Chronic Interferon-Alpha Administration Disrupts Sleep Continuity and Depth in Patients with Hepatitis C: Association with Fatigue, Motor Slowing, and Increased Evening Cortisol

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Background: Consequences of chronic exposure to cytokines of the innate immune system on sleep in humans and the association of cytokine-induced sleep alterations with behavior, motor performance, and cortisol secretion are unknown.

Methods: Thirty-one patients with hepatitis C without pre-existing sleep disorders underwent nighttime polysomnography, daytime multiple sleep latency testing, behavioral assessments, neuropsychological testing, and serial blood sampling at baseline and after ~12 weeks of either treatment with the innate immune cytokine interferon (IFN)-alpha ($n = 19$) or no treatment ($n = 12$). Fatigue and sleepiness were assessed using the Multidimensional Fatigue Inventory and Epworth Sleepiness Scale.

Results: Interferon-alpha administration led to significant increases in wake after sleep onset and significant decreases in stage 3/4 sleep and sleep efficiency. Rapid eye movement latency and stage 2 sleep were significantly increased during IFN-alpha treatment. Decreases in stage 3/4 sleep and increases in rapid eye movement latency were associated with increases in fatigue, whereas decreases in sleep efficiency were associated with reduced motor speed. Increased wake after sleep onset was associated with increased evening plasma cortisol. Despite IFN-alpha-induced increases in fatigue, daytime sleepiness did not increase. In fact, IFN-alpha-treated patients exhibited decreased propensity to fall asleep during daytime nap opportunities.

Conclusions: Chronic exposure to an innate immune cytokine reduced sleep continuity and depth and induced a sleep pattern consistent with insomnia and hyperarousal. These data suggest that innate immune cytokines may provide a mechanistic link between disorders associated with chronic inflammation, including medical and/or psychiatric illnesses and insomnia, which, in turn, is associated with fatigue, motor slowing, and altered cortisol.

Key Words: Cortisol, cytokines, depression, fatigue, hepatitis C, hyperarousal, insomnia, interferon-alpha, neuropsychology, polysomnography, sleep

Cytokines of the innate immune system, including interferon (IFN)-alpha, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha, are important mediators of inflammation and have long been known to induce symptoms of depression including alterations in sleep (1–11). For example, studies in rodents have shown that acute administration of innate immune cytokines or cytokine inducers such as lipopolysaccharide (LPS) suppresses rapid eye movement (REM) sleep, while increasing nonrapid eye movement (non-REM) sleep, especially stage 3/4 sleep, also referred to as slow wave sleep (SWS) (3,4,6,12). At high doses, however, innate immune cytokines can disrupt non-REM sleep in rodents and reduce SWS (3). In humans, acute effects of innate immune cytokines are more complex and, like in rodents, appear to be dose-dependent. For example, low-dose IL-6 suppresses non-REM sleep in the first half of the night, while increasing non-REM sleep (and SWS) in the second half of the night (7,8). In addition, low-dose LPS increases non-REM sleep, whereas high-dose LPS suppresses non-REM sleep (13). Consistent with the effects of acute cytokine administration on laboratory animals, acute administration of LPS or innate immune cytokines to humans has been reliably reported to suppress REM sleep (7,9–11).

Although early interest in sleep abnormalities in psychiatric disturbances focused on REM sleep (with the observation that decreased REM latency may be a biological marker of major depression) (14–16), subsequent studies have suggested that patients with major depression perhaps even more reliably exhibit disruptions in non-REM sleep, especially impairments in sleep initiation/continuity (i.e., latency to sleep onset, wake after sleep onset, and sleep efficiency) as well as reductions in SWS (17–19). This general pattern of sleep disruption is also highly prevalent in a variety of medical illnesses including cancer, cardiovascular disease, and autoimmune and inflammatory disorders. Indeed, these illnesses have all been associated with various measures of sleep disruption and secondary insomnia, including reduced sleep efficiency and increased wake after sleep onset (20–23). Given the association of these medical illnesses as well as major depression with evidence of chronic activation of innate immune responses, these data suggest that innate immune cytokines may serve as a mediator of sleep alterations in these disorders. Nevertheless, there are limited data on the effects of chronic exposure to innate immune cytokines on sleep, and no study to our knowledge has employed polysomnography (PSG) in this regard. Moreover, while much animal literature and a handful of human studies have reported on the effects of short-term cytokine exposure (3–11), these findings

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may provide limited insight into sleep changes associated with chronic inflammation as might be expected in chronic medical and/or psychiatric disease (24).

Patients undergoing long-term treatment with the innate immune cytokine IFN-alpha provide a unique opportunity to address how—and to what degree—chronic inflammation affects sleep in humans (25). While an effective therapy for hepatitis C virus (HCV) infection and cancer, IFN-alpha induces significant behavioral changes including depression, fatigue, and sleep disturbances in a high percentage of patients (26–29). Much like other inflammatory stimuli (e.g., LPS) that induce behavioral changes, IFN-alpha also activates other innate immune cytokines, including TNF-alpha, IL-1, IL-6, and their soluble receptors (25,30–33), which have been shown to correlate with development of behavioral disturbances including sleep changes during IFN-alpha treatment (25,31,33). For example, in patients receiving IFN-alpha for HCV, unidirectional relationships among inflammation, sleep, and mood disturbance were observed, such that plasma IL-6 predicted poor sleep and poor sleep, in turn, predicted development of depression (25). In addition, IFN-alpha has been shown to induce neurocognitive changes (motor slowing), a flattened diurnal cortisol slope, and increased evening cortisol (31,34). These neurocognitive and neuroendocrine changes are typical of those observed following experimental sleep disruption (35–38).

