Sleep Disturbances in HIV

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President's Column

As we approach the Annual Meeting of the Association of Professional Sleep Societies in Washington, D.C. (May 28-June 1, 1996), I would like to thank Jerome Siegel, Ph.D. and other members of the Program Committee for organizing a meeting which should be exciting and stimulating in all respects.

The meeting will be associated with the Great American Sleepwalk on Washington on May 29 11:00 am to 4:00 pm. This is a wonderful opportunity for members of the Sleep Research Society to educate Members of Congress and the patient advocacy groups on the importance of basic and clinical biomedical research in general and sleep specifically. I cannot over-emphasize the importance of face-to-face contact with congressmen and their staff in increasing federal funds to support basic, clinical, and applied research, as well as research training. This type of education and lobbying is particularly effective when you are accompanied by patients and their families who have been suffering from sleep related disorders and conditions. In addition, you should try to establish on-going relationships with congressmen and to write to them to support increased federal funding for research. For further information, please contact Jennifer Torgrimson at (507) 285-4364, Email at jtorgrim@millcomm.com, or FAX at 507-287-6008.

The lobbying effort is particularly timely for members of the SRS since Harold Varmus, M.D., Director of the NIH, has recently approved the National Sleep Disorders Research Plan from the National Center on Sleep Disorders Research. Many members of SRS contributed to the writing of this research plan. Since no resources have been allocated to support the research plan, the Sleepwalk will provide us with an opportunity to ask for Congressional help in its implementation.

Finally, I am pleased to say that the leaders of the SRS and the American Sleep Disorders Association have worked hard and well during the past year to improve communication and cooperation between the two societies. We will want to strengthen the field of sleep in all its many areas. We are continuing to discuss ways in which to achieve these goals by bringing the research, clinical, applied, and academic domains together in a synergistic and mutually supporting relationship or structure. We welcome further discussion about the future of our field at the Annual Meeting and, especially, at the Business meeting in Washington.

I hope to see you in Washington!
Editor's Column

We are now well into the second decade of the worldwide pandemic caused by the human immunodeficiency virus (HIV). A handful of sleep researchers have been documenting the changes in sleep associated with HIV infection. When weighed against the worldwide research effort, these investigators represent a small fraction. Nevertheless, their findings have made a tremendous impact because changes in sleep are an important and persistent clinical symptom of HIV infection. Here some of these investigators review their findings.

The precise mechanism by which HIV alters sleep is unknown. This might be because as Pollmacher and Holboer point out that “the impact of viral infections on sleep has hardly been investigated.” These authors offer several strategies that might be used to understand the sleep-immune interactions in HIV. Nevertheless, as reviewed by Opp and colleagues, there is a substantial body of work at the basic research level implicating cytokines in sleep regulation. Increased levels of cytokines are associated with the pathophysiology of HIV and they are most likely to also contribute to the sleep disturbances associated with the HIV infection.

Opp and colleagues detail their interesting new findings with HIV-gp120, a glycoprotein that is the binding site for the virus. Darko and colleagues detail their findings in cats with feline immunodeficiency virus (FIV) which represents an animal model of HIV.

These investigators and those that were not able to contribute to this issue have made significant advances in our understanding of sleep changes in HIV.

Important gaps remain.

• There are no details about sleep in acute HIV infection. In fact, there is no objective assessment of sleepiness with the MSLT in acute HIV infection.

• More research is needed on the effects of viral infections on sleep.

• Data is beginning to emerge that sleep deprivation affects immunocompetence. How this is done is unknown. This could show that sleep is a beneficial adaptive response to preserve host-defense mechanisms.

Articles

Mechanisms of HIV-induced Alterations in Sleep: the Role of Cytokines in the CNS

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Introduction

Tissues of the immune and nervous systems are targets of the human immunodeficiency virus (HIV). Research on the neurological aspects of HIV infection [Neuro-AIDS (acquired immunodeficiency syndrome)] has focused largely on the etiopathogenesis of a broad spectrum of neurologic diseases. With the exception of studies on sleep, there are few, if any, reports concerning HIV actions within the CNS as they pertain to altered behavior prior to the onset of neurodegenerative processes, or the onset of AIDS. Many of the biochemical messengers responsible for communication within the immune system, e.g. cytokines, are involved also in the regulation of sleep. A consistent finding of polysomnographic studies conducted on HIV-infected individuals is one of altered nighttime sleep.

Furthermore, excessive daytime sleepiness and fatigue are prominent and persistent symptoms of HIV infection [see (5), and this issue for reviews]. The precise mechanisms whereby HIV alters sleep are not known. We review evidence in this paper suggesting that viral products, particularly the HIV envelope glycoproteins, contribute to altered behavior, and that these actions may be mediated, in part, by cytokines.

HIV targets tissues of the immune and nervous systems

Although HIV, and the acquired immunodeficiency syndrome that results from it, affects directly or indirectly virtually every organ system in the body, it is tissues of the immune and nervous systems.
that are primarily affected. The progression from HIV infection to AIDS generally consists of a brief acute period (days to weeks) of mononucleosis-like illness (4,37,38) followed by a prolonged, yet variable length, period during which HIV-infected individuals are asymptomatic for AIDS. Opportunistic infections or malignancies then occur, either after the appearance of constitutional symptoms of AIDS (fever, weight loss, malaise, fatigue, diarrhea, etc.), or directly from the chronic asymptomatic phase without expression of constitutional symptoms (24). Early in the pandemic, neurologic interest in HIV infection focused on opportunistic infections of the CNS, and on the prevalence of brain tumors [reviewed (14)]. Beginning in the mid 1980s however, a series of findings were reported that cumulatively resulted in HIV being reassessed as a neurotropic virus [reviewed (14)]. These findings included recovery of HIV from the cerebrospinal fluid (CSF) and brains of AIDS patients, increased anti-HIV antibody titers in the CSF, the demonstration of HIV RNA in microglial nodules of subacute encephalitis, and HIV DNA levels in the brain were found to be higher than those in the lymph nodes spleen or liver. Finally, HIV was shown to be a member of the lentivirus subfamily of retroviruses; in their natural hosts, lentiviruses cause persistent infection of mononuclear cell populations and lead to chronic multisystem disease including chronic encephalitis. There is now a broad spectrum of neurological diseases attributed to HIV, though the pathogenesis for these diseases are poorly understood [see for example (2,8,21,48)].

Sleep is altered during viral infections, including HIV

Sleep is altered during the course of microbial infections, including those in which a virus is the etiologic agent. The implications of viral infections for alterations in sleep were clearly demonstrated by von Economo (44); profound alterations in sleep were observed in patients that had viral-induced lesions in the hypothalamus. However, the relationship between sleep and infection has only recently received systematic investigation, despite common experiences of sleepiness during infectious disease, and the age-old practice of recommendation by physicians of bed rest as an aid in recuperation. Although changes in sleep have not as yet been completely characterized over the course of an infectious condition in humans, there is now a growing body of evidence from animal models of acute infection that sleep is altered and that cytokines are likely to be involved. Sleep patterns during infection have been most thoroughly characterized in the rabbit; inoculation of rabbits with either bacterial or fungal organisms results in sleep alterations [reviewed (20,41)]. Rabbits subjected to an abortive infection with influenza virus also exhibit enhanced sleep (16). These studies in rabbits using an abortive influenza infection, in addition to quantifying changes in multiple parameters through the course of a viral challenge, indicate that replication of the virus per se is not necessary to alter sleep and suggest that host defense responses to intact virus or viral components play a critical role in the behavioral responses to viral challenge.

