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Disordered sleep, nocturnal cytokines, and immunity: interactions between alcohol dependence and African-American ethnicity

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Abstract

Sleep disturbance is one of the most prominent complaints of alcohol-dependent patients. In view of recent evidence that the immune system is integrated with other homeostatic processes ultimately regulated by the brain, the influence of sleep on host defense mechanisms and the expression of proinflammatory and T helper cell cytokines deserves attention in alcohol dependence. Although not all immune alterations found in alcohol-dependent persons are related to disordered sleep, it is exceedingly important to know whether sleep influences immunity in alcoholism because of the recognized impact of disordered sleep on infectious disease risk. Conversely, feedback systems are also operating between the brain and the immune system, and abnormalities in the expression of cytokines might contribute to sleep disturbances in alcohol-dependent persons. In this review, we identify the immune alterations found in association with alcohol dependence and discuss the implications of these findings for infectious disease risk, with particular attention to the interaction between African-American ethnicity and alcoholism in contributing to this risk. We provide evidence that sleep disruption occurs in association with alcohol dependence and that African-American alcohol-dependent persons show greater abnormalities in sleep and sleep regulatory processes than shown by Euro-American alcohol-dependent persons. The relations among alcoholism, sleep, and immunity are discussed, with an emphasis on understanding how the cytokine network is altered during sleep in the African-American alcohol-dependent populations. The potential is to use cytokine agonists or antagonists to determine whether physiologic changes in cytokines have a role in the homeostatic regulation of sleep in human beings, which has tremendous implications for the development of novel treatments of alcohol-related sleep disorders.

Keywords: Alcoholism; Sleep; Immunity; Cytokines; African-American

1. Introduction

Disturbances of sleep are prominent in alcohol-dependent patients, persist into recovery, and predict those alcohol-dependent persons who are most likely to relapse (Gillin et al., 1994). The complex cytokine network is one system that is hypothesized to be associated with declines of sleep depth and loss of delta sleep in alcohol-dependent persons. Basic observations demonstrate that proinflammatory and T helper cell subtype 1/T helper cell subtype 2 (T_H1/T_H2) cytokines have a physiologic role in the regulation of sleep with both somnogenic and inhibitory effects, depending on the cytokine, dose, and circadian phase (Opp & Imeri, 1999).

African-American alcohol-dependent persons may be particularly vulnerable to the effects of alcohol dependence, as this understudied group shows greater abnormalities in natural and cellular immune responses than shown by Euro-American alcohol-dependent persons (Irwin & Miller, 2000). Coupled with these immune changes, African-American alcohol-dependent persons also show more profound abnormalities of sleep with substantial loss of delta sleep (Irwin et al., 2000) and impairments in the homeostatic regulation of sleep as evidenced by an inability to recover from sleep loss (Irwin et al., 2002). Moreover, losses of delta sleep and increases of REM sleep correlate with alterations in the nocturnal expression of proinflammatory and anti-inflammatory cytokines in this at-risk patient population (Redwine et al., 2003). The relations among alcoholism, sleep, and immunity are discussed below, with an emphasis on understanding how the cytokine network is altered during sleep in the African-American alcohol-dependent population.

2. Infectious disease risk in alcohol dependence

Alcoholism constitutes a public health problem that affects some of the most underserved groups worldwide

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(Nelson & Kolls, 2002). Alcohol dependence is associated with an increased incidence and severity of infectious diseases, including pneumonia (Sternbach, 1990), tuberculosis (Buskin et al., 1994), bacteremia (Sternbach, 1990), spontaneous peritonitis (Sternbach, 1990), hepatitis C (Balasekaran et al., 1999), cancer (Weiderpass et al., 2001), and possibly HIV infection (Crum et al., 1996).

The mechanisms that account for increased infectious disease risk are poorly understood, although abnormal immune responses and cytokine expression are thought to contribute. In animals, chronic (days of) alcohol ingestion inhibits natural killer (NK) cell activity (Abdallah et al., 1988; Gallucci & Meadows, 1995; Meadows et al., 1989); alters interleukin (IL)-2–stimulated NK cell activity and lymphokine-activated killer (LAK) cell activity (Gallucci et al., 1994); and is associated with a reduced response of T cells to a variety of mitogens (Cook, 1998; Jerrells, 1993). Likewise in human beings, alcohol dependence is associated with declines of NK cell activity, alterations of T cells, and increases in circulating levels of proinflammatory cytokines (Irwin et al., 1990; Song et al., 1999), although results of some studies have revealed no changes of NK cell responses in alcohol-dependent persons (Kronfol et al., 1993).

