Central Nervous System and Peripheral Immune Functions and the Sleep-Wake System

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This paper reviews the relationship of aspects of the immune system to the sleep-wake system in animals and humans. In addition to the influence of certain cytokines such as interleukin-1 (IL-1) on the sleeping-waking brain, circadian measures of plasma IL-1 and peripheral immune cellular functions, for example, natural killer cell activities and cortisol are related to the sleep-wake system in humans. Changes in the circadian patterns of immune functions over the menstrual cycle are associated with the amount of progesterone and slow wave sleep. The harmonious inter-relationship of the circadian pattern of the immune, endocrine and sleep-wake systems may be important in the cause and functions of sleep.

Key Words: sleep, interleukin-1, natural killer cells

INTRODUCTION

Despite the phenomenal scientific advances in the past 35 years about sleep physiology and its role in health and illness, two fundamental questions remain unresolved. What is the cause of sleep? What is the function of sleep? We have not advanced much beyond Samuel Johnson's pronouncement over 200 years ago that "...no researcher has yet found either the efficient or final cause; or can tell by what power the mind and the body are thus chained down in irresistible stupefaction; or what benefits the animal receives from this alternative suspension of its active powers" (Webb 1975).

Historically sleep was thought to occur as a result of an accumulation of toxic metabolites that dissipated during sleep. This notion of a humoral-toxin or "hypnotoxin" dates back more than 80 years. In 1909 Ishimori, in Japan, demonstrated that his dogs fell asleep following subcutaneous injection of a brain extract obtained from dogs that had been deprived of sleep (Inoue 1989). About the same time, Legendre and Pieron in France demonstrated that intraventricular injections of cerebral spinal fluid taken from dogs deprived of sleep induced sleep behavior in the recipient dogs (Pieron 1913). They proposed that an endogenous toxin facilitated sleep. Until recently, there has been little interest in natural humoral, soporific substances. Rather, attention has focused upon the following: electrophysiologic studies of central nervous system (CNS) cellular functions that relate to sleep-wake behavior; neurochemical transmitter studies (for example, cholinergic, serotonergic, and catecholamine mechanisms associated with waking, rapid eye movement (REM) and non-REM sleep) and neuropharmacologic studies of synthetic hypnogenic agents and their CNS neuroreceptors, such as benzodiazepines. These methods describe the transitions between sleep-wake behavior or neurophysiologic changes that occur with sleep. However, none of these methods provide insights into the biochemical or humoral mechanisms that may be responsible for initiating and maintaining sleep, initiating and promoting wakefulness or conditions under which such mechanisms may be altered. Recent studies suggest that neuro-immune-endocrine functions are intimately linked to sleep-wake regulation. This paper proposes to review the evidence for immunoendocrinologic

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activities as important to CNS mechanisms that are involved in sleep and wakefulness. The elucidation of these humoral regulatory mechanisms for sleep-wakefulness may provide insight into the functional significance of sleep.