Sleep is altered in response to viral challenge under conditions when the virus does replicate, i.e. during true viral infection. Male Swiss-Webster mice inoculated intranasally with mouse-adapted influenza virus (H1N1-A/PR/8/34) exhibit enhanced nonrapid eye movements sleep (NREMS) and suppressed REMS that persists 72 - 96-h (10). Similarly, C57BL/6 mice inoculated intranasally with A/HKx31-H3N2 influenza virus respond with enhanced NREMS and suppressed REMS for a period of at least 96-h (39). BALB/c mice, however, inoculated with this same influenza virus preparation exhibit reduced REMS but little alteration in NREMS (39,40). These data indicate that enhanced sleep associated with influenza infection occurs in some, but not all, mouse strains, and may result from the ability of the animal to mount an interferon (IFN) response to the virus; IFN production during viral infections is greater in C57BL/6 mice than in BALB/c mice (7). IFN is another somnogenic cytokine, providing additional evidence of a role for cytokines in mediating somnogenic responses to viral challenge.

HIV infection and cytokine cascades

HIV may be isolated from CSF during the period of primary HIV infection indicating that HIV enters the CNS shortly after exposure (6,38). Cytokines, including the somnogenic cytokines IL-1 and TNF, may be detected within the CNS during primary infection (38), during chronic infection when individuals are asymptomatic (12,42), and late in the infection when patients are symptomatic for ARC or AIDS (3,8,22,42,47). These reports, and others, clearly indicate that cytokine concentrations within the CNS may be elevated throughout the entire course of HIV infection (11). Furthermore, cytokine profiles exhibit dynamic alterations throughout the course of HIV infection (11,23). It is also clear that sleep is altered at every stage of HIV infection studied thus far. Therefore, the hypothesis that HIV-induced changes in cytokine concentrations or profiles within the CNS may
contribute to altered behavior during HIV infection is strongly supported by indirect data.

There are obvious limitations to the study of HIV actions within the CNS of living individuals. The search for suitable animal models for determining CNS actions of this virus has become a priority at the National Institutes of Health (27,43). One model that shows promise is the feline immunodeficiency virus (FIV) model. FIV is a lentivirus that is closely related to HIV, it is a natural pathogen of domestic cats, and it produces an immunodeficiency syndrome with CNS sequelae that are similar to those of HIV ((13, 33); see also Darko et al., this issue). As yet however, there are no reports concerning FIV-induced changes in cytokine profiles either systemically or within the CNS; appropriate reagents are a limiting factor in this regard. We review data indicating that a rat sleep model may be useful for the study of HIV-induced alterations in sleep. This model is not a model of HIV infection since HIV does not normally replicate in rat cells. From the perspective of altered sleep/wake behavior however, there are several advantages to using rats to determine actions of HIV within the CNS. 1) The sleep of rats is definable, and in many ways, resembles that of humans. 2) Rats respond to HIV glycoproteins (gp) with increased cytokine concentrations and altered sleep. 3) Intact, viable HIV is not necessary to elicit cytokine and behavioral responses within the CNS of rats. 4) Specific antagonists for rat IL-1b and TNFα are commercially available and effective (see for example (29), and may be used as tools to determine the extent to which these cytokines are involved in HIV-induced alterations in sleep.

The HIV gp120 alters rat sleep-wake behavior

HIV gp120 is the binding site for the virus, is shed from the virus, and may be recovered from the CNS. Therefore, gp120 is one of the components of HIV that is likely to be “seen” by the CNS. HIV gp120 stimulates IL-1b and TNFα from human and rat glial cells in vitro (18,19,25,26), and in freely behaving rats (35,46). It was of interest to us to determine whether gp120 alters rat sleep.

ICV administration at dark onset of low doses of gp120 (20 ng) does not alter sleep in rats. However, 100 ng of gp120 administered by the same route initially enhances, and subsequently suppresses NREMS (31); NREMS enhancement is confined to postinjection hours 3-4, whereas NREMS suppression occurs 11-12 hour postinjection. These alterations in NREMS are paralleled by changes in REMS. After higher doses of gp120 (500 ng), NREMS is enhanced for about 8-h postinjection without affecting REMS (31). Increases in delta power during NREMS occur after the 500 ng dose of gp120, and sleep-wake architecture becomes fragmented. Alterations in sleep induced by gp120 are specific for the protein; all biological activity in this assay system is lost following heat-inactivation of the protein (31). The gp120-induced alterations in sleep are similar in several respects to those observed after ICV administration of IL-1: 1) low doses of IL-1 induce biphasic NREMS responses (15) similar in magnitude to those of gp120, but with a more rapid onset (hours 1-2 postinjection), 2) IL-1 enhances delta power during NREMS in the rat (30), and 3) fragmented sleep-wake architecture is a hallmark of high doses of IL-1. However, there are some differences in responses to gp120 as compared to those of IL-1. First, brain temperature is not altered by any of the gp120 doses tested thus far. Second, REMS is not altered by low doses of IL-1, but is suppressed as IL-1 doses increase (28,30); at low doses, gp120 enhances REMS and NREMS, and the highest dosages of gp120 tested thus far do not suppress NREMS.

The IL-1 receptor antagonist (IL-1ra) transiently blocks responses to gp120

If the effects of gp120 on sleep-wake activity are mediated, in part, by IL-1, then interfering with the binding of IL-1 to its receptor should alter gp120-induced alterations in sleep. Preliminary data support this hypothesis. Rats into which 500 ng gp120 are administered ICV prior to dark onset exhibited enhancements in NREMS (unpublished data) similar to those previously reported for this dose (31), i.e. NREMS was enhanced during postinjection hours 1-8. When the same rats were pretreated with the IL-1ra prior to the administration of gp120, the initial increase in NREMS was blocked. This inhibition was limited to the first postinjection hour; values for NREMS thereafter did not differ from those obtained after gp120 alone. The short period of inhibition of gp120 effects by the IL-1ra is likely due to the fact that the half-life of the IL-1ra is very short, about 10-min in blood (9). Nevertheless, these data indicate that blocking the binding of IL-1 to its receptor interferes with the initial NREMS response to the 500 ng dose of gp120.

Microinjection of gp120 into the dorsal hippocampus increases NREMS

HIV gp120 administered ICV diffuses
throughout the cerebral ventricular system; subsequent effects may be mediated by diverse sites of action. Microinjection studies may provide information about sites of action. Although other brain regions are thought to play a greater role in the regulation of sleep (e.g. hypothalamus, basal forebrain), we selected the dorsal hippocampus as a target for initial microinjection studies because, 1) we are particularly interested in interactions between HIV products and cytokines; the hippocampus contains the greatest density of IL-1 receptors in rodent brain (1,36), and 2) previous reports indicate that microinjection of gp120 into the hippocampus increases IL-1 activity in the rat brain (35,46).

The amount of NREMS increased, relative to values obtained after vehicle administration, when 100 ng gp120 was microinjected into the dorsal hippocampus (Opp et al., unpublished data). This increase in NREMS was limited to postinjection hours 5 - 8, and was concurrent with increases in REMS and reductions in waking. These alterations appear to result from increases in bout numbers, rather than bout duration. The delayed NREMS responses following gp120 administration by this route (relative to ICV administration) supports the hypothesis that these effects may be mediated, in part, by IL-1; IL-1 was detected 2.5 h after microinjection of gp120 into the hippocampus (35). These responses to microinjection of 100 ng gp120 are similar, in some respects, to those observed following ICV administration of this dose; REMS increased in parallel with NREMS, these increases appear to reflect changes in bout number, and brain temperature was not altered by this manipulation.