Given the cross-sectional nature of the above-noted clinical studies, conclusions about the contribution of abnormal immune responses to subsequent risk of infectious disease are limited. In one prospective study, the investigators defined the expression of the proinflammatory cytokine IL-6, relative to the antiinflammatory cytokine IL-10, in alcohol-dependent persons and control subjects before and after surgical resection of upper digestive tract tumors (Sander et al., 2002). In addition, patients were monitored during the postoperative period for occurrence of infectious complications. In comparison with findings for control subjects, alcohol-dependent persons had higher rates of infectious complications after surgery, including wound infections and pneumonia. Furthermore, these alcohol-dependent persons showed a fourfold increase in the expression of IL-10, which led to decreases in the ratio of IL-6 to IL-10 and increases in the occurrence of postoperative complications (Sander et al., 2002).

3. African-American ethnicity and alcohol dependence: infectious disease risk

Morbidity and mortality rates due to infectious diseases are increased in African-Americans, as compared with findings for Euro-Americans, even after adjustment for social factors (Levine et al., 2001; Rogers, 1992). For example, the mortality rate in HIV-infected persons is higher among African-Americans than among Euro-Americans (odds ratio, 2.38) (Bright et al., 1996). In fact, there is evidence that alcoholism and ethnicity may have additive effects on disease outcomes. For example, it is well known that alcohol dependence is associated with increased mortality, and the results of one study showed that deaths because of alcohol are even higher in men and in African-Americans (Sutocky et al., 1993). Conversely, findings from another study revealed that African-Americans evidence no protective effects of moderate drinking on all cause mortality (Sempos et al., 2003). Finally, African-American ethnicity is a significant, independent risk factor (odds ratio, 2.4) for hepatitis C infection among veterans with alcohol-related liver disease (Mendenhall et al., 1993).

In view of the importance of ethnicity on infectious disease risk and progression, Irwin and Miller (2000) investigated the additive as well as interactive effects of alcoholism and ethnicity on declines of NK cell responses and alterations of proinflammatory and immunoregulatory cytokines. Natural killer cell activity, IL-2–stimulated NK cell activity, and concanavalin-A–stimulated peripheral blood mononuclear cell production of T_H1 (IL-12, IL-2), T_H2 (IL-10), and proinflammatory (IL-6) cytokines were compared in 31 hospitalized alcohol-dependent patients and 31 age-matched control subjects who were stratified on the basis of ethnicity. Alcohol dependence was associated with a reduction of NK cell activity, and African-American alcohol-dependent subjects showed the greatest decline of NK cell activity and stimulated NK cell activity compared with findings for control subjects and Euro-American alcohol-dependent persons. In addition, abnormalities of cytokine expression were found only in the African-American alcohol-dependent persons. Peripheral blood mononuclear cell production of the proinflammatory cytokine IL-6 was reduced, whereas production of the negative immunoregulatory T_H2 cytokine IL-10 was increased in the African-American alcohol-dependent persons, but not in the Euro-American alcohol-dependent population. African-American ethnicity did not have an additive effect. Rather, regression analyses confirmed that alcohol dependence and African-American ethnicity interacted to predict changes in the expression of IL-6 and IL-10 that were not associated with alcohol dependence or ethnicity alone. Although the clinical implications of these alterations in immunity are not yet known, efficient control of virus infections may depend on NK cell responses and the appropriate lymphokine profile. In addition, the increased prevalence of hepatitis C in African-Americans (Murphy et al., 1996) may reflect a lack of T_H1 cytokine production, an increase in T_H2 release, or both, similar to the immune alterations that were found in African-American alcohol-dependent persons.

4. Mediators of immune abnormalities in alcohol-dependent populations

Immune alterations observed in alcohol dependence are likely influenced by multiple factors, including, among others, differential expression of immune mediators (e.g., cytokines) owing to genetic heterogeneity (Szabo & Mandrekar, 2002); nutritional deficiencies (Watzl & Watson, 1993); and liver

disease (Deaciuc, 1997). With regard to genetic factors, higher levels of IL-6 are associated with a genetic variant in the IL-6 gene (*IL-6-174GC*) in persons who drink more than 30 g of alcohol daily but not in nondrinkers, and this overexpression of IL-6 has implications for cardiovascular disease morbidity (Jerrard-Dunne et al., 2003). In addition, advanced alcohol-related liver disease is more likely to occur among heavy drinkers who possess a single base pair substitution at position 627 (C→A) in the IL-10 promoter region. With regard to alcohol and diet, interferon-gamma (IFN-γ) is modulated by both alcohol and dietary deficiencies (Watzl & Watson, 1993). Together, the results of these studies indicate that genetic and nutritional factors contribute to immune alterations. In addition, in some instances these effects are additive, whereas in other instances differences are expressed only in the midst of heavy drinking. However, the individual contribution of genetic or nutritional (or both) factors to immune abnormalities in the general population or African-Americans (or both groups) who are heavily drinking is not yet defined.

