytokine storm" and oxidative stress explain the development of delirium in COVID-19 patients, which occurs during intense therapy. Results from assessment of Chinese experience in the management of these patients reported by Shang et al. [34] suggest the use of melatonin formulations to prevent delirium.

The melatonin formulation Sonnovan contains 3 mg of melatonin. Indications for prescription are sleep impairment and desynchronosis. Sonnovan is also used as an adaptogen for changes in time zone. The medication is given as one tablet 30–40 min before going to bed.[1]

Conclusions. Thus, there is now sufficient evidence that the state of sleep itself, independently of the operation of the body's internal clock, supports improvements in measures of immune system activity. Habitual insufficiency of sleep is accompanied by changes in immunity, apparent as increases in proinflammatory cytokine levels. This process is associated with increases in morbidity and mortality. Compensation for sleep deficiency is accompanied by an effect consisting of improvements in measures of the body's immune defense. Correction of sleep disorders in insomnia using nonpharmacological and pharmacological methods is accompanied by decreases in proinflammatory changes. Use of melatonin formulations in sleep disorders in the context of immune defense has potential in connection with improvements in antioxidant and immunomodulatory effects.

This article was prepared with support from Canonpharma Production.

[1] *Sonnovan. Instructions for Use, Composition, Analogs, Dosage, Side Effects*, https://www.rlsnet.ru/tn_index_id_87600.htm, site active on June 25, 2020.

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