**HIV gp120 induces IL-1b and IL-10 mRNA expression in the rat hypothalamus and hippocampus**

HIV gp120 induces cytokine expression within the rat CNS. In our model, IL-1 is considered an "agonist" since the primary effect of IL-1 on sleep is one of enhancement. IL-10 was recently described as a "cytokine synthesis inhibitory factor" due to its ability to inhibit cytokine synthesis (including IL-1) by stimulated monocytes/macrophages. IL-10 is elevated late in HIV infection, and has been implicated in the progression to AIDS (11,23). In our model, IL-10 is considered an "antagonist" since ICV administration of IL-10 reduces spontaneous NREMS in rats (32). The temporal relationship between the expression of cytokines that enhance sleep (e.g. IL-1) and those that inhibit sleep (e.g. IL-10) may be important in modulating sleep-wake behavior, and may contribute to the fragmented nighttime sleep reported in HIV-infected individuals. We have initiated studies to determine gp120-induced alterations in IL-1b and IL-10 mRNA expression in the rat CNS.

ICV administration of 100 ng gp120 into rats maintained under identical conditions as those used in sleep studies induced IL-1b and IL-10 mRNA expression in the hypothalamus (31). IL-1b mRNA was detected in the second postinjection hour. Since enhanced NREMS after this dose of gp120 occurs in postinjection hours 3 - 4 (31), these observations provide additional support for the hypothesis that gp120 effects may be mediated, in part, by IL-1 [e.g. ICV gp120 P IL-1b gene expression (2 h postinjection) P enhanced NREMS (3 - 4 h postinjection)]. The same temporal pattern for gp120-induced IL-1b mRNA appears to occur in the hippocampus (Opp et al., unpublished data). HIV gp120-induced IL-10 mRNA expression in the hypothalamus occurs earlier than that of IL-1b, being evident in the first postinjection hour (31). Although the definitive experiments have not been conducted and the kinetics of IL-10 synthesis inhibition in vivo are unknown, gp120-induced expression of IL-10 may occur prior to that of IL-1b to provide time-critical regulation of IL-1 (and other proinflammatory cytokine) actions; early IL-10 gene expression may provide adequate time for IL-10 protein synthesis to occur with subsequent inhibition of IL-1 synthesis.

**Conclusions and Perspectives**

There has been an intense and concerted research effort on both systemic and CNS effects of HIV. However, only a small fraction of this research has focused on the prominent and persistent changes in sleep associated with HIV infection. These HIV-induced alterations in sleep may occur in the absence of overt psychiatric symptoms associated with anxiety or depression. Data reviewed herein support the hypothesis that HIV-induced alterations in sleep may be mediated, in part, by cytokines. The precise mechanisms for such alterations remain to be determined. The use of molecular techniques in conjunction with well-defined behavioral models may prove to be a useful approach in the elucidation of these aforementioned mechanisms.

One of the current approaches to identifying activated areas of the brain is the use of the production of transcription factors as markers of activation. Depending upon the particular factor and the gene(s)
activated, these markers may have varying degrees of specificity. Probably the most common marker of this type, c-fos, is an inducible protein which combines with c-jun to form the AP-1 transcription factor. The use of fos and jun in determining sleep-wake state-dependent activation of brain regions/structures has become increasingly popular (see, for example, the last issue of the Sleep Research Society Bulletin). However, the AP-1 transcription factor is used by many genes in the nervous system, as well as genes in non-neural tissues. Therefore, Fos is relatively nonspecific as a measure for expression of a single or few genes, although it is certainly useful as a marker of general activation (45).

In mechanistic terms, a more specific and informative marker would be a transcription factor restricted to the specific gene(s) of interest. Based on the studies described above, in which cytokines appear to play a critical role, a more mechanistic approach would be to target transcription factors that are specific for enhancing cytokine gene expression. To date, transcription factors specific for a single cytokine have not been described. However, nuclear factor kappa B (NF-kB) promotes the expression of genes related to immune function and relevant to the alterations in sleep described above. IL-1β, TNF-α and IFN are three sleep-related cytokines with gene expression induced by NF-kB (34). Likewise, more recently described transcription factors with even greater gene specificities, such as the nuclear factor for IL-6 gene expression (NFIL6) (17) may prove in the future to be even better candidates for cytokine-specific markers.

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References


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**Sleep-Wake Disturbances In HIV-Infected Patients - A Potential Model Of The Interactions Between Sleep And The Immune System**

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**What are the major questions about HIV-related sleep-wake disturbances?**

Disturbed initiation and maintenance of sleep (DIMS) and daytime fatigue are common complaints in HIV-infected persons. This is not surprising during the late stages of the disease, when severe opportunistic infections overwhelm the body, including the CNS. But, about one quarter of otherwise healthy patients complain much earlier, during the first years of early chronic HIV infection, about sleep disturbances and disabling daytime fatigue (Moeller et al., 1991; Darko et al., 1995). The resulting decrease in subjective well-being and in psychosocial function warrant per se research on the characteristics and causes of altered sleep-wake behavior in HIV-infected persons. Furthermore, the increasing knowledge on sleep-immune interactions raises additional, more
fundamental issues, rendering sleep-wake disturbances in HIV-infected subjects an even more important area of research (see Table 1).

Table 1. WHY SLEEP-WAKE BEHAVIOR IN EARLY CHRONIC HIV INFECTION IS AN IMPORTANT RESEARCH TOPIC?

- DIMS and fatigue are frequent and disabling problems for many patients.
- Sleep-wake complaints may have, among others, immunopathological causes. Therefore, it may be possible to develop specific treatments.
- Insufficient and disturbed sleep may aggravate immunodeficiency and accelerate the course of the disease.
- Detailed knowledge about the pathophysiology of sleep and wakefulness in HIV infection may help in understanding sleep-immune interactions in general.

First of all, it is likely that immunopathological mechanisms are involved in HIV-related sleep-wake complaints. As a result of intriguing preclinical work performed during the last 20 years, mainly by the group of James Krueger, it is now beyond any doubt that the activation of specific and non-specific immunological pathways interferes with the regulation of sleep and wakefulness. In animal models, many details of the underlying mechanisms have been delineated, pointing to a central role of the proinflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) as modulators of sleep (Krueger and Toth, 1994). As well in animal models, it has been shown that the effects of cytokines on sleep can be blocked by specific antagonistic strategies. Because proinflammatory cytokines are involved in the pathophysiology of HIV infection it is reasonable to hypothesize that they are also involved in DIMS and fatigue and that attempts to develop specific treatment strategies would be promising. However, our present knowledge about the effects of host defense activation on sleep in humans is much more scanty than in animals and the available evidence (reviewed by Pollmächer et al. 1995) suggests considerable differences among species.

A second area of interest is the possible impact of disturbed sleep on immunocompetence in HIV-infected individuals. It is plausible to assume that the interactions between mechanisms regulating sleep and those regulating the immune system are bi-directional. Despite the ancient belief that sleep supports the host defense, our current understanding about the extent to which and how sleep is a beneficial adaptive response to infection is very limited. In a number of studies sleep deprivation has been shown to alter indirect measures of immunocompetence (reviewed by Moldofsky, 1994). However, the relevance of these changes for the in vivo host response to infection remains unknown.

Finally, knowledge about the pathophysiology of sleep and wakefulness in HIV-infected subjects may enrich our understanding of sleep-immune interactions in general. Viral infections are among the major causes of morbidity throughout the world. It is beyond doubt that sleepiness, unrefreshing sleep and fatigue, frequently associated with these diseases, contribute significantly to the resulting disabilities. Nonetheless the impact of viral infections on sleep has hardly been investigated. The few data available suggest that there can be profound and, in the case of Epstein Barr Virus infection, long-lasting effects (see Pollmächer et al., 1995). Furthermore, DIMS and fatigue are among the most frequent complaints in the general population, and in a large proportion of cases use of our present diagnostic repertoire does not lead to satisfying results. Immunological causes have recently been inferred to play a role. This is particularly true for the chronic fatigue syndrome (Moldofsky, 1995) for which, however, no consistent immunological abnormality has been shown so far. The present concepts and hypotheses regarding chronic fatigue would benefit considerably from detailed knowledge about the interactions of sleep and the immune system in diseases with definite immunopathology such as HIV infection.

