

Reciprocal Relationship Between Sleep and the Immune Response: A Survey

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Abstract: It is well known that sleep restriction or impairment results in an increase of the risk of get an infectious disease. As well, once a subject is sick due to an infectious disease, his sleep pattern changes completely. For a number of years these facts have been interpreted as the result of the alteration or lost of the main sleep function, the restoration of the defense system. Nevertheless, the experimental evidences to support this idea are surprisingly scarce. In a recent study on several species, a positive correlation was found between total sleep time and the number of circulating immune cells and, in addition, the species with longer sleep periods had reduced levels of parasitic infections. Experimental impairments of sleep, result in alterations in both the cellular and the humoral immune response. Early experiments on sleep restricted humans showed an increase of monocytes and natural killer (NK) cells, with a significant decrease of lymphocytes T. Concerning the immune humoral response, several cytokines have shown a close relationship with sleep. Some of them are capable of induce sleep when administered to specific regions in the brain. As well, some of them display significant changes when sleep is altered. Thus, it seems that sleep has an influence on the cellular and humoral immune response and, in turn, cytokines regulate the sleep pattern. The full understanding of this relationship could enable us to open new approaches in the therapeutic management of immune diseases. This paper reviews some of the most conspicuous data on these reciprocal influences.

Keywords: REM sleep, immune response, sleep-wakefulness, cytokines.

INTRODUCTION

Although the function of sleep is not fully elucidated yet, it has been known for a number of years that sleep plays a restorative role on most of the organic functions. Restriction of sleep due to social or working conditions leads to a notorious impairments of human capabilities [1]. Even when the onset of sleep is delayed the performance of subjects before easy task is deteriorated. When a subject has a restriction of the duration of his sleep, the number of failures in driving simulators is quite similar to the number of failures that a subject intoxicated with alcohol display in the same task [2]. Thus, even with a slight modification of sleep the organism starts to lost vital functions as attention and performance.

CELLULAR IMMUNE RESPONSE

Concerning immune response in human beings, when continuous wakefulness is prolonged for 40 hours a significant decrease of NK cells activity is observed [3]. Pioneering studies performed by Palmlad and colleagues [4] in healthy women volunteers showed that, after 77 hours of prolonged wakefulness, no changes were observed in the number of polymorphonuclear leukocytes, monocytes or lymphocytes B. However, the authors found that interferon production by virus protein stimulated lymphocytes

increased during the sleep deprivation and this increase remains significant even after 5 days of recovery period. In addition when the leukocyte phagocytic activity was assessed, a biphasic response was observed, with an initial decrease during sleep deprivation and a significant increase after 5 days recovery period.

Although this study was the first to explore in humans the effect of sleep lost in immune function, some controversies can be observed regarding its design. The study was performed in healthy women without paying much attention to the hormonal levels or the moments of the menstrual cycle. In addition, the experiment was performed in a simulated battle field environment continuous at 95 dB battle noise and with the subjects firing an electronic rifle. The stress component of this design was not properly assessed.

In a second study [5], the same group analyzed the effects of sleep deprivation for 48 hours in healthy young men. In this experiment, venous blood draws were done before and after sleep deprivation and lymphocytes were stimulated with phytohemagglutinin (PHA). Results showed that blastogenesis induced by PHA decrease during sleep deprivation. This decrease was significant when compared with values observed before sleep deprivation and the values observed after a five days recovery period. However, in this study the sleep of the subjects during the pre-deprivation assessment and during the recovery period was fragmented. Some memory tests were performed and the subjects were

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awake several times during the night, inducing a possible alteration of lymphocyte activity assessment.

In addition to these observations, Moldofsky and colleagues [6] performed similar studies. Healthy male volunteers were sleep deprived for 64 hours and venous blood was drawn every two hours before and during sleep deprivation. Besides the assessment of cortisol, the authors studied the activity of the NK cells and the lymphocyte blastogenesis induced by both PHA and pokeweed mitogen (PWM). The main finding in this study was a clear difference between both mitogens. During baseline sleep, both PHA and PWM induce an increase of blastogenesis. However, during sleep deprivation, PWM-induced blastogenesis increased while PHA-induced blastogenesis decreased.

