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Sleep as a behavioral model of neuro-immune interactions

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Abstract. The central nervous system, by a variety of mechanisms engages in constant surveillance of the peripheral immune system. Alterations in the status of the peripheral immune system induced by an invading pathogen for example, are quickly detected by the central nervous system, which then responds by altering physiological processes and behavior in an attempt to support the immune system in its efforts to eliminate the pathogen. Sleep is one of several behaviors that are dramatically altered in response to infection. Immune-active substances such as the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor, either directly or indirectly *via* interactions with neurotransmitters or neurohormones are involved in the regulation of sleep. Because these cytokines increase during infection, they are likely candidates for mediating the profound alterations in sleep that occur during infection. Since regulation of behavior is the function of the central nervous system, infection-induced alterations in behavior provide a unique model for the study of neuro-immune interactions.

Key words: cytokine, behavior, infection, neurotransmitter, review

Review

INTRODUCTION

There is now irrefutable evidence that the central nervous system and the immune system engage in bi-directional communication. The seminal studies of Besedovsky and colleagues (Besedovsky et al. 1977) indicating that firing rates of neurons in the hypothalamus increase during the peak antibody response to primary immunization began the modern era of investigation into what is now known variously as neuroimmunology, psychoneuroimmunology, psychoneuroendocrinology, or a variety of other terms. However, the basic observation that the central nervous and immune systems communicate is ancient. It has been the practice of physicians for millennia to advise their patients to sleep during the course of an illness, and we have all experienced feelings of sleepiness and lethargy during mild infections such as a cold or the flu. There are also other infection-induced alterations in behavior, and they may be dramatic. For example, when animals are sick, not only do their sleep patterns change, they become lethargic with reduced locomotion, they eat less, do not groom or care for themselves as they would normally, and sexual behavior and social interactions are reduced (reviewed in Hart 1988). The mechanisms responsible for these changes in behavior are diverse, but ultimately behavior is regulated by the central nervous system, and behavioral alterations during infection result from interactions between the central nervous and immune systems. Studies of alterations in behavior induced by systemic infections provide a framework within which hypotheses concerning mechanisms of communication between the central nervous and immune systems may be tested.

We will focus our attention in this paper on one specific behavior, sleep. Sleep may be viewed as the integrated output of multiple physiological processes. For example, physiological processes as diverse as thermoregulation, respiration, cardiovascular function, and neuronal activity are all altered in a specific fashion during sleep. Invasion of the host by a pathogen results in changes in these physiological processes with subsequent alterations in sleep. As such sleep may serve a sensitive index of homeostasis. In this paper we provide a brief overview of infection-induced alterations in sleep and discuss potential mechanisms responsible for these changes.

INFECTION-INDUCED ALTERATIONS IN SLEEP

Microbial challenge induces a myriad of host responses that incorporate immunological, physiological, and behavioral processes, among others. For example, infection-induced alterations in sleep generally coincide with the production of fever, leading some to question whether these changes in sleep are merely byproducts of the febrile response. However, this is not the case since the sleep responses may be dissociated from the fever, and in some cases the fever may actually persist long after sleep has returned to normal. The complex relationships between infection-induced alterations in sleep and fever have been recently reviewed (Opp 1999a) and will not be dealt with further in this paper.

To date, alterations in the sleep of rabbits, mice, cats, rats, and humans have been described in response to bacterial, viral, fungal, or protozoan pathogens (reviewed in (Toth 1999). Infection-induced alterations in sleep have perhaps been best characterized in rabbit following bacterial infections (reviewed in Toth 1995, 1999). Although the precise temporal responses to infection vary with pathogen and route of infection, acute infections are generally characterized by an initial increase in non-rapid eye movements (NREM) sleep, followed subsequently by a reduction in NREM sleep to levels below those observed prior to infection. In contrast to the initial enhancement of NREM sleep, rapid eye movements (REM) sleep is generally inhibited or suppressed. The specific pathogen, the route of inoculation, and the animal species are all important determinants of the time course of subsequent effects on sleep. For instance, the onset of NREM sleep enhancement induced by gram-negative bacteria is more rapid than that induced by gram-positive bacteria (Toth and Krueger 1989). The sleep response to microbial infections is also influenced by the status of systems that modulate immune responses. For example, immunosuppressive and anti-inflammatory doses of glucocorticoids attenuate sleep responses of rabbits to bacterial challenge (Toth et al. 1992). Although the *in vivo* replication of the pathogen may contribute to the alterations in sleep, replication of the pathogen *per se* does not seem to be essential; inoculation of rabbits with killed bacteria, isolated bacterial cell walls, or components of bacterial cell walls that have been phagocytized by mammalian macrophages all result in sleep alterations that are generally similar to those induced by viable bacteria. For example, muramyl peptides (the monomeric building blocks of bacterial cell wall peptidoglycan) and endotoxin and its lipid A moiety (components of the cell wall of gram-negative bacteria) increase the amount of NREM sleep when administered intravenously, intraperitoneally, intranasally, or intracerebroven-