Which pathophysiological aspects of HIV infection can affect sleep-wake behavior?

The course of HIV infection can be divided into three phases. Weeks to months after virus inoculation most patients experience a spontaneously resolving flu-like disease characterized by a high rate of virus replication and the build-up of specific (although insufficient) immunity. The following years of early chronic infection represent a long-lasting 'clinically latent', predominantly asymptomatic period. It should be stressed, however, that during this phase viral replication does not completely stop. CD4 counts slowly but progressively decline and there is a significant albeit not dramatic increase in the incidence
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<td>Direct effects of infection</td>
<td>Immunoadaptation (acute phase responses, B-cell activation, increased levels of cytokines and soluble cytokine receptors, etc.)</td>
<td>Functional impairment of infected brain tissue. immunoadaptation within the CNS.</td>
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<td>Indirect effects</td>
<td>Acute and chronic non-opportunistic infections</td>
<td>Neuroendocrine adaptation Stress Psychosocial adjustment Anxiety Depression Cognitive and personality impairment Dementia</td>
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of non-opportunistic (e.g. viral) infections (Pantaleo et al., 1993). Finally, late chronic HIV infection, starting at a median of 10 years after virus inoculation, is characterized by a rapid breakdown of immunocompetence and severe opportunistic infections.

In the following we will focus on early chronic HIV infection because with regard to the acute illness there are no data on alterations in sleep and wakefulness and with regard to the late stage of severe immunodeficiency the possible factors influencing sleep-wake behavior are too numerous to enable the investigation of their detailed causes. As shown in Table 2, there are several aspects of early chronic HIV infection that may affect sleep-wake behavior. These can be divided into direct and indirect effects of the infection and, in addition, into those occurring systemically or within the CNS. Differentiation between central and peripheral immunopathological effects of HIV infection is of importance because, despite numerous communication pathways, systemic and CNS immunoregulation differ considerably. With respect to the effects of host defense activation on sleep this is well illustrated by the finding that proinflammatory cytokines have differential effects on sleep depending on whether they are administered systemically or intracerebroventricularly (Krueger and Toth, 1994). Although the present contribution focuses on the possible involvement of immunopathology in HIV-related sleep-wake disturbances it is important to stress that HIV infection also has many indirect effects on the CNS that interfere with sleep regulation such as neuroendocrine adaptation, psychopathological symptoms and impairment of cognition.

What is known about sleep and wakefulness in HIV-infected patients?

No details are known about sleep and wakefulness in acute HIV infection, but it can be assumed that fatigue is a common symptom in this clinical condition as it is in other acute viral infections. However, polygraphic night sleep recordings or objective assessment of sleepiness with the Multiple Sleep Latency Test (MSLT) have not been done.

Sleep during chronic HIV infection has been investigated more extensively. Most studies point to a progressive deterioration of night sleep, which starts in otherwise asymptomatic subjects many years prior to the development of AIDS-related complex or AIDS (Kubicki et al., 1989; Wiegand et al., 1991). Night sleep is characterized by increasing amounts of wakefulness and stage 1 sleep, decreased stage 2 sleep and, in general, a moderate increase in sleep onset latency. The cyclic alteration of non-REM and REM sleep deteriorates. The amount of slow wave sleep (SWS; stages 3 and 4 sleep) is preserved for a long time. There has been one study reporting an increased

amount of SWS in asymptomatic HIV positive homosexual men compared to published normative data (Norman et al., 1990). However, this finding could not be confirmed by others (Wiegand et al., 1991). When Norman and colleagues (1992) undertook a second investigation which included an age- and gender-matched control group, the total and relative amounts of SWS were unaffected. However, in the HIV-infected subjects SWS was more evenly distributed across the night than in the control subjects. Recently, White et al. (1995) confirmed that SWS is shifted to the second part of night sleep in asymptomatic HIV-infected subjects. With regard to REM sleep, so far no major changes have been found in early chronic HIV infection. In one of our studies we found a slight reduction in REM latency (Wiegand et al., 1991). REM latency was negatively correlated with the degree of depressive symptomatology, suggesting that its reduction is a secondary effect.

Quantitative sleep EEG analysis has been performed in only a few studies so far. Terstegge and colleagues (1993) reported a significant reduction in the spectral power of the 11.5 to 13 Hz range which supports the finding of a decreased sleep spindle density in HIV infected subjects (Kubicki et al., 1989). It is noteworthy that the authors did not find any changes in the low-frequency (delta) range.

As already mentioned, fatigue is a frequent complaint in asymptomatic HIV-infected patients. However, fatigue does not translate directly into increased sleepiness because studies using the MSLT yielded unremarkable results (Norman et al., 1990). Consistent with many studies on DIMS of other origin, neither fatigue nor the subjective sleep disturbance in HIV infection correlate tightly with the results of polysomnography.

Is immunopathology involved in HIV-related sleep-wake disturbances?

The studies performed so far have tried to control for secondary causes of sleep-wake disturbances resulting from stress, impaired psychosocial adjustment, psychiatric disorders or symptoms and structural brain damage. Although this can never be achieved completely, it seems justified to conclude that immunopathology plays a significant role in the alterations of night sleep and daytime alertness seen in early chronic HIV infection.

This view is supported by evidence provided by studies investigating the influence of experimental host defense stimulation on sleep in healthy humans (reviewed by Pollmächer et al., 1995). Endotoxin, a cell-wall component of gram-negative bacteria, induces a well characterized host response that mimics the early events which take place during infection, including the release of cytokines, TNF-α in particular, neuroendocrine activation and temperature increase. It was shown many years ago that large amounts of endotoxin induce severe sleep disruption, including increased wakefulness, increased stage 1 sleep and decreased REM sleep. However, much lower doses that only slightly elevate TNF-α levels and rectal temperature may even promote sleep by decreasing wakefulness and increasing non-REM sleep (Pollmächer et al., 1993). Furthermore, preliminary results from an ongoing study by our group suggest that subpyrogenic doses which increase TNF-α without affecting temperature may have the potential to increase SWS in healthy subjects.

Animal data suggest that TNF-α and IL-1β may be the pivotal mediators of endotoxin’s effects on sleep (Krueger and Toth, 1994). In the model of human low-dose endotoxemia the influence of TNF-α may be more important than that of IL-1β because endotoxin does not increase systemic IL-1β levels and IL-1 receptor blockade does not attenuate the human host response to endotoxin (for details see Pollmächer et al., in press).

There are a number of reports of increased levels of TNF-α in HIV-infected subjects, especially in the later stages of the disease. In early chronic infection this finding is less consistent, which is not surprising because a waxing and waning of immunoactivation is more likely than a continuous monotonous increase. The effects of higher doses of endotoxin on sleep described earlier, which are probably mediated by TNF-α, may explain the progressive sleep deterioration during the later stages of HIV infection. On the other hand, the effects of subpyrogenic doses of endotoxin on sleep may help to understand why in the earlier stages increased SWS may occur.