CNS immune functions and the sleep-wake system

For experimental purposes, various authors have demonstrated that specific immunological active peptides or neuroendocrine hormones influence the sleeping-waking brain. However, in reality the immune and neuroendocrine systems do not operate in isolation. Indeed, there is an intimate link between these systems with considerable evidence for a molecular basis for bidirectional communication between them (Blalock 1989). Specific sleep-promoting immunologically-active peptides that have been identified include Factor S (Krueger 1982), muramyl peptides (Pappenheimer 1983; Masek and Kadlec 1983; Krueger et al 1984), interleukin-1 (IL-l) (Krueger et al 1983; Tobler et al 1984; Krueger et al 1984), IL-2 (De Sarro et al 1990), alpha interferon (De Sarro et al 1990; Krueger et al 1987), tumor necrosis factor (Shoham et al 1987), prostaglandin D_2 (Ueno et al 1983), vasoactive intestinal peptide (Jouvet 1984; O'dorisio et al 1984) and delta-sleep inducing peptide (Graf and Kastin 1984; Yehuda 1986). Another immunologically-active substance, prostaglandin E_2, has been identified that promotes wakefulness. Indeed, Hayaishi argues for a primary reciprocal regulatory influence of prostaglandin D_2 and prostaglandin E_2 on the sleep-wake system of animals (Hayaishi 1991). However, Krueger et al were not able to demonstrate such an effect on rabbit sleep-wake physiology (Krueger et al 1992). Rather than the specific humoral model of Hayaishi, Krueger proposes that cytokines and specifically IL-l, are involved in a complex interaction of various immunologically-active and neuroendocrine substances that have been identified as influencing the sleep-wake system (Krueger 1990). Those neuroendocrine hormones that inhibit sleep and IL-l include corticotropin-releasing factor, adrenocorticotropic hormone, alpha melanocyte-stimulating hormone and glucocorticoids (Krueger (1990). On the other hand, those hormones that stimulate sleep and IL-l include insulin, growth hormone releasing factor, growth hormone, melatonin and somatostatin (Krueger 1990). Although the effects of the microinjection of IL-1 into various basal forebrain sites indicate that there are separate sites for sleep and fever, no specific sleep centre has been identified within the brain stem (Walter et al 1989). Nevertheless, IL-1 and other cytokines play a regulatory role on the sleeping-waking brain, especially in the presence of infectious disease (Opp et al 1992). Toth, Krueger and colleagues have shown that the pyrogenic and somnogenic effects of microbial challenge depend upon the type of infectious organism and the route of its administration in the animal. For example, E. coli, administered intravenously to rabbits, showed a more rapid increase in slow wave sleep than when the animals were similarly inoculated with S. aureus (Toth and Krueger 1989). In another study, these authors showed that the induction of pasteurellosis in rabbits by intranasal administration facilitated a later and longer somnogenic and pyrogenic effect than if this pathogen was given intravenously (Toth and Krueger 1990). However, the somnogenic and pyrogenic effects of infectious agents do not require viable organisms but can occur in the presence of bacteria killed by heat or isolated bacterial cell walls (Johannsen et al 1990).

These recent reports that describe a link of infectious products to the promotion of slow wave sleep and febrile response in animals relate to earlier discoveries of the structure and function of a newly isolated sleep-promoting substance, Factor S. Factor S was shown to contain muramic acid and to be similar to the synthetic adjuvant muramyl dipeptide (Krueger et al 1982; Pappenheimer 1983). Muramyl peptides were originally derived from the cell wall of bacteria; they also occur endogenously in mammalian tissues and fluids (Krueger et al 1984). These peptides are capable of promoting sleep, fever and immunologic activity (Blalock 1989; Krueger et al 1982). Pretreatment of rabbits with the IL-1 receptor antagonist or a soluble IL-1 receptor attenuates the somnogenic and pyrogenic actions of muramyl dipeptide (Imeri et al, in press). Thus, the somnolent and pyrogenic effects of muramyl dipeptide occur through the aegis of the cytokine, IL-1 (Pappenheimer 1983; Krueger et al 1984; Lafrancier and Lederer 1984) and are thought to be mediated by the CNS serotonergic system (Masek and Kadlec 1983). Therefore, Factor S, certain muramyl peptides and IL-l are capable of promoting slow wave sleep and fever in animals (Krueger et al 1984). This increased slow wave sleep produced by IL-1 persists even when the fever is blocked by an antipyretic agent (Krueger et al 1984).

However, there are other important characteristics of IL-1. IL-1 has been demonstrated to be a product of various peripheral cells (macrophages, keratinocytes, Langerhan's cells, corneal epithelial cells, gingival cells, renal mesangial cells), as well as being a product of astrocyte-glial cells of the CNS. The wide distribution of this endogenous cytokine suggests its importance, not only as a mediator of the acute phase febrile response in inflammatory disease, but also as a modulator of metabolic functions that involve the CNS and the immune system (Dinarello 1988). Therefore, because IL-1 and other immunologically-active cytokines are capable of promoting sleep in animals and are crucial in influencing a variety of immunologic functions, it is tempting to consider how these humoral agents and their metabolic influences may serve as the key to unlock the secrets of the nature of sleep-immune relationships in humans.