David Dinges and his group [7, 8] performed also an observation on total sleep deprivation and immune function. Healthy young volunteers included men and women were included in the study. The sleep deprivation lasted for 64 hours and subjects were sampled before, during and after sleep deprivation. The authors analyzed total blood white cells, monocytes, granulocytes, lymphocytes and different subsets as lymphocytes B, T, helper, NK among others, eosinophils. The authors also stimulate lymphocytes blastogenesis with PHA, PWM and they include another mitogens, concanavalin-A (Con-A). The results showed a significant increase in the counts of white blood cell, granulocytes, monocytes and different subsets of NK cells (CD56 and CD57). Some lymphocytes subsets showed no changes during sleep deprivation as lymphocytes B, T and helper. As well, no changes were observed in mitogen-induced blastogenesis of lymphocytes induced by PHA, PWM and Con-A. The only subset that showed a significant decrease was the T-helper cells.

In this study, the authors introduced by the first time the assessment of interleukin (IL) plasma levels, including IL-1Beta, IL-2, IL-6 and IL-12. In addition, plasma levels of tumor necrosis factor alpha (TNF) and gamma interferon (IFN-gamma) were determined. Results showed no significant variations concerning plasma levels of IL-2, IL-6, IL-12 and TNF. Concerning IL-1 and IFN γ , an initial trend to increase was observed during sleep deprivation, followed by a clear decrease after sleep deprivation.

However, the most common experience for a modern human being, living in a large city is the restriction of sleep, instead of the total sleep lost. Therefore, Irwin and colleagues [9] analyzed the effect on immune response of partial sleep deprivation, allowing the subjects to sleep either during the first half of the night or during the second part. In the first study reported by this group, the assessment of NK cells activity was determined in healthy males. Blood samples were obtained in the morning after normal sleep night during three consecutive days. At the same hour after a partial sleep deprivation. Subjects were awoken at 03:00 in the morning and were kept awake. Last sample was taken after a recovery night of sleep. They found that partial sleep deprivation induced a decrease of NK activity that was correlated with basal values, i.e., the higher the basal values the greater decrease after sleep lost.

Thereafter, the same group [10] analyzed the effects of sleep deprivation during the first half of the night. Results showed a reduction of NK activity. In addition, the authors reported a reduction of IL-2 production by lymphocytes stimulated with Con-A. After a recovery night, the levels of NK activity returned to basal values but the production of IL-2 remains decreased, confirming that only a slight loss of sleep could induce a significant impact on immune response.

The decrease of NK cells after sleep lost was confirmed by a Turkish group. Healthy males were sleep deprived for 48 hours. The levels of NK decreased during sleep deprivation and returned to basal levels during the recovery period. In this study the authors compared the results with those obtained in a control group [11].

Besides experimental reports, there are other sources of information to support the influence of sleep on immune response in humans. Studies on shift workers that commonly experience sleep disturbances, display a notorious decrease of their immune function. This impairment in the immune response has been correlated with the increase frequency of the respiratory tract infections that this group often suffers [12, 13. Cited in: 10].

Several diseases impair normal sleep. Among them, the most conspicuous is, of course, chronic insomnia. Savard *et al.*, in 2003 [14], performed a study in insomniac patients assessing immune parameters including lymphocytes subsets. Compared to results obtained in healthy subjects, insomniac patients showed a significant decrease in CD-3, CD-4 and CD-8 lymphocyte subsets. Unexpectedly, no changes were observed concerning NK cells activity or IL-1, IL-2 and IFN production.

Recently, in a novel approach, Preston and colleagues [15] analyzed the possibility that sleep has evolved across the species to allow the organism special protection against parasitic infections. To test this hypothesis, the authors performed a correlation analysis of total sleep time and the number of circulating immune cells. The authors analyzed the characteristics of 26 mammalian species concerning their total sleep duration. On the other hand, the number of immune cells was correlated with the data of sleep. Neutrophils, which are the largest component of innate immune system and are linked to the rapid response against pathogens, show a positive direct correlation with sleep duration. The mammalian species that show higher amounts of total sleep also show the bigger numbers of circulating neutrophils. Lymphocytes are also an important component of white cell count and are related to the acquired immune response. Lymphocytes also show a significant positive correlation with sleep duration. In addition, basophils and eosinophils which are a relatively minor component of the white cell count and have been linked to parasitic challenge also showed a significant positive correlation with sleep duration. Unexpectedly, monocytes are the only component of white cells that did not show any significant association with sleep duration.