Furthermore, experimental endotoxemia can be helpful in understanding HIV-related fatigue, which, as already mentioned, is not accompanied by reduced sleep onset latencies during the MSLT. Although doses of endotoxin that consolidate night sleep go along with increased subjective alertness the following morning (Pollmächer et al., 1993), a recently completed study by our group showed that endotoxin can induce subjective fatigue without altering sleep onset latency during the
day. In this study, healthy subjects were injected with endotoxin during the day following pretreatment with granulocyte-colony stimulating factor, which increases endotoxin-induced surges in plasma TNF-α and rectal temperature (Pollmächer et al., in press). In addition, the subjects underwent a multiple napping procedure similar to the MSLT. Endotoxin did not affect mean sleep onset latency, but transiently suppressed non-REM sleep and increased subjective sleepiness (Herrmann et al., unpublished results).

As we have shown, the model of human experimental endotoxemia provides helpful ways of conceptualizing sleep-wake disturbances in HIV-infected persons. But of course, it will always remain tentative to compare the acute effects of a bacterial cell-wall component to those of a viral, chronic and slowly progressing disease.

What are the perspectives of sleep research in HIV infected subjects?

One major gap in the available knowledge about the interactions of sleep and the immune system in HIV infection is that very few study have dealt with sleep and the immune system in parallel. Some studies have assessed CD4 counts as indicators of disease progression. However, because T cells are unlikely to affect sleep directly, we propose that blood and CSF levels of cytokines that are probably involved in sleep-immune interactions be investigated. In addition to TNF-α that is a promising candidate for the above mentioned reasons, we propose to include in those investigations also TNF receptors. Soluble forms of these two receptors are present in the circulation even in healthy subjects in considerable amounts. They modulate the biological activity of TNF-α in a complex way and have recently been recognized to be much more sensitive markers of the activation of the TNF/TNF receptor system than TNF-α itself (Diez-Ruiz et al., 1995).

It should be noted here that the promising route of investigating sleep and cytokine levels in parallel has already been opened, since Darko and colleagues (1995) recently reported on a decoupling of nocturnal fluctuations in TNF-α levels from the non-REM/REM cycle, albeit in one HIV infected subject only. Another line of research pursued by this group involves the model of feline immunodeficiency virus infection, which will allow more sophisticated experimental approaches than those that are possible in a clinical setting.

Another issue that may be of relevance for future research is the impact of HIV-related sleep disturbances on the course of the illness. Sleep deprivation studies point to alterations of in vitro immunocompetence (Moldofsky, 1994). In addition, preliminary results of ongoing studies in our laboratory suggest that 40 hours of sleep deprivation suppresses endotoxin-induced increases in plasma TNF-α and soluble TNF receptor levels. However, at present these results do not allow the formulation of testable hypothesis regarding the interaction between sleep disturbances and the course of illness in HIV infection.

One goal of the efforts to understand the mechanisms underlying HIV-related sleep-wake disturbances is to develop specific therapeutic approaches. With regard to TNF-α, specific antagonistic strategies are already available. However, they antagonize most of the pleiotropic actions of TNF-α and it seems questionable that, overall, this would be beneficial for HIV infected patients. In this context, it is noteworthy that classical approaches to the treatment of DIMS may also affect the immune system. Benzodiazepines which ameliorate sleep in HIV patients (Henkes et al., 1989) are potent immunomodulators. For example, a single intravenous injection of midazolam profoundly suppresses the in vitro TNF-α secretion capacity of peripheral blood mononuclear cells (Taupin et al., 1991). Furthermore, in vivo effects of hypnotic drugs on the immune system have been described. We recently found that the atypical antipsychotic clozapine, which has strong sedative properties, slightly increases the plasma levels of TNF-α and of both of its soluble receptors (Pollmächer et al., in press). Therefore, the question arises of how the immune system of HIV-infected persons is affected by hypnotic medication which is prescribed for a considerable number of these patients. In addition, it seems to be of general interest to which extent immunomodulation by hypnotic drugs may be involved in their effects on sleep.

In summary, there is considerable evidence suggesting that immunopathology plays a role in HIV-related sleep-wake disturbances despite their multifactorial origin. We are just beginning to understand the underlying mechanisms, which probably involve proinflammatory cytokines. Additional research is needed to define these mechanisms in more detail.
and the interactions between sleep disturbances and disease progression. Finally the search for specific treatments of immunopathologically mediated DIMS and fatigue that do not interfere with the compromised immune system of HIV-infected subjects in a negative way seems warranted.

References


Please submit your comments, suggestions and news items to the Editor, Shiroman@Warren.Med.Harvard.Edu.

Please note that the Dr. Shiromani’s phone number has changed to 508-583-4500x1878 and the new Fax number is 508-895-0002. In any case, e-mail is the best route of communication.
Sleep and Lentivirus Infection: Parallel Observations Obtained from Human and Animal Studies

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(NOTE: This article is a précis of two recent reviews by the authors on this subject. For further details see: Henriksen et al. In: HIV and Dementia M.B.A. Oldstone and L. Vitkovic (Eds.) pp 167-186, Springer-Verlag (Berlin), 1995; and, Darko et al. Advances in Neuroimmunology 5: 57-77, 1995)

Introduction
The disrupted sleep reported in subjects with human immunodeficiency virus (HIV-1, genus: Lentivirus) infection is recognized as being an increasingly important clinical symptom of the syndrome because of the contribution poor quality sleep makes to the fatigue, disability, and disintegration in the quality of life that befalls these patients. The chronic asymptomatic stage of HIV infection is associated with the most intriguing and pathognomonic sleep structure changes. Especially robust is the increase in slow wave sleep, particularly in latter portions of the sleep period. This finding is rare in other primary or secondary sleep disorders. Indeed, sleep structure alterations are among the most replicable of several pathophysiological sequelae in the brain associated with early HIV infection. Evidence supports the fact that these sleep architecture changes are unlikely due to psychosocial factors and they occur before medical pathology is evident. They are not associated with stress, anxiety, or depression. Moreover, evidence is accumulating to support a role for the somnogenic immune peptides (TNF alpha and IL-1 beta - see Opp, this Bulletin) in the sleep changes and fatigue observed in HIV infection. These peptides are elevated in the blood of HIV-infected individuals, and are somnogenic in clinical use and some animal models. The peripheral production of these peptides may also have a role in the regulation of normal sleep physiology. The lentivirus genus contains both HIV and the feline immunodeficiency virus (FIV), a new and exciting animal of the human disease. The use of the FIV model of HIV infection may provide a way to further investigate the pathophysiological mechanisms of these invasive, neurotoxic viruses affecting sleep.

AIDS and Sleep
June 1991 marked the end of the first decade of the worldwide pandemic of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome. Given the intensity of HIV research during the past 15 years, it is surprising that only a modest amount of investigation has been done on the prominent sleep changes associated with HIV. Indeed, electrophysiological tests may be particularly sensitive indicators of subclinical neurological involvement with early HIV infection. During the early stages of HIV infection, deterioration occurs in thought processes, including reasoning, memory, and reaction time, before the existence of any conspicuous neuropathology, (National Institutes of Health, 1993). Development of specific sleep disturbances in HIV infection could be proposed as a response to life stress, since stressful life events have long been known to initiate or contribute to poor sleep (Kales & Vgontzas, 1992; Paulsen & Shaver, 1991; Healey et al., 1981). However, except perhaps for frequent arousals, the sleep changes noted in HIV infection cannot be attributed to stress or anxiety (Norman et al., 1988-B). In HIV infection sleep disturbance occurs as an early symptom, before other medical symptoms or signs appear, and is readily demonstrated in asymptomatic HIV seropositive individuals. The sleep disturbance associated with HIV infection is not ordinary insomnia or typical of stress-related changes.