The relationship of certain cytokines such as IL-1 to sleep-wake behavior in man has been described (Moldofsky et al 1986). A 24 hour study of measures of plasma IL-1 activity in six male subjects showed that IL-1 and IL-2 activity were related to the sleep-wake cycle and not specifically to clock time. Maximal plasma IL-1 activity occurred

at sleep onset, was followed by a rise in plasma IL-2 activity and appeared to be related to a decline in plasma cortisol and the appearance of slow wave sleep. In particular, plasma IL-1 activity was greater during slow wave sleep in comparison to daytime waking, wakefulness after bedtime, stages 1 and 2 sleep. The data are consistent with the proposal that IL-1 activity is associated with sleep.

Recent clinical studies have confirmed and extended these initial observations. The nocturnal rise in IL-1 secretion in the plasma was found to occur during the sleep of undisturbed subjects. But, IL-1 in the plasma was not detected in two subjects who had difficulty with their sleep due to the stress of the study procedures. Moreover, an inverse relationship was found between plasma beta endorphin and IL-1 which suggests that negative feedback exerted by corticotropin releasing hormone on IL-1 may be influenced by stressful situations (Covelli et al 1992). In another study, measures of plasma IL-1 and IL-6 were increased during sleep but no temporal association was found with stages of sleep (Gudewill et al 1992). However, tumor necrosis factor alpha (TNF) was not related to sleep. In some subjects, the cytokines were not detectable. There are, currently, major difficulties in measurement of cytokines such as IL-1 due to the sensitivity of the assay, the presence of known inhibitors (for example, interleukin-1 receptor antagonist), unknown inhibitors, and to the determination of the significance of IL-1 and other plasma cytokines to central nervous system functioning.

In order to determine whether IL-1 is related to behavioral sleep, IL-1 activity was studied in subjects who were deprived of one night of sleep and remained awake for 40 hours. IL-1 activity was found to be greater during the night of deprived sleep than at any other time during the baseline sleep and subsequent recovery nocturnal sleep (Moldofsky et al 1989). Although the increased IL-1 activity did not occur with physiologic or behavioral evidence of sleep, the increase in plasma IL-1 occurred during a time of subjective sleepiness. In a recent study on sleep and immune functions of women, increased IL-1 activity occurred, not only during sleep, but also during the mid-afternoon, at a time of normal predisposition to sleepiness (Moldofsky et al submitted for publication). The changes in diurnal IL-1 activity were unrelated to the phase of the menstrual cycle, as determined by the amount of plasma progesterone secreted over 24 hours.

Therefore, plasma IL-1 activity is associated with a predisposition to sleepiness or the appearance of sleep in males and females. This observation does not necessarily imply that there are coincidental analogous increased IL-1 activities or other sleep-promoting cytokines within the CNS that directly influence the sleep system. Moreover, plasma measures of cytokines that are related to sleep in humans may have no sleep-promoting effect when injected into animals. For example, IL-6 is pyrogenic and not somnogenic by injection in rabbits (Opp et al 1989), but plasma IL-6 levels are increased during sleep in humans (Gudewill et al 1992). However, the literature on animals does suggest that IL-1 is directly involved with the sleeping-waking brain. IL-1 activity and IL-1 measured in the cerebrospinal fluid from the third ventricle of cats showed that there is increased IL-1 during sleep *versus* wakefulness (Lue et al 1988). The association of immunologically-active cytokines with sleep in man may be merely coincidental and related to circadian autonomous peripheral biologic mechanisms. However, IL-1 activity increased during the night of sleep deprivation in man (Moldofsky et al 1989). Similar changes in IL-1 occur in rabbits deprived of sleep (Opp et al 1992). Furthermore, IL-1 derived from astrocytes enhances slow wave sleep in the rat (Tobler and Borbély 1984). The sleep and febrile responses promoted in the rabbit by IL-1 are blocked by a specific IL-1 receptor antagonist (Opp and Krueger 1991).