Increasing evidence also supports the notion that biobehavioral factors might contribute to immune abnormalities found in African-American alcohol-dependent persons. Disordered sleep and sleep deprivation result in alterations of NK cell activity and cellular immunity, as measured by stimulated IL-2 production and the ratio of T_H1/T_H2 cytokines (Irwin et al., 1992, 1996; Redwine et al., 2003). Basic research findings have further demonstrated a bidirectional interaction between sleep and cytokines, in which disordered sleep has consequences for immune competence and cytokine expression has effects on sleep regulatory processes. Thus, a research approach that emphasizes the interplay of sleep on the homeostatic regulation of immunity within a psychoneuroimmunologic framework is highly relevant to understanding the mechanisms that contribute to immune abnormalities in alcoholism.

5. Alcoholism and disordered sleep

Considerable evidence indicates that sleep is abnormal in alcohol dependence. Alcohol-dependent patients commonly report sleep difficulties, and this problem is one of the most refractory symptoms to resolve over the course of recovery from alcohol dependence (Brower et al., 1998; Drummond et al., 1998; Gillin et al., 1994). Compared with findings for control subjects, alcohol-dependent persons show a reduction of total sleep time, fragmentation of sleep, and loss of stages 3 and 4 (delta) sleep (Allen et al., 1971; Johnson et al., 1970; Snyder & Karacan, 1985; Williams & Rundell, 1981), with severity of alcohol dependence being associated with abnormal sleep in alcohol-dependent persons (Gillin et al., 1990a). For example, prolonged sleep latency correlates with duration of sobriety in alcohol dependence; duration of the first REM period is associated with the number of drinks per drinking day within three prior months; and decline of delta sleep is inversely related to the maximum number of withdrawal symptoms an alcohol-dependent person has ever experienced.

6. Alcoholism and African-American ethnicity: disordered sleep

In view of findings implicating electroencephalographic (EEG) sleep disturbance as a predictor of relapse (Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998), increased attention to factors that contribute to EEG sleep abnormalities and outcome in primary alcohol dependence is needed. As reviewed above, results of recent epidemiologic studies seem to indicate that ethnicity is an important factor associated with outcome in alcohol-dependent patients. However, virtually no data have addressed the profile of sleep abnormalities by ethnicity in alcoholism. Interestingly, in affective-disordered patients, African-American patients show less total sleep, less delta sleep, and less REM sleep compared with findings for Euro-Americans who were carefully matched by age, gender, socioeconomic status, and depression severity (Giles, 1998).

Irwin et al. (2000) compared polysomnographic and spectral sleep EEG measures in male primary alcohol-dependent inpatients ($n = 31$) and age-matched comparison control subjects ($n = 31$) stratified by African-American and Euro-American ethnicity. Alcohol-dependent persons were abstinent on average for more than 2 weeks before assessment of EEG sleep. In this group of diagnostically homogeneous primary alcohol-dependent persons, the hypothesis was supported that African-American alcohol-dependent persons would have more disturbances in their sleep than would be experienced by Euro-American alcohol-dependent patients. Indeed, as compared with findings for the other three groups, African-American alcohol-dependent persons had the longest sleep latency, the shortest REM latency, and the most pronounced loss of delta sleep. In the spectral analyses, delta and theta powers were also lowest in the African-American alcohol-dependent individuals compared with findings for the other three groups. Regression analyses found that the effects of alcohol dependence on EEG measures of sleep continuity, sleep architecture, and REM sleep were determined mainly by the interaction between alcohol dependence and African-American ethnicity. Indeed, when the interaction between alcoholism and ethnicity was entered into the regression analyses, the unique contribution of alcohol dependence was no longer significant for sleep latency, delta sleep, and REM latency. Rather, the interaction term predicted these EEG sleep measures.