tricularly, although the response differs in terms of latency and duration (reviewed Toth 1995, 1998).

Sleep is also altered during the course of viral infections. Although the effects on sleep of several viruses have been determined in different animal species, responses of mice have been the best characterized in this regard (e.g., Fang et al. 1995, Toth et al. 1995). The precise responses to influenza challenge in mice are genetically influenced. For example, C57BL/6 and Swiss Webster, but not BALB/c, mice inoculated intranasally with influenza virus exhibit enhanced NREM sleep and suppressed REM sleep that persists 72–96-h (Toth 1996). C57BL/6 mice produce large amounts of IFN in response to viral challenge whereas BALB/c do not. These observations suggest that the alterations in sleep of mice under these conditions are determined in part by the amount of IFN the animal produces in response to the virus (Toth 1996); IFN is somnogenic (see below). Rabbits also respond to influenza virus, although the virus does not fully replicate in this species. Nevertheless, rabbits subjected to an abortive infection with influenza virus also develop enhanced NREM sleep. These observations indicate that as with bacteria, replication of the virus *per se* is not necessary to alter sleep (Kimura-Takeuchi et al. 1992b). Furthermore, there are discrete components of the virus that are capable of altering sleep; viral double-stranded RNA enhances NREM sleep in rabbits (Kimura-Takeuchi et al. 1992a).

Humans infected with the human immunodeficiency virus (HIV) exhibit alterations in sleep long before they are symptomatic for AIDS, and prior to the virus invading the central nervous system (reviewed Darko et al. 1992, 1995). Since the early studies of Norman and colleagues (Norman et al. 1990, 1988) many reports indicate sleep alterations during HIV infection (reviewed Darko et al. 1995). Although the specific changes reported in the sleep of HIV infected individuals vary across and within studies, generally it is the timing and amount of human stage 3 and stage 4 sleep that is altered. Paradoxically, increases in slow wave sleep are usually accompanied by frequent awakenings, i.e., sleep is fragmented. There are several animal models appropriate for determining potential mechanisms by which HIV alters sleep before it can be detected in the central nervous system; rats and cats respond to administration of HIV and feline immunodeficiency virus envelope glycoproteins, respectively, with alterations in sleep that share many of the features reported in humans (Prospéro-García et al. 1994, Opp et al. 1996).

Sleep is also altered in response to infection with parasites. Perhaps the most infamous of sleep-altering parasites are some subspecies of the protozoan *Trypanosoma brucei,* the causative agent in humans of sleeping sickness (Pentreath 1989, Buguet et al. 1993). The observation that sleep alterations in rabbits inoculated with trypanosomes develops in temporal correlation with periods of parasitemia (Toth et al. 1994) suggest that, in this case, the *in vivo* proliferation of the organism is an important determinant of the sleep response. In addition to these recurring periods of hypersomnolence, there is a gradual loss of the normal circadian organization of sleep-wake activity (Buguet et al. 1993, Montmayeur and Buguet 1994, Toth et al. 1994, Grassi-Zucconi et al. 1995).

CYTOKINES AS MEDIATORS OF INFECTION-INDUCED ALTERATIONS IN SLEEP

In spite of differences in physical or chemical structures, all the microbial agents reviewed thus far affect sleep and are potent modulators of the host defense response. Cytokines, which are but one component of host defense, mediate many of the immunological and behavioral sequelae of bacterial or viral diseases. There are several lines of evidence indicating that behavioral responses to infection are mediated, at least in part by cytokines. For example, the bacteria, viruses, and protozoans discussed above all alter cytokine production (e.g. Andersson et al. 1992, Ulich et al. 1992) and cytokines levels are altered *in vivo* during infection (e.g. Dinarello 1992, Levy 1994). Since many cytokines are active in the central nervous system, and are well-documented modulators of many behaviors, including sleep (see Hart 1988 for a review), it is likely that they may play an important role in mediating infection-induced alterations in sleep. We briefly review below some of the evidence that supports this hypothesis. The interested reader is referred to a recent and more detailed review of this topic (Opp 1999b).