IL-1 appears to conform to most of the Borbély and Tobler criteria for a specific endogenous or sleep-enhancing substance (Borbély and Tobler 1980). That is, IL-1 induces and/or maintains physiologic sleep. The action appears to be similar in the several different animal species studied to date (Opp et al 1992; Tobler and Borbély 1984). The substance occurs naturally. Spontaneous changes in the sleep-wake cycle are associated with changes in IL-1 activity (Moldofsky et al 1986). The structure of IL-1 has been described (Gubler et al 1986). However, the proposition that there should be one specific endogenous sleep substance is not upheld by the data that show that various endogenous agents affect sleep. Once more, the notion of an endogenous sleep-promoting agent implies that the natural condition of the body is to be awake. Such natural sleep-promoting agents may not operate within Borbély and Tobler's suggested criterion of a defined dose-effect relationship (Borbély and Tobler 1980) as might be expected with an artificial hypnotic. Pharmacologic hypnotic agents do indeed show a dose-related abbreviated onset to, or imperative facilitation of sleep. However, natural substances may function as permissive agents that require a specific time interval within which to operate, as well as suitable behavioral conditions and inhibition of competing biologic substances. Common experience indicates that special time intervals when the need for sleep becomes urgent can be overcome by external stimulation, willpower or use of stimulating caffeine beverages. Once that time interval of sleepiness passes we feel alert until a later time when the sleepiness returns. Such specific time windows for sleepiness during the early hours of the morning and mid-afternoon are well known. These periods of predisposition to sleepiness are separated by times for resistance to sleep (Lavie and Weller 1989). Some animal experimental studies do suggest that sleep-promoting substances function best or influence immunologic activities at a certain time within the 24 hour sleep-wake cycle. These substances include: DSIP (Yehuda 1986; Inoue et al 1984) prostaglandin D_2 (Inoue et al 1984), uridine (Inoue et al 1984), Factor S (Krueger 1985), muramyl peptide (Fornal et al 1984) and IL-1 (Opp et al 1991). However, as shown in the experimental sleep deprivation studies, pro-

longed wakefulness in man and animals is accompanied by a predisposition to sleep and an increase in IL-1 and possibly other sleep- promoting substances.

Peripheral immune functions and the sleep-wake system

As shown by research on animals and indirectly inferred in human clinical studies, interest has focused upon immunologic and endocrine influences on the electroencephalogram (EEG) and behavioral measures of the sleeping-waking brain. However, in addition to the EEG and behavioral measures of sleep-wakefulness, there are coincident alterations in the peripheral pattern of immune and endocrine functions. Generally speaking, two methods have been employed in animal and human studies to determine peripheral immune and endocrine functions of the sleep-wake system. One method involves depriving subjects of sleep and assessing the biologic changes during the deprivation and recovery episodes. The other method involves the assessment of immune and endocrine correlates to sleep and wakefulness.

Disturbances in sleep in animals and immune functions

Sleep deprivation. The major difficulty with the sleep deprivation paradigm has been the lack of controls for the stimuli used to prevent sleep (Rechtschaffen et al 1983). When the stimuli were controlled, prolonged sleep deprivation (approximately 30 days) of rats produced death without evident causal disease. However, examination of bodily organs showed general physical debilitation, skin lesions and swelling of the paws. At death there was a reduction in weight of the liver and spleen and increased weight of the adrenal gland (Rechtschaffen et al 1983). The changes in the body suggested altered immune functions but measures of cellular immune functions showed no change in splenocyte proliferation and antibody-secreting cellular responses (Benca et al 1989). This study was flawed by the small sample size, one sample from each animal and the large variability in the measures that were used. Recently, Everson (1993) found that the host defense of the immune system of those moribund rats deprived of sleep is impaired. Blood cultures from these rats revealed opportunistic microbes to which there was no febrile response. Other studies have shown that selective sleep stage deprivation, that is, rapid eye movement (REM) deprivation in rats, resulted in a reduced primary antibody response to sheep red blood cells (Solomon 1969). After mice had been deprived of REM for three days, there was increased uptake of sheep red blood cell's antigen in peritoneal macrophages, but decreased uptake in the spleen and liver (Casey et al 1974). Similarly, Brown et al (1989) showed that rats challenged with sheep red blood cells following eight hours of sleep deprivation showed reduced antibody responses three days later. However, IL-1 and muramyl dipeptide prevented this decreased antibody response (Brown et al 1989a). Subsequently, these researchers showed that immunity to influenza virus infection of the lungs of mice was suppressed following sleep deprivation (Brown et al 1989b). Recently, Toth and Krueger showed that duration and amount of slow wave sleep enhancement in rabbits following microbial challenge with E. coli, S. aureus or C. albicans was a prognostic indicator of survival from the infection. That is, those animals who showed reduced slow wave sleep and higher levels of plasma corticosterone showed much higher mortality (Toth and Krueger, 1993). While most of these sleep deprivation studies provide evidence for impaired peripheral immunologic response, morbidity and mortality, the neuroendocrine-immune mechanisms require further detailed study.