In addition, the authors analyzed the correlation of each one of the main sleep components, rapid eye movements sleep (REM) and non rapid eye movements sleep (NREM), with immune cells. No significant variations were found for each one of the sleep stages. Both stages seem to positively

correlate with immune cells. Furthermore, the authors also analyzed the correlation between sleep duration and parasitic infections levels in 12 mammalian species. In this case, a negative correlation was found. The longer duration of sleep significantly correlates with the lower level of parasitic infection. Thus, the authors conclude that sleep evolved to protect animals from parasitic infections.

In laboratory animals, prolonged sleep deprivation has proved to have a lethal effect. Animals died after approximately 19 days. Carol Everson [16] suggested in 1993 that lethal effect of sleep deprivation could be link to the complete failure of host defenses. After a sustained sleep deprivation of about 24 days, blood cultures were analyzed and showed an invasion of opportunistic microbes. Furthermore, these microorganisms did not produce febrile responses. It must be pointed out that these were healthy animals that did not receive any pathological agent. The observed bacteremia develops just after sleep deprivation which indicates a total failure of the immune response.

To further define the effect of sleep deprivation, Everson and Toth [17] analyzed the development of the bacterial invasion in deprived animals. To this aim, they made tissue cultures of several organs and assess microbial growth. An early sign detected was the infection of the mesenteric lymph nodes with bacteria that supposedly translocated from the intestine. Bacterial presence were later found in several extraintestinal sites, suggesting that this is the mechanisms by which bacteria in sleep deprived animals reach the whole organism leading to death. Formation of colonies was detected mainly in the liver and the lungs.

Using the same paradigm of prolonged sleep deprivation, Everson [18] analyzed white blood cell count in bone and blood. Likewise, immunoglobulins, cytokines, chemokines and endotoxin concentration in serum were assessed. Results showed a significant increase of leukocytes identified as neutrophils. The increase reach 70 % at the end of the 18 days of sleep deprivation, that was significantly different from the 46% observed during the baseline period. Monocytes increased almost three times compared to baseline values. Immunoglobulins display a trend to increase that, however, did not reach statistical significance. IL-1 showed a significant increase only after 15 and 20 days of sleep deprivation. No other significant cytokines variations were detected. The chemokine macrophage chemotactic protein-1 increased during sleep deprivation. Endotoxin concentration in serum increased in sleep deprived animals since 5 days of sleep deprivation and this increase remain significantly different from control animals until the 20 days of sleep deprivation. These data supports the idea that lethal effect of sleep deprivation is the result of bacteremia due to host response failure.

It must be pointed out that, both in humans and in animals, sleep lost is supposedly a very stressful situation. However both in humans and in animals some reports indicate that sleep deprivation does not share the main characteristics of common stressors. In humans, several reports indicate that plasma levels of cortisol and urinary excretion of catecholamines are not elevated after sleep deprivation [19].

In experimental animals, several procedures have been proposed for sleep deprivation. One of the most commonly used for a number of years was the so-called "island technique" that was develop by Michel Jouvet in 1963 [20]. In brief, the technique consists in placing an animal, rat or cat on a small platform surrounded by water. The animal must remain on the platform where can be stand up or seated and, in this condition, they can reach slow wave sleep. As REM sleep is accompanied by muscle atonia, the animal fall into the water each time he tried to enter in REM sleep. A huge volume of papers have been published using this technique to elucidate REM sleep function [21]. As can be easily noticed this technique has several stressful components. First, as the platform is 10 cm high the animal must remain immobilized at the top. Second, the animal remains isolated for several days. Third, each time he falls into the water, the animal must swim and climb to be on the platform again.

To discard the stress component in the results obtained using the island technique, several modification have been proposed. Our group modified the original technique and decreased the height of the platform to 4.5 cm, so the water level also decreased to 3 cm. Thus, the animals are allowed to come down from the platform and move freely in the cage, until they decided to come back to the platform and get some slow wave sleep [22].

Recently, the method was modified in an effort to diminish even more the stress component of this technique. To avoid another stressful component, isolation, a method using multiple platforms was developing. In this case, a group of rats is placed in a tank, usually with more platforms than animals [23]. This modification diminishes the stress component which can be further decreased if the animals had been previously kept in socially stable groups [24].