The term cytokine refers to a relatively large group of low molecular weight proteins that mediate many aspects of immunity, inflammation, tissue remodeling and embryonic development. Although virtually all cytokines were originally described as products of the immune system, we now know that circulating cytokines modulate central nervous system processes, that many cytokines are produced and are biologically active with-

in the central nervous system, and that receptors for many cytokines are also found within the central nervous system. These observations concerning the production, activity and receptor distribution within the central nervous system for at least some cytokines also suggests the possibility that they may play a role in the regulation/modulation of normal physiology in addition to mediating responses to immune challenge.

Although many cytokines have been characterized and cloned, studies on their ability to modulate sleep have focussed primarily on three groups; the interleukins (IL; primarily IL-1), tumor necrosis factors (TNF), and interferons (IFN). Other cytokines, such as IL-2, IL-4, IL-6, IL-10, fibroblast growth factor, nerve growth factor and granulocyte-macrophage colony-stimulating factor, have also been studied with regard to sleep. However, in most cases these cytokines have been the subject of limited experiments that have resulted in single reports that may be either preliminary or anecdotal in nature, or are based on correlative associations without any evidence that direct intervention with the system of interest alters sleep. Clarification of a role for these cytokines in sleep regulation awaits additional experimental evidence, and they will not be discussed further in this paper.

IL-1β is a pleiotropic cytokine that belongs to a gene family that includes IL-1α and the IL-1 receptor antagonist (IL-1ra). These molecules bind to two IL-1 receptors (type I and type II). Upon activation by the ligand, the type I receptor complexes with an accessory protein, which results in signal transduction. IL-1 has been the most extensively studied cytokine with regard to the regulation of sleep. Both IL-1β and IL-1α are somnogenic, but most studies of IL-1 effects on sleep have used IL-1β. The somnogenic properties of IL-1 have been describe by several laboratories, and this cytokine has been shown to alter the sleep of rabbits, rats, mice, cats and monkeys (reviewed Opp et al. 1992, Krueger et al. 1994).

Although not all the species respond to IL-1 in the same way, the most common effect is an increase in NREM sleep accompanied by REM sleep inhibition, although at low effective doses REM sleep is not necessarily inhibited. In rats, NREM sleep enhancement by IL-1 is characteristically biphasic; there is an initial increase that lasts about 1-h, and after a 2 - 3 h delay during which NREM sleep is not greatly altered, the majority of the increase in NREM sleep becomes apparent. (Opp et al. 1991, Gemma et al. 1997, Imeri et al. 1997, Opp and Toth 1998). In highly circadian species such as the rat, the sleep responses to IL-1 are modulated by circadian processes (Opp et al. 1991, Lancel et al. 1996, Opp and Toth 1998). Thus, during the light period of the light:dark cycle, the predominant effect of IL-1 is to increase electroencephalogram delta wave activity without greatly altering NREM sleep duration, whereas during the dark period of the light:dark cycle NREM duration is generally enhanced with little effect on electroencephalogram delta wave activity.

IL-1 and other cytokines induce the synthesis/secretion of multiple neurotransmitters, neuropeptides and hormones that have been implicated in sleep regulation. As such, the observation that sleep is altered in response to IL-1 does not directly implicate IL-1 in the regulation of sleep because the effects of cytokines on sleep may be mediated by other systems. An example of such interactions are those that occur between IL-1 and the growth hormone-releasing hormone/growth hormone axis (Payne et al. 1992, Obál Jr. et al. 1995). Growth hormone-releasing hormone is somnogenic, and inhibition of this hypothalamic releasing factor attenuates IL-1-induced changes in sleep. The role of neuropeptides and hormones as mediators of responses to cytokines has been reviewed elsewhere (Krueger and Obál Jr. 1993) and will not be discussed further. Nevertheless, observations that direct intervention with the IL-1 system using specific receptor antagonists or antibodies alters spontaneous sleep in normal animals provide strong supporting evidence of a role for IL-1 in sleep regulation. The interested reader is referred to recent reviews that provide a more detailed discussions of the role of IL-1 in the regulation of sleep (Opp 1998b, Krueger and Fang 1999).