Based on the studies reviewed below, it is probable that the sleep architecture deterioration associated with HIV infection is physiological in origin with few if any psychosocial causes. The sleep changes found vary with the progression of HIV infection. The
acute illness immediately after infection has among its prominent symptoms poor subjective sleep quality, fatigue, and lethargy. Polysomnographic study of sleep has not been done during this stage of the infection. The chronic asymptomatic phase of the illness has several associated changes in sleep, including increased percentage slow wave sleep shifted to the latter part of the night, decreased sleep efficiency index, defined as the time spent asleep divided by the total recorded period, more arousals and awakenings during the sleep period, an increased number of shifts to stage 1 sleep, lower percentage of stage 2 sleep, a decreased percentage of rapid eye movement (REM) sleep, an increase in the number of REM periods, a decrease in mean duration of REM periods, and subjective complaints of initiating and maintaining sleep. The decreased sleep efficiency index, increased number of awakenings, increased shifts to stage 1, and increased number of brief REM periods represent fragmentation of healthy sleep structure. The clinical result of these sleep changes would be expected to be a subjective experience of poor sleep quality with a feeling during the day that not enough sleep has been achieved, accompanied by the feeling of sub-optimal alertness, despite a more than adequate time in bed trying to sleep. Estimates of the proportion of HIV positive subjects who will have fatigue severe enough to interfere with their lives range between 11% to 57%, compared to 5% or less in HIV negative control subjects (Darko et al., 1992).

Primary HIV illness occurs within two to four weeks after exposure with infection. It consists of a three to fourteen day acute mononucleosis-like syndrome (mean 10 days, standard deviation = 4.4 days). The symptom pattern of primary infection occurs in at least 50% to 70% of patients (Epstein, 1993), with studies describing it in as many as 92.3% of subjects (Tindall et al., 1988). Signs and symptoms include lethargy, malaise, fever, sweats, a truncal maculopapular rash, arthralgias, myalgias, headaches, diarrhea, photophobia, pharyngitis, and generalized lymphadenopathy. Seroconversion to presence of antibody against HIV usually occurs one to three months later. The symptoms of the acute infection usually evanesce, though the lymphadenopathy may persist. AIDS is defined by severely low CD4 T-cell numbers (< 200 cells per microliter), the development of opportunistic infections, specific secondary neoplasms known to be associated with HIV infection, or other AIDS-defining pathology, including encephalopathy. Progressive dementia occurs, though not as inevitably as earlier thought.

Sleep and Fatigue in Acute HIV Infection
Lethargy and malaise are common during this acute pre-seroconversion illness, and these symptoms often became chronic, persisting for weeks to months after the end of the acute illness (Tindall et al., 1988). Whether sleep itself is altered is less clear. Sleep disturbance, impairment of normal daily activities due to fatigue, and sick leave from work were folded into an attempted diagnosis of psychological depression. However, upon evaluation by psychiatry, subjects were found not to meet criteria for major depression, but they did have prominent daytime fatigue and lethargy, along with sleep disturbance, severe enough in some cases to interfere with work and other activities of daily living. Because the acute illness after infection is often not seen, few studies have been able to examine it. These few have not examined either sleep disturbance or fatigue (Niu et al., 1993; Kinloch-de Loës et al., 1993; Sinicco et al., 1990). It may be valuable to know how early in the infection the sleep alterations occur, especially if early intervention can delay later functional disability. Given the evanescent quality of this disorder in patients, there is little hope of extensive study of this question. The HIV model is a more practical approach for testing relevant hypotheses (vide post).

Sleep and Fatigue in Early Chronic HIV Infection
Immediately after the acute infection and for a prolonged time, subjects may be in an antibody-negative asymptomatic carrier state. In a minority of patients this state can last for several years. The virus may be latent, or replicating so slowly that immune surveillance is inadequate to rid the body of the disease. However, using sensitive polymerase chain reaction (PCR) methods for HIV-specific nucleic acid sequences can detect viral epitopes in non-virus-producing HIV-containing blood cells. More commonly patients convert to antibody-positive asymptomatic carriers one to three months after initial infection.

Sleep complaints frequently accompany early chronic infection with HIV (Norman et al., 1990-A; Brown et al., 1990; Brown et al., 1991-A; White et al. 1995). Dr. Suzan Norman-Jaffe was the pioneer in the area of polysomnographic sleep studies in subjects with HIV infection. Her group's studies were focused on asymptomatic seropositive individuals. All were homosexual men with similar life-styles, and none had neuropsychiatric illness. Most of the individuals studied had normal clinical and neurological examinations except for daytime fatigue. None were sleep-deprived shift workers and none were taking

medications known to affect sleep, confirmed by urine toxicology screen. All were given a clinical interview and studied by standard polysomnography for two nights. No typical disorders of sleep were found (e.g., obstructive sleep apnea, oxygen desaturation). The subjects did not have recent sleep deprivation or delayed sleep phase, and findings could not be attributed to medication use, anxiety, or depression. Subjects showed the same sleep changes whether or not they were using azidothymidine (AZT; Norman et al., 1990-B). The findings across these several studies are remarkably consistent, and have been largely replicated by others studying sleep in early asymptomatic HIV infection, including ourselves (White et al., 1995; Darko et al., 1995).

The most prominent and replicable finding in HIV positive subjects compared with control subjects is a significant increase in percentage of slow wave sleep through the night, especially an increase in slow wave sleep during the latter part of the sleep period (Norman et al., 1987; Norman et al., 1988-B; Norman et al., 1990-A; Norman et al., 1990-B; Norman et al., 1990-C, White et al., 1995). In normal, healthy individuals, slow wave sleep usually predominates during the first third of the night, and is far less pronounced in the second half of the sleep period. Dr. Norman was among the first to suggest that the elevated levels of the somnogenic monokine IL-1 in HIV disease may promote the increase in slow wave sleep (Norman et al., 1987). The HIV patients have a significantly lower mean sleep efficiency index (Norman et al., 1987; Norman et al., 1988-B; Norman et al., 1990-C; Norman et al., 1992). Awakenings and arousals were significantly increased in the HIV positive subjects (Norman et al., 1988-B; Norman et al., 1990-A; Norman et al., 1990-B; Norman et al., 1990-C; Norman et al., 1992). The HIV patients further showed sleep fragmentation as evidenced by a significantly increased number of shifts in stage 1 (Norman et al., 1988-B; Norman et al., 1990-A; Norman et al., 1992). HIV-infected subjects had a significant increase in number of REM periods though average REM durations were significantly decreased (Norman et al., 1990-A, B). Significant decreases in sleep latency and total percentage stage 2 sleep were also seen in the HIV positive group compared to normative data (Norman et al., 1990-A, B). Many of these asymptomatic subjects have sleep complaints, including problems of initiating or maintaining sleep and daytime fatigue. However, in subsequent studies, a poor correlation was found between the subjective sleep complaints and sleep indices derived from visual scoring of polysomnographic sleep EEG recordings (Norman et al., 1992). This observation suggests that the changes found with visual scoring of polysomnographic EEG records may not reflect the subjective sleep disturbances self-reported in this population and illustrates the need to measure both objective and subjective parameters of sleep in these subjects.

In one of our studies of HIV seropositive asymptomatic homosexual men compared with HIV seronegative control subjects matched for age, gender, and sexual orientation, fatigue interfered with the daily activities of the HIV group significantly more than the control group. The most significant difference between these two groups occurred with the dangerous situation of sleepiness while driving. The HIV infected patients had sleepiness interfere with their driving significantly more often than the control subjects (Darko et al., 1992). In a more recent study, we examined the question of sleep changes with a controlled, cross-sectional, prospective study. As reported by others, we found that the healthier HIV subjects (CD4 cell counts in the normal range of 400 to 1200 cells per microliter) had a significantly higher percentage of slow wave sleep in both the middle third, and in the last third, of the sleep period (White et al., 1995).