The cause of these EEG sleep differences between the African-American and Euro-American alcohol-dependent groups is unknown. Several factors that influence sleep physiology were controlled in the experimental design. For example, both racial groups were medication free; on similar

diurnal sleep–wake schedules; and similar in terms of socioeconomic status, marital status, education level, alcohol consumption histories, other drug use, liver function test results, and laboratory procedures. Importantly, ethnicity alone did not contribute to changes in sleep continuity, delta sleep, or REM sleep, although African-American ethnicity was associated with decreases of REM density and REM duration during the first period. Environmental stress is thought to have an impact on sleep quality and continuity, and it is reasonable to hypothesize that African-Americans, in comparison with Euro-Americans, suffer from more unpredictable and uncontrollable life events with associated chronic (months) stress (Anderson & Armstead, 1995).

Despite the severity of sleep disturbance and the extent of sleep abnormalities in alcohol dependence, there has been limited effort to understand whether sleep regulatory processes are altered in alcohol-dependent patients. Sleep deprivation is one naturalistic strategy used to probe the homeostasis of sleep. In healthy adults, sleep deprivation leads to a selective enhancement of the slow wave sleep fraction of non-REM sleep, with robust increases in stage 4 sleep (Borbely et al., 1981) and delta power (Armitage, 1995). Indeed, the generality of this finding has prompted the hypothesis of a specific relation among prior waking, sleep capacity, and slow wave sleep in which both neuronal and humoral mechanisms (i.e., the accumulation of possible sleep-promoting substances such as cytokines) regulate sleep (Borbely & Wirz-Justice, 1982; Krueger & Obal, 1993). Whether alcohol-dependent individuals show impairments in the plasticity of slow wave sleep in concert with delta sleep deficits at rest was evaluated in a further study.

Using partial sleep deprivation, Irwin et al. (2002) examined the extent to which abnormal sleep is reversible in alcohol-dependent subjects. Polysomnographic and spectral sleep EEG measures were compared in male primary alcohol-dependent inpatients ($n = 46$) and age-matched comparison control subjects ($n = 32$) at baseline and recovery sleep after a night of partial sleep deprivation in a sample stratified by ethnicity. At baseline, the alcohol-dependent individuals showed increases in stage 1 and REM sleep and decreases of stage 2, stage 3, and delta sleep compared with findings for the control subjects. Similar to a previous finding from our laboratory (Irwin et al., 2000), spectral analyses also revealed that delta power was disturbed as a function of alcohol dependence, with alcohol-dependent individuals having lower delta power. In addition, African-American ethnicity alone was associated with declines in stage 2, stage 3, delta sleep, and delta power compared with findings for Euro-Americans. These findings contrast with results of a prior study in our laboratory (Irwin et al., 2000), which showed no unique effect of African-American ethnicity on sleep. Differences may be due to the larger sample in the more recent study (Irwin et al., 2002) and the repeated nights of evaluation. As predicted, interactions among alcohol dependence, ethnicity, and night were also found. Measures of stage 4 sleep duration differentially changed across the night in the four groups. Euro-American control subjects showed a more robust increase of stage 4 from baseline to recovery night compared with findings for African-Americans, whereas stage 4 sleep was unchanged or decreased in the two alcohol-dependent groups. A similar pattern of results was also found for duration of delta sleep. Finally, the ratio of delta power has been thought to be an important measure of the distribution of delta sleep over the night. Delta ratio was also found to be lower in alcohol-dependent persons overall and in African-Americans, with group difference found during recovery night but not at baseline. In other words, sleep deprivation induced decreases of delta ratio in alcohol-dependent persons, but not in control subjects.

These findings, taken together with macroarchitectural and microarchitectural evidence of delta sleep loss in alcohol-dependent persons, further implicate abnormalities of delta sleep and its regulation in alcohol dependence. Loss of slow wave sleep is a characteristic of alcohol-dependent individuals' sleep disturbance that sleep deprivation did not ameliorate. Differences in homeostatic regulation of slow wave, stage 4 sleep were particularly striking. Control subjects showed increases of stage 4 sleep, whereas alcohol-dependent persons had recovery levels of stage 4 sleep that decreased. Similar findings were found in the comparison of the African-American control and alcohol-dependent groups, although African-American control subjects showed less robust increases of stage 4 sleep than recorded for Euro-Americans.

The neurobiologic mechanisms that underlie abnormal sleep continuity and loss of sleep depth in association with alcohol exposure remain largely unknown. Results of studies in animals indicate that cytokine abnormalities can interfere with depth of sleep (Krueger & Toth, 1994), and, as reviewed below, the complex cytokine network may be one system that contributes to the declines of sleep depth in alcohol dependence. The results of other studies show that abnormalities in the nocturnal secretion of melatonin are associated with disturbances of sleep continuity in African-American alcohol-dependent persons (Kühlwein et al., 2003).