On the other hand, another popular method to achieve total sleep deprivation was developed by Allan Rechtschaffen and his group in Chicago [25]. In brief the methods and apparatus are as follows: in a large tank fill with water up to 2.5 cm height. A large round platform (46 cm diameter) is horizontally located 2 cm above the water level. The platform is divided by an acrylic wall in two halves. A pair of rats is located in each half of the platform in exactly the same conditions. The animals are usually implanted with electrodes for sleep recording. The animals are kept in these conditions for a habituation period of about seven days. During this period rats are recording continuously and usually 46 % of wakefulness, 48% of NREM sleep and 6% of REM sleep can be observed. During the period of sleep deprivation, the electroencephalographic (EEG) signal of the sleep deprived rat triggers the rotation movement of the platform. When the EEG signal meets the criteria of sleep, the rotation movement start and the animals are forced to walk. Thus, the deprived animal is not allowed to sleep while the control animal can sleep but is facing exactly the same conditions as the deprived rat. This procedure increases wakefulness to more than 90% and decrease sleep to less than 10% of mainly transitional sleep. REM sleep is reduced to about 1% [26].

Thus, despite the efforts to decrease the stress component of the sleep deprivation methods, it seems that stress is a factor that always has to be taken into account in sleep

deprivation studies. The results obtained in any given study are due to sleep lost or are due to the stress component of the deprivation technique. Furthermore, as stress response implies a significant effect of immune response, studies that analyze the impact of sleep lost in immune system, should take stress into account.

With that idea in mind, our group compared the effect of short and long term REM sleep deprivation with the effect of short and long term stress by immobilization [27]. Immobilization stress has been reported as a powerful stressful situation for rats. REM sleep deprivation was achieved by placing the animals in a tank with multiple platforms for either one day and for 10 days. Immobilization stress was achieved by placing the animal inside a small plexiglass cylinder for 6 hours one day or 6 hours daily during 10 days.

Results showed that REM sleep deprivation induce a significant increase in NK cells, even with just one day of deprivation. This increase is even bigger after 10 days. Percentage of lymphocytes T, decrease significantly the first day and remain equally decreased after 10 days of REM deprivation. Percentage of lymphocytes B did not show any significant variation. On the other hand, immobilization stress did not show any effect on NK cells. In addition, percentage of lymphocytes B increases while percentage of lymphocytes T decreases during the first day, but no significant changes were detected after 10 days. These results indicate that sleep lost has a specific effect of the immune response that seems not to be due to any stress component.

As mentioned above, in the modern urban societies the most common experience is not the total loss of sleep but the marked restriction of sleep time. To address this issue, the Brazilian groups of Andersen and Tufik [28] performed a study on REM deprived animals for both a short (24 hours) and long (96 hours) periods. As well, the authors studied a group of rats restricted of sleep for a 21 day period. Sleep restriction was achieved by placing the animals in the multiple platform tank for REM deprivation but only for 18 hours a day.

REM sleep deprivation for 24 hours has no effect on total leukocytes or monocytes. REM deprivation for 96 hours increases significantly leukocytes and the increase is even bigger during the recovery period. Monocytes showed a trend to increase that is bigger and reach significance during the recovery period. Sleep restriction showed the opposite effect. Total leukocytes decrease after 21 days of restriction and returns to control values after the recovery period. Monocytes also showed a trend to decrease in both conditions. Neutrophils are slightly disturbed in all the condition. Only a significant increase was observed during the recovery period after 96 hours of REM deprivation. Lymphocytes decrease after 24 hours of REM deprivation and also after 21 days of sleep restriction. Concerning immunoglobulins, IgM increases significantly after sleep restriction and remains high after recovery period. Interestingly, cortisol increases only after 96 hours of REM deprivation.

Thus, it seems clear that sleep deprivation or restriction has marked effects on cellular immune response. These

effects are not due to the stressful conditions in which usually sleep manipulation is done. As well, it seems that the effect of sleep disturbances on the immune system depends on the duration and the characteristics of the sleep impairment technique.

HUMORAL RESPONSE

Besides immunoglobulins, there is another large family of proteins known as cytokines. These proteins are linked to immune response to infection, inflammation, injury and stressors. Madje in 1994 [29] grouped cytokines in pro- and anti-inflammatory cytokines; chemokines, cellular immunity potentiating cytokines, antibody potentiating cytokines; antiproliferative cytokines and hemopoietic cytokines. Cumulative evidence indicates that a number of them are expressed not only in the immune system but in other organs as in the brain and some of them participate actively in the acute phase response to trauma and infection. This is a complex response that involves the orchestration of several systems [30].