To determine the impact of chronic exposure to an innate immune cytokine on human sleep architecture, a longitudinal, case-controlled design using overnight PSG and daytime multiple sleep latency testing (MSLT) in patients receiving IFN-alpha plus ribavirin for HCV was conducted. In addition, the relationship between cytokine-induced changes in sleep parameters and changes in behavioral symptoms, neurocognitive function, and circadian neuroendocrine activity known to be affected by sleep disruption was examined. Finally, associations between IFN-alpha and other innate immune cytokines and sleep changes were explored.

Methods and Materials

Subjects

Thirty-one HCV-positive subjects (17 male subjects, 14 female subjects) as determined by serum anti-HCV antibodies or HCV-RNA by reverse transcription-polymerase chain reaction were enrolled. To ensure medically stable HCV patients without an urgent need for IFN-alpha therapy or psychiatric treatment, exclusion criteria included decompensated liver disease; liver disease from any cause other than HCV; unstable cardiovascular, endocrinologic, hematologic, renal, or neurologic disease (as determined by physical examination and laboratory testing); <24 on the Mini Mental State Examination (39); and history of schizophrenia or bipolar disorder and/or diagnosis of major depression or substance abuse/dependence within 6 months of study entry (determined by Structured Clinical Interview for DSM-IV) (40). Subjects with evidence of a preexisting sleep disorder, as determined by an apnea-hypopnea index >15 (i.e., >15 sleep apnea-hypopnea episodes per hour of sleep) or a periodic leg movement index >25 (i.e., >25 leg movements with or without arousal per hour of sleep) during adaptation or baseline sleep nights, were also excluded. Subjects were required to be off all antidepressants, antipsychotics, and mood stabilizers for at least 4 weeks (8 weeks for fluoxetine) before study entry and throughout the study. Subjects were also required to be off other medications known to affect sleep including narcotics, benzodiazepines, and nonbenzodiazepine sedative/hypnotics for 2 weeks before baseline and 48 hours before the 12-week sleep assessment. Of the 31 subjects included in this study, 25 (15 IFN-alpha-treated, 10 control subjects) participated in a study of IFN-alpha effects on neuroendocrine function and 24 (15 IFN-alpha-treated, 9 control subjects) participated in a study of IFN-alpha effects on neurocognition (31,34).

Study Design and Polysomnography Assessments

A prospective, longitudinal, case-control design was used to examine sleep in HCV patients before (visit 1) and following ~12 weeks (visit 2) of either treatment with IFN-alpha plus ribavirin (treatment group) or no treatment (control group). All IFN-alpha-treated subjects received pegylated IFN-alpha-2b (Pegintron, Schering Plough, Kennilworth, New Jersey) or pegylated IFN-alpha-2a (PEGASYS, Roche, Basel, Switzerland) administered subcutaneously once weekly. Participation in treatment versus control groups as well as type of IFN-alpha was determined by patients and their physicians and was not controlled by study protocol. Because of lack of urgency of IFN-alpha therapy in this stable population of HCV patients, decisions regarding initiation of IFN-alpha were largely based on scheduling convenience. In the event that a patient met criteria for IFN-alpha-induced major depression during the study, the patient immediately underwent research assessment and was referred for psychiatric care.

All study procedures took place in the Emory General Clinical Research Center (GCRC). To allow for accommodation to the GCRC environment and to screen for sleep disorders, subjects underwent 1 night of PSG in the GCRC 1 week before study initiation. On study visits 1 and 2, subjects underwent 2 nights of PSG (Methods and Materials in Supplement 1). For statistical analyses, PSG results were averaged across these 2 nights during each visit. Each night, lights out occurred at 10:00 PM, and each morning, subjects were awakened at 7:15 AM. On the second full day of the GCRC stay, MSLT was conducted in a subset of subjects (IFN-alpha: $n = 17$; control: $n = 10$) at 10:00 AM, 12:00 noon, 2:00 PM, and 4:00 PM (Methods and Materials in Supplement 1) (41). Multiple sleep latency testing results, including latency to sleep onset and cumulative sleep time, were averaged across the day for statistical analyses.

During each GCRC admission, blood was withdrawn from an indwelling catheter into ethylenediaminetetraacetic acid-coated tubes hourly from 9:00 AM to 9:00 PM for assessment of plasma cortisol, as well as TNF-alpha and its soluble receptor, soluble TNF receptor 2 (sTNFR2). Following sampling, blood was immediately centrifuged at 1000*g* for 10 minutes at 4°C. Plasma was removed and frozen at −80°C until assay. For IFN-alpha-treated subjects, visit 2 was scheduled 4 to 5 days following the last IFN-alpha injection. Plasma IFN-alpha was assessed at 4:00 PM on both visits to ensure treatment adherence and to correlate with sleep measures. Urine drug screens were conducted at each visit to rule out substance abuse.

Subjects provided written informed consent, and study procedures received a priori approval by Emory University Institutional Review Board.

Behavioral and Neuropsychological Assessments

Depression was evaluated by trained clinician-raters using the mood disorders module of the Structured Clinical Interview for DSM-IV and the Montgomery-Asberg Depression Rating Scale (40,42) (Methods and Materials in Supplement 1). Due to the profound nature of IFN-alpha effects on behavior, it was not considered feasible to uniformly blind clinician-raters to treat-