TNF, like IL-1 is a pleiotropic cytokine that is constitutively expressed in normal brain. There are two forms of TNF, TNFα and TNFβ. Although TNFβ is somnogenic, most sleep studies have used TNFα. TNFα immunoreactive neurons have been described in the central nervous system, and TNF receptors are expressed in normal brain and the soluble form of the receptor occurs normally in cerebrospinal fluid. There are two cell surface TNF receptors, although it appears the 55 kDa form is responsible for mediating TNF-induced alterations in sleep (Fang et al. 1997). Enhanced NREM sleep following TNF administration has been described in rabbits, mice and rats, and is generally accompanied by reductions in REM sleep (Krueger and Fang 1999). A role for TNF in sleep regulation is supported several lines of evidence that are generally similar to the type of evidence implicating IL-1 in sleep regulation reviewed (Opp

1998b, Krueger and Fang 1999). Plasma TNF concentrations exhibit circadian rhythms that correlate with EEG slow wave activity in humans and peak concentrations are detected during sleep; in rat brain, TNF mRNA and protein exhibits a diurnal variation with peak concentrations occurring during the light period of the dark:light cycle, the time when rats sleep the most. Direct and specific intervention with the TNF system using receptor antagonists, antibodies, or binding proteins, reduces spontaneous NREM sleep in otherwise normal animals.

There is generally limited evidence implicating IFN in the regulation of physiological sleep. Human recombinant IFNα induces cortical electroencephalogram synchronization in the rat (De Sarro et al. 1990), increases NREM sleep in rabbits (Krueger et al. 1987, Kimura et al. 1994), and reduces latency to REM sleep in monkeys (Reite et al. 1987). IFNs probably are more important as mediators of somnogenic responses to viral challenge. As reviewed previously, responses of mice to influenza virus infection depends on the amount of IFN produced (Toth 1996).

A POTENTIAL ROLE FOR INTERACTIONS BETWEEN CYTOKINES AND NEUROTRANSMITTERS IN MEDIATING INFECTION-INDUCED ALTERATIONS IN SLEEP

The activation of the immune system induces profound alterations in several neurotransmitter systems (reviewed in Imeri et al. 1998a). The neurochemical changes induced in the central nervous system by immune challenge are complex, and may result in alterations in behavior. The interactions between serotonin (5-HT) and IL-1 may be important in determining the behavioral outcomes of an acute infection.

The findings that central or peripheral administration of IL-1 activates the serotonergic system by enhancing 5-HT release and metabolism (Gemma et al. 1991, 1994, Shintani et al. 1993, Linthorst et al. 1994) and turnover (Mefford and Heyes 1990, Dunn 1992, Zalcman et al. 1994), as well as by raising brain tryptophan levels (Dunn 1992), suggests multiple levels of interaction for these substances. The effects of IL-1 on the serotonergic system are specific and receptor mediated (Gemma et al. 1991). In freely behaving animals, serotonergic activity exhibits state-specific changes; it increases during wakefulness and decreases during sleep (Cespuglio et al. 1990, Imeri et al. 1994, Portas and McCarley 1994). These phasic 5-HT state-specific changes are not disrupted by IL-1; they persist and are superimposed on the tonic, overall increase in 5-HT activity induced by IL-1 (Gemma et al. 1997).

Central administration of IL-1 alters sleep, induces fever and anorexia, activates the hypothalamic-pituitary--adrenal axis, and suppresses sexual and locomotor behavior. Serotonin plays a role in each of these behaviors and processes, suggesting that 5-HT may mediate in part some IL-1 actions (De Simoni et al. 1995). In rats, the initial NREM sleep response to IL-1 is associated with an increase in serotonergic activity in the medial preoptic area (Gemma et al. 1997). The observation that the initial increase in NREM sleep induced by IL-1 is abolished in rats in which brain serotonin has been depleted by *para*-chlorophenylalanine (PCPA) (Imeri et al. 1997) also supports the hypothesis that 5-HT may be a mediator of IL-1 actions. Serotonin may mediate these effects of IL-1 on sleep by interacting with the 5-HT_2 receptor; the increase in NREM sleep following IL-1 administration is partially blocked when rats are pretreated with a 5-HT_2 receptor antagonist (Imeri et al. 1998b).