Altered circadian sleep-wakefulness. Few animal studies have attempted to determine whether changes in circadian sleep regulation would influence peripheral functions of the immune and endocrine systems. A decreased immune response to mitogen stimulation with Concanavallin A and reduced local graft *versus* host assay (popliteal lymph node assay) response were found in rats subjected to weekly reversals in the light-dark cycle for two months (Kort and Weijma 1982).

Normal sleep-wakefulness and peripheral immune functions. Most tissues have a 24 hour rhythm of mitotic activity with maximal activity during the time of rest and sleep (Adam 1980). However, peripheral cellular functions may not be simply tuned to a sleep-wake or rest-activity cycle. As indicated above, muramyl peptides, which are constituents of bacterial cell wall peptidoglycan, are found in various mammalian tissues and are capable of promoting sleep via IL-1 production from activated macrophages. In addition to their sleep-promoting and pyrogenic affects, muramyl peptides are immunoadjuvants, protective against infections, induce smooth muscle contractility and serve as antitumour agents (Karnovsky 1986). The capability to synthesize these somnogenic and pyrogenic muramyl peptides depends upon macrophages which digest bacteria (i.e., staphylococci) (Johannsen et al 1991). Because bacteria readily enter the body and are eliminated by macrophages, it is thought that the resultant steady production of muramyl peptides might function as vitamins that influence the sleep-wake system (Johannsen et al 1991).

Disturbances in sleep in humans and immune functions

Sleep deprivation. Several studies have shown that peripheral immune functions are altered following sleep deprivation. Seventy-two hours of sleep deprivation resulted in reduced phagocytosis by polymorphonuclear granulocytes, increased interferon production by lymphocytes and increased plasma cortisol (Palmblad et al 1976). Forty-eight hours of wakefulness was followed by reduced phytohemagglutinin (PHA) mitogen response (Palmblad et al 1979). However, these studies are flawed by their reliance on single morning blood samples and the emotional distress of the experimental procedure.

Our study of the effects of 40 hours of wakefulness not only showed increased plasma IL-1 and IL-2 functions during the night of wakefulness, but also dramatic changes in

cellular immune functions. The nocturnal pokeweed mitogen (PWM) response that occurs during the normal baseline 24 hour sleep-wake cycle was delayed by sleep deprivation. PHA mitogen response showed no change with sleep loss. The activity of natural killer (NK) cells did not decline during nocturnal wakefulness as it had during baseline sleep. The NK activity remained reduced throughout the night of resumed sleep. These changes in peripheral immune functions were unrelated to changes in the circadian pattern of cortisol, thus indicating that the changes did not occur as the result of possible physiological stress of the procedures that were employed in the study (Moldofsky et al 1989).