Sleep Deterioration and Fatigue in Advanced HIV Infection

German researchers have been the most productive in examination of more ill patients with AIDS, with additional investigation again done by Dr. Norman's group. Patients with AIDS have more severe sleep disruption than individuals with less advanced HIV infection. Sleep complaints are frequent (Kubicki et al., 1988) and HIV encephalitis has been proposed as a possible etiology (Terstegg et al., 1989). Typical polysomnographic findings include an increased number of awakenings and arousals (Norman et al., 1988-A; Kubicki et al., 1988; Kubicki et al., 1989; Weigand et al., 1991-A), resulting in a decrease in sleep efficiency (Weigand et al., 1991-A). The subjects had an increase in stage 1 sleep (Kubicki et al., 1988; Weigand et al., 1991-A), a decrease in percentage of stage 2 sleep (Norman et al., 1988-A; Kubicki et al., 1988; Kubicki et al., 1989; Weigand et al., 1991-A), and a decrease in percentage REM sleep (Norman et al., 1988-A; Kubicki et al., 1988; Kubicki et al., 1989). While total sleep time was elevated, if awakenings are removed from the recording time, average time actually spent asleep was reduced (Kubicki et al., 1988). This
finding of shorter total time asleep has been replicated (Kubicki et al., 1989; Weigand et al., 1991-A). A dramatic reduction in sleep spindles was found (Kubicki et al., 1988; Kubicki et al., 1989). Unlike the sleep of asymptomatic HIV subjects, percentage of slow wave sleep is often markedly reduced (Norman et al., 1988-A; Kubicki et al., 1988; Kubicki et al., 1989). Our group has replicated this finding (White et al., 1995). While this drop in percentage of slow wave sleep in advanced HIV infection returns the percentage to normal levels, this drop does not mean that sleep architecture has returned to normal. AIDS is often characterized by severely fragmented sleep, with a complete destruction of normal sleep structure (Norman et al., 1988-A; Kubicki et al., 1988).

**The Feline Immunodeficiency Virus Model of Clinical HIV Infection and Sleep**

In 1987, Niels Pedersen and his colleagues at the University of California at Davis discovered a new lentivirus in the domestic cat population (Pedersen et al. 1987) Pedersen termed this new virus "Feline Immunodeficiency Virus" (FIV) to reflect the clinical syndrome observed in the infected subjects. It was soon evident that this syndrome was associated with a striking immune deficiency similar to human AIDS. Cats experimentally infected with FIV by transfer of whole blood or plasma develop a lymphadenopathy as well as a variety of neurological, physiological and behavioral sequelae strikingly similar to those found in human AIDS (Elder, J., and Sever, J., 1988; Yamamoto et al., 1988; Hurtrel et al., 1992; Dow, s. ert al., 1990; Henriksen, S., et al., 1995) and (Poddell, M. et al., 1991) for review. It appears that bite wounds inflicted during cat fights are a primary mode of natural FIV transmission, therefore, FIV-induced feline AIDS is primarily a disease of free-roaming male cats (Yamamoto, et al., 1991).

A comparison of the genomic structure of FIV and HIV-1 is instructive (for review, see Elder, J., and Philips, T., 1994). Both lentiviruses contain the major gene regions *gag*, *pol*, and *env*, typical of all the retroviruses. Also, they both are bordered by long terminal repeats, which encode regulators of transcription and facilitate entry of the viral genome into the host cell DNA. Typical of lentiviruses, both FIV and HIV-1 contain additional coding capacity for regulatory elements that influence the relative level and success of the infection.

CNS tropism of both HIV-1 and FIV leads to similar neurological and pathophysiological signs (See Lafrado, L. et al., 1993). In addition to deficits in central sensory and peripheral sensory and motor conduction velocity measures, recent observations in sleep architecture abnormalities have been reported for both HIV-1-infected (see above) and FIV-infected subjects (Henriksen, S., et al., 1995) A recent study by our group examined 13 specific-pathogen-free cats infected with the Maryland strain of FIV (FIV-MD) and 6 age matched, sham inoculated control cats to assess the effects of FIV infection on the CNS. All 13 infected cats seroconverted within 8 weeks post inoculation, with virus recovered from peripheral mononuclear cells. A decrease in the CD4/CD8 ratio occurred in the infected group relative to the control group. This difference in the CD4/CD8 ratio occurred early, persisted for one year, and was primarily due to a decrease in the number of circulating CD4 cells in the FIV-infected cats relative to the control cats. Similar findings have been reported by several other groups in either naturally or experimentally infected cats. Neurologic changes in the infected cats included marked alterations in sleep patterns, delayed visual and auditory evoked potentials, delayed pupillary reflex, and delayed righting reflex (Phillips, T., 1994). As in the human, early in the FIV infection, infected cats had displacement of slow wave sleep toward the later portion of the recording period.

Another recently concluded study by our group examined 5 specific-pathogen-free cats, again infected with FIV-MD (See Henriksen et al., 1995). During sleep periods the FIV-infected cats spent 50% more time awake, had 40% more sleep-wake stage shifts, and had 30% less REM sleep than 3 sham inoculated control cats. The infected cats also had significantly delayed latency-to-sleep and latency-to-REM-sleep onset. Some of the infected cats had markedly increased cortical spindle activity (8 - 13 Hz) during slow wave sleep. A shift in slow wave sleep to the latter part of the sleep period was also seen. These changes all occurred well before secondary physical changes related to immunodeficiency had arisen. The FIV-infected cats had no overt signs of systemic morbidity, such as hyperpyrexia or body weight loss. FIV-infected cats had autonomic nervous system changes (e. g., pupillary reflexes), increased incidence of minor infections (e. g., cutaneous ulcers, acne, oral infections), and minor behavioral changes similar to those seen in patients with HIV infection.

The sleep changes described in FIV infection are similar to sleep changes described in HIV-infected patients, e. g., increased slow wave sleep and
displacement of slow wave sleep into the latter part of the sleep period, more awakenings and arousals, increased time spent awake during the sleep period, and a decrease percentage of REM sleep (Norman et al., 1987; Norman et al., 1988-B; Norman et al., 1996-A, B, C).

An advantage of the FIV model is time course, i.e., cats infected less than one year show changes similar to patients infected for three to seven years. This acceleration of pathology can permit intracerebroventricular injection of cytokines, viral coat proteins, or quinolato to test for mimicking of functional pathology; can facilitate testing of viral isolates with differing neutropism or neurotoxicity; can provide the opportunity for examination of brain at necropsy, e.g., for frontal lobe neuron density, and can allow for rapid testing of drugs that may delay brain-based disability. The drugs of relevance are many, and their testing may provide a reliable and meaningful path toward understanding how to prolong vitality in HIV-infected patients. Pentoxiphylline and thalidomide, with their inhibition of TNF alpha and viral replication, are likely candidates. Animal trials may allow discovery of any biological ability of peptide T to affect virus replication or immune system function, and the most efficacious dosage and delivery route. Memantine and other N-methyl-D-aspartate antagonists offer intriguing possibilities, given their effect in human dementia, and in protecting neurons from damage by HIV-1 coat protein gp 120 (Lipton, 1992). Anabolic steroids have effects that may yield clinical efficacy upon testing in a feline model. Cyclosporine or other immunosuppressant medications can be used to test the arguable hypothesis that the immune system responses accelerate HIV infection. A brain-selective cyclooxygenase-2 inhibitor induced by inflammation, HIV fusion proteins to stimulate immune responses, exotoxin fusion proteins to target antibodies to virus infected cells, ribozyme anti-virus constructs, anti-sense nucleotide drugs based on reducing inflammatory and toxic cytokine cascades, and a protease inhibitor that is effective against FIV and HIV, all may soon become available for possible testing in the feline model. This model may further be helpful in illuminating the changes in virus susceptibility and pathogenesis on a background of opiate or psychostimulant abuse. The FIV model provides a unique opportunity to study the mechanisms by which this retrovirus or the response to the virus interferes with brain function or damages neurons or supporting CNS cells.