Serotonin has also been shown to mediate the NREM sleep promoting effects of another well known immune-active substance, muramyl dipeptide (MDP), the synthetic analog of muramyl peptide. Muramyl peptides are well-known somnogenic substances (reviewed in Krueger and Majde 1994); the administration of MPs tailored from bacterial cell walls, as well as of MDP, induces NREM sleep and fever (Krueger et al. 1982, Johannsen et al. 1991). There is evidence suggesting that MPs/MDP interact with the serotonergic system at multiple levels: (1) 5-HT turnover is increased in response to MPs (Masek and Kadlec 1983), (2) MPs have specific binding sites on macrophages and glial cells and 5-HT competes for these binding sites, and (3) MDP inhibits 5-HT uptake by human platelets, whose serotonergic system is commonly considered to resemble that of the CNS (Polanski and Karnovsky 1992). At least some effects of MPs/MDP may be mediated through interactions with the serotonergic system. The finding that MDP does not alter sleep-wake activity and brain cortical temperature when given to PCPA-pretreated rats suggests that 5-HT is essential for MDP to exert effects on sleep (Imeri et al. 1997).

In addition to the effects of IL-1 on the serotonergic system, there is a second facet of interactions between these substances that may be important in determining

behavioral outcomes to immune challenge; 5-HT also stimulates IL-1 release (Silverman et al. 1989). IL-1 could therefore be one of the sleep factors through which it has been proposed that 5-HT exerts its somnogenic effects (Jouvet et al. 1983). Observations that some cytokines, such as IL-6 do not affect sleep yet activate the serotonergic system, whereas others, such as TNF promote NREM sleep without activating the serotonergic system (reviewed in Imeri et al. 1998a), indicate that cytokine-induced alterations in behavior may be dissociated from those alterations induced in neurochemical systems. These reported dissociations reinforces the fact that the net behavioral effects of an immune challenge are not dependent on the activation of a single neurochemical system.

In addition to IL-1-induced changes in serotonergic activity, there are other neurotransmitter systems affected by IL-1 that may contribute to alterations in sleep in response to this cytokine. For example, the cellular mechanisms thought to be responsible for the effects of benzodiazepine hypnotics include the activation of central GABA-ergic inhibitory neurotransmission (Muller 1995); IL-1 induces activation of the GABA-ergic system (Miller et al. 1991). The potentiation of GABA effects could explain IL-1 effects on sleep, although *in vivo* data are needed to establish the importance of this action. In addition, the observation that TNF does not affect GABA transmission indicates that somnogenic cytokines may act through different mechanisms (reviewed in Imeri et al. 1998a). The inhibitory effects of IL-1 on acetylcholine (Ach) release could be relevant in sleep regulation, although thus far these actions have only been studied in hippocampal slice preparations (Rada et al. 1991). IL-1 inhibits REM sleep. Since REM sleep is facilitated by the cholinergic system (Jones 1989, De Simoni et al. 1995), this action of IL-1 may reflect a decrease in ACh transmission. The observation that IL-2 (whose somnogenic properties are controversial (Nisticó and De Sarro 1990, Opp and Krueger 1994) may increase or decrease ACh depending on the dose used indicates the importance of determining effects of multiple doses for cytokines before any conclusion are drawn about their possible role in the regulation of sleep. IL-1 also activates the noradrenergic, dopaminergic, and histaminergic systems; all of which promote wakefulness (Jones 1989, De Simoni et al. 1995, Monti 1995). These neurochemical changes induced by IL-1 may thus facilitate the return to normal sleep-wake activity after immune challenge.

CONCLUSIONS

There are dramatic and complex alterations in behavior during infection. Since the regulation of behavior is the function of the central nervous system, infection-induced alterations in behavior provide a unique model within which to elucidate aspects of bi-directional communication between the central nervous and immune systems. We have in this paper briefly reviewed evidence that one behavior, sleep, is altered during infection, and that cytokines are likely to play an important role in these alterations. The alterations in sleep in response to infection may be mediated within the central nervous system by actions of cytokines on several neurotransmitter systems, including the serotonergic, cholinergic, and gabaergic systems. Observations such as those reviewed in this paper suggest that sleep as a behavior may be a useful model for elucidating further the interactions between the central nervous and immune systems.

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