In our 64 hour study of the effects of prolonged wakefulness, there was disruption of the normal undisturbed diurnal pattern of PWM and NK cell activities. Furthermore, two of the five subjects who participated in the study experienced upper respiratory infections and one subject encountered asthmatic symptoms for the first time within the week following the study (Moldofsky et al 1989). These studies show that sleep deprivation does alter the diurnal pattern of cellular and humoral immune functions. Although this is anecdotal evidence, sleep deprivation may predispose some vulnerable people to infectious illness. This notion is consistent with the animal experimental studies.

Altered circadian sleep-wakefulness. A variety of studies have shown circadian variation in the cellular immune system. Eosinophils, mononuclear cells, lymphocytes, T and B cells are increased between midnight and 2 a.m. (Haus et al 1983; Pownall 1984; Ross et al 1980; Bertouch et al 1983). Circadian variations in polymorphonuclear phagocytosis was not shown in one study (Bongrand et al 1988). However, these chronobiologic studies rely on infrequent sampling over 24 hours (as few as four and often no more than six per day), statistical extrapolations based on the assumption of a diurnal cosinor function, few or no overnight samples, and no reference to sleep physiology. One study of circadian concentrations of salivary prostaglandins E_2, F_2 and I_2 required that subjects be awakened from sleep for collection of saliva, but showed peak concentrations of these substances during nocturnal sleep (Rigas and Levine 1983). In our initial study on the relationships of IL-1 and IL-2 and cellular functions to the diurnal wake-sleep cycle, sleep effects could not be distinguished from circadian changes. By displacing sleep to two-hour naps at six-hour time intervals starting at midnight and concluding after the 6 p.m. nap, NK activity was found to be associated with sleep (Shahal et al 1992). That is, whenever the subjects slept, there was a coincident decline in NK activity. NK activity was at its lowest level during stage 4 sleep *versus* wakefulness. Although rectal temperature and plasma cortisol showed the typical reduction during the night and early morning rise, both the temperature and plasma cortisol were reduced during sleep compared to wakefulness. Plasma IL-1 activity was higher during stage 4 sleep than during wakefulness. There were no specific sleep-related changes with plasma IL-1 receptor antagonist and IL-2 or responses to PHA and PWM. This study demonstrates that aspects of cellular (NK cells) and humoral (i.e. IL-1) activity are related to sleep rather than diurnal influences. Plasma cortisol and temperature showed both diurnal and sleep-related effects.

Normal sleep-wakefulness and peripheral immune functions. Sleep-related cellular immune functions differ between young men and women. In our initial study of young men, B cell lymphocyte responsiveness assessed with the *in vitro* PWM test showed greater activity during nocturnal sleep while plasma cortisol declined. NK cell activity precipitously declined following sleep onset and reached its lowest level with onset to stage 4 sleep. The reason for this diminished activity is unknown, but may relate to either reduced function of NK cells or their disappearance from the circulation with distribution in the tissues to perform immune surveillance and lysis of pathogenic cells. Similar NK functional changes were observed in young women during the low progesterone phase of the menstrual cycle. However, during the high progesterone phase, stage 4 sleep was delayed and reduced, as were NK cell activities (Moldofsky et al 1991).

CONCLUSIONS

Given the observed changes in plasma IL-1 with sleep in humans and the experimental evidence that IL-1 is synthesized by a wide variety of cells (Dinarello 1988), it is possible, then, that IL-1 and other sleep-promoting and inhibiting immunologically-active cytokines operate both within the CNS and the periphery. Furthermore, as indicated in the human studies, mitogen responses and NK cell activities during wakefulness differ from those during sleep. These observations oblige us to forego the traditional conception that sleep and wakefulness are functional activities only of the brain. If indeed genetic control of certain peripheral cellular functions is linked to the sleeping-waking brain, then the mechanisms that govern those intracellular and extracellular functions need to be determined. Future research should lead to an understanding of how such regulatory operations of the peripheral cells of the immune system are coordinated with the circadian sleep-wake system. Thus far, the research shows an interrelationship not only of the immune and endocrine systems (Blalock, 1989), but also an intimate involvement of sleep-wakefulness with both these systems. The harmonious interrelationship of the circadian pattern of immune-endocrine and sleep-wake systems may be important in the cause and the function of sleep.

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