Potential Mechanisms of Sleep Pathophysiology in Early Chronic HIV Infection

The sleep changes in early chronic HIV infection are the most intriguing. The scant descriptions of sleep in acute primary HIV infection leave this a poorly understood area, and the sleep deterioration of end stage HIV infection (ARC and AIDS) is consistent with the sleep decay seen in severe medical illnesses from other etiologies. The confirmed increase in slow wave sleep in early chronic HIV infection, and the related frequent complaint of disabling daytime fatigue, are unusual and not readily explained. Several investigators in sleep physiology have proposed likely mechanisms (Opp et al., 1992; Shoham et al., 1987; Krueger et al., 1986).

TNF alpha (cachectin) is a 17-kilodalton polypeptide (157 amino acids) which, after gaining access to the circulation, acts like a hormone and induces a broad spectrum of systemic changes in neurological, metabolic, hematological, and endocrinologic systems. Under normal circumstances, little biologically active TNF alpha is present within macrophages, because the gene controlling its expression is subject to strong repression. After an appropriate stimulus, such as platelet activating factor, lipopolysaccharide, or interferon-gamma, transcriptional and post-transcriptional events lead to the rapid synthesis and release of TNF alpha, after which the macrophages may be resistant to further stimulation. In addition, the plasma half-life of TNF alpha is short (15 to 17 minutes) in humans. This evidence suggests that the appearance of TNF alpha in the bloodstream may be rapid and short-lived.

IL-1 is a 17.5 kilodalton polypeptide (159 amino acids) which, similar to TNF alpha, affects nearly every tissue and organ system (Dinarello, 1991). Both are pro-inflammatory cytokines in that they induce the expression of a variety of genes and the synthesis of several proteins that, in turn, induce acute and chronic inflammatory changes. IL-1 induces cellular production of TNF alpha (Dinarello & Savage, 1989). IL-1 has two molecular forms, alpha and beta, and despite only a 26% amino acid homology (the two forms are the products of different genes), both forms induce a wide variety of similar biological changes, including systemic effects such as sleep, fever, ACTH release, and increased sodium excretion (Dinarello & Savage, 1989).
TNF alpha is elevated (up to 300 pg/ml) in sera of CDC C AIDS subjects (Reddy et al., 1988; Lahdevirta et al., 1988; Hober et al., 1989; Maury & Lahdevirta, 1990), and cells from HIV positive subjects produce increased amounts (1.5 to 6 times control subject levels) of TNF alpha (Wright et al., 1988; Lau & Livesey, 1989; Roux-Lombard et al., 1989; Voth et al., 1990). Importantly, even in situations with elevated serum TNF alpha and progressive encephalopathy, cerebrospinal fluid TNF alpha is not increased (Mintz et al., 1989; Gallo et al., 1989). It seems problematic that peripheral TNF alpha and IL-1 beta may elicit central effects since normally access of peptides of this size to brain would be limited by the blood brain barrier. However, TNF alpha and IL-1 beta may enter the CNS by several proposed routes. In HIV infection, their entry may be enabled by inflammation and a consequent compromise of the blood brain barrier, e.g., migrating macrophages (Bocci, 1988). In healthy subjects with an intact blood brain barrier, TNF alpha and IL-1 beta may enter through one of the areas of access of the peripheral circulation to the CNS which bypass the blood brain barrier, e.g., organum vasculosum of the lamina terminalis, median eminence, or area postrema (Blatteis, 1989; Shibata & Blatteis, 1991; Broadwell, 1991). Further, an active transport mechanism has been proposed for human IL-1 alpha (Banks & Kastin, 1991, Banks et al., 1991); arguably, a similar mechanism could exist for IL-1 beta and TNF alpha.

The cells producing the TNF alpha and IL-1 beta that affect sleep could be either systemic (peripheral) in location or reside within the CNS. In animal models TNF alpha has been found to be somnogenic whether given intravenously or intracerebroventricularly (Shoham et al., 1987). Injection of TNF alpha into a rabbit intravenously (30 microgram) or intracerebroventricularly (5 microgram) increases both slow wave sleep and average slow wave voltage. Similar results were found with IL-1 beta (Opp et al., 1992, Shoham et al., 1987). This slow wave sleep induction is the change seen in chronic asymptomatic HIV infection. It has been proposed that cytokines act directly on somnogenic neural networks to alter sleep (Opp et al., 1992), an hypothesis supported by the ability of IL-1 to alter neuronal activity in brain regions like the hypothalamus that are thought to involved in sleep regulation (Shibata, 1990). Given the above, it seems plausible that aberrant increases in TNF alpha and IL-1 beta production could contribute to the hypersomnia and fatigue of HIV infection.

We have pursued studies to examine this hypothesis. HIV seropositive subjects with normal CD4 lymphocyte number, HIV subjects with low CD4 number, and healthy control subjects spend three consecutive nights in the sleep laboratory. Subjects are pre-ARC and pre-AIDS by clinical criteria other than possible low CD4 cell count. Blood sampling during sleep for assay of TNF alpha and IL-1 beta is conducted on the third night. Assay sensitivity is 500 femtograms per milliliter for TNF alpha and 5 picograms per milliliter for IL-1 beta. Sleep EEG is analyzed by both visual scoring based on 30-second epochs and quantitated electroencephalographic techniques (QEEG) performed on each digitized sleep record for the delta frequency band (0.5 to 4.0 Hertz). This QEEG frequency domain approach decomposes a wave form series into a sum of sinusoidal elements, thus giving quantitative estimates of power (spectral power estimates) for each epoch. For data analysis we use the square root of power, or spectral amplitude estimates. Cross-Correlation Plots are then constructed for the QEEG delta frequency amplitude, TNF alpha, and IL-1 beta, and Pearson correlation coefficients between curves are calculated.

In all subjects we are finding a previously unrecognized nocturnal cyclic variation in plasma TNF alpha and IL-1 beta levels. In control subjects and in HIV patients with normal CD4 cell count (400 to 1200 cells per microliter) we are seeing tight coupling (high correlation between curves) between sleep EEG delta frequency spectral amplitude and each somnogenic monokine, TNF alpha and IL-1 beta. This coupling seems to deteriorate with progression of HIV infection. For the HIV seropositive patients whose CD4 counts are less than 400 cells per microliter, correlation between monokines and delta amplitude through the night's sleep is poor.

Of relevance to these findings are recent reports that there are increased levels of TNF alpha messenger RNA (mRNA) in the frontal subcortical white matter of brains of demented HIV infected patients, when compared to both non-demented HIV infected patients and healthy control subjects (Wesslingh et al., 1993; Glass et al., 1993).

Percentage and time of delta sleep are two of the classically examined sleep parameters. Based on visually-scored sleep stages, delta sleep is increased yet individuals are fatigued in early, asymptomatic HIV infection. In other populations decreases or interruptions in delta sleep are associated with fatigue.
The use of QEEG analysis may resolve this apparent paradox. Further, the fatigue of HIV infection may be lessened by treatment specifically aimed at decreasing the elevated systemic level of the two relevant somnogenic monokines, TNF alpha and IL-1 beta. Examples of medications that may have application include pentoxifylline, which inhibits TNF alpha production by acting as a specific inhibitor of TNF alpha mRNA synthesis, and thalidomide, which inhibits TNF alpha production by enhancing TNF alpha mRNA degradation.

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