On the other hand, since the beginning of the XX century, sleep researcher have actively look for the sleep substance. For a number of years, researchers look for a humoral factor responsible for the regulation of sleep. Mostly using sleep deprived animals, they analyzed cerebrospinal fluid, blood, urine and of course, the brain to look for this substance. These lines of research leads to a huge number of sleep factors. These factors have been defined as endogenous substances that fill some criteria to clearly show its relationship with sleep regulation [31, 32].

Both lines of research were convergent and during the nineties, cytokines become members of the group of the proposed sleep factors. James Krueger group published a number a papers regarding this issue [for review see.33]. Initially, Krueger was working in the characterization of the muramyl peptide, a sleep factor isolated from human urine and rabbit brain. The peptide was somnogenic when applied in rabbits, cats, rats and monkeys [34]. In addition, muramyl peptides activities are mediated by the production of cytokines, specially IL-1 and TNF [35].

Despite the existence of a number of cytokines, the information regarding the participation on sleep control, involves mainly IL-1 and TNF. Electrophysiological, biochemical and molecular genetic studies have shown a specific effect on sleep-wake behavior. Concerning IL-1, experiments on several species showed a systematic increase in NREM sleep (For review see: 33). In humans patients who received treatment with IL-1 shows a clear increase of diurnal sleepiness [36]. IL-1 has brain receptors that are widely distributed and they are located in brain structures that are linked to sleep regulation. Likewise, IL-1 is interacting with classical neurotransmitters that are involved in sleep regulation [37].

Sleep regulation has a major component located in the basal forebrain and preóptica area. Administration of IL-1 in this region, through a microdialysis probe in a freely moving rat, reduce firing rate of neurons identified as wake-related neurons. In addition, sleep-related neurons increased their firing rate. These observations were done when the animal was awake. When the administration was done during NREM sleep, no alteration of the firing rate of sleep-related

neurons was observed. Additionally, a IL-1 receptor antagonist was perfused before the administration of IL-1. As consequence, the effects of IL-1 in both wake-related and sleep-related neurons were significantly diminished. The results indicate that IL-1 influence sleep by suppressing the activity of wake promoting neurons and activating sleep related neurons. These actions are mediated by a specific receptor located in these neurons [38].

TNF has also shown a similar action in the same area. Microinjection of TNF directly into the preoptica promotes NREM sleep and suppresses REM sleep [39]. In addition both TNF and IL-1 are affective when applied to primary cultures of hypothalamic and hippocampal neurons. Low doses of both cytokines increases cytoplasmic Ca^{2+} , an essential step for neurotransmitters release and this effect is blocked by selective antagonists [40, 41].

In addition, growing evidence supports also the participation of other cytokines as sleep regulators. For instance Interferon alpha (IFN) which is reputed for its antiviral activity also has proved to influence the regulation of sleep [42]. A number of viral infections such as influenza, human immunodeficiency virus (HIV) and feline immunodeficiency virus (FIV) alter drastically the sleep pattern. In addition, viral infections usually induce the production of IFN by almost all nucleated cells. In addition, several brain regions express INF receptors and the administration of IFN induce NREM sleep in rats and rabbits. Thus, it seems that IFN plays a major role in the regulation of sleep, especially on those alterations observed as consequence of viral infections.

Relatively recently another interleukin emerge as a possible sleep regulator, IL-6. The presence of IL-6 in plasma shows circadian variations. It reach its highest concentration during sleep and its lowest during wakefulness [43]. In addition, in healthy humans that have been sleep deprived, a significant increase is observed in plasma levels of IL-6 [44]. Furthermore, subcutaneous administration of IL-6 to humans induces a significant increase of slow wave sleep and a reduction of REM sleep [45]. Likewise, in sleep disorders characterized mainly for the presence of excessive diurnal sleepiness, IL-6 has been found elevated in plasma [46]

CONCLUDING REMARKS

Growing evidence clearly indicate that immune system have a close relationship with the nervous system and with the endocrine system. The intense communication among these three systems seems to play a major role in the maintenance of homeostatic equilibrium. On the other hand, sleep is also a crucial phenomenon to keep the organism in a healthy balance to face the environmental challenges during wakefulness. Thus, the adequate reciprocal influences between sleep and the immune system seems to be a major condition for health. Thus, disturbances of sleep will have an effect on the immune response and, vice versa, components of the immune response will modify the sleep pattern. The full understanding of these relationships will certainly open new avenues in the search for therapeutic alternatives particularly, of sleep disorders and autoimmune diseases.

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