7. Disordered sleep and cytokines in African-American alcohol-dependent persons

Results of studies with animals provide compelling evidence that sleep is closely intertwined with three classes of cytokines: T_H1 (e.g., IFN-γ), antiinflammatory/T_H2 (e.g., IL-10), and proinflammatory (IL-6) cytokines. Less is known about the relations between sleep and cytokines in human beings. However, it appears that normal sleep onset is associated with increases of circulating levels of IL-6 (Bauer et al., 1994; Born et al., 1997; Gudewill et al., 1992) independent of circadian-dependent mechanisms (Redwine et al., 2000), and that sleep amounts and sleep depth negatively correlate with daytime levels of this proinflammatory cytokine

(Vgontzas et al., 1997, 1999). Sleep also has an impact on T_H1 cytokine expression. Nocturnal levels of the T_H1 cytokines IL-2 and IFN-γ are reported to increase during sleep, with declines in the production of these T_H1 cytokines after sleep loss (Born et al., 1997).

In addition to the effects of sleep on cytokine expression, basic observations indicate a bidirectional interplay between sleep and cytokines. For example, proinflammatory, T_H1, and T_H2 cytokines have all been found to have a role in the regulation of sleep (Benca & Quintas, 1997; Krueger & Toth, 1994). In animals, proinflammatory cytokines, such as IL-1, tumor necrosis factor, and IL-6, increase delta sleep (Hogan et al., 2003; Kapas et al., 1992; Opp et al., 1991), with similar somnogenic effects reported for the T_H1 cytokine IFN-γ. In contrast, the antiinflammatory/T_H2 cytokine IL-10 inhibits slow wave sleep (Opp et al., 1995). In human beings, Spath-Schwalbe et al. (1998) found that a low dose of IL-6 (0.5 μg/kg) decreased delta sleep in the first half of the night at a time when IL-6 levels were still elevated, whereas administration of low doses of IL-2 (10,000 IU/kg) failed to alter sleep (Lange et al., 2002).

To determine the consequences of disordered sleep on immunity and to explore whether abnormal cytokine expression is associated with alterations in sleep continuity or sleep depth in alcohol dependence, Redwine et al. (2003) investigated the relation between EEG sleep and nocturnal cytokine expression in alcohol-dependent persons compared with that in control subjects. Expression of IFN-γ, IL-10, and IL-6 was measured in view of the hypothesized bidirectional relation between these cytokines and sleep. In addition, the relative balance of IFN-γ/IL-10 and of IL-6/IL-10 was determined as decreases in the ratio of these cytokines are associated with increased infectious disease risk in alcohol dependence, partly by altering cellular immune responses and NK cell activity (Biron et al., 1999; Constant & Bottomly, 1997; Street & Mosmann, 1991). Blood samples, for assessment of immune functioning, were taken repeatedly across the nocturnal period before sleep onset and during sleep to evaluate the hypothesized bidirectional relations between sleep and cytokines.

Consistent with previous findings from our laboratory, alcohol-dependent persons showed disordered sleep, with losses of delta sleep and increases of REM sleep (Gillin et al., 1990b; Irwin et al., 2000). The nocturnal production of cytokines and activity of NK cells differed between alcohol-dependent persons and control subjects. For example, a differential change in nocturnal expression of IFN-γ/IL-10 was found in alcohol-dependent persons, with a shift toward a T_H2 cytokine response after the onset of sleep and a predominance of this T_H2 response that persisted throughout the night. In contrast, control subjects showed an increase in the relative expression of T_H1 cytokines during the later half of the nocturnal period. The nocturnal production of IL-6 also changed differently in the alcohol-dependent persons versus control subjects. During the early part of the night, alcohol-dependent subjects showed lower amounts of IL-6 expression, but subsequently higher amounts during the second half of the night, compared with findings for control subjects. Finally, alcohol-dependent persons showed low levels of NK cell activity across the night compared with findings for control subjects, with increases of NK cell activity occurring across the night in control subjects, but not in alcohol-dependent persons.

To evaluate whether abnormalities of sleep architecture were associated with measures of nocturnal immunity independent of the effects of alcohol consumption, Redwine et al. (2003) examined the consequences of disordered sleep on immune measures obtained at the end of nocturnal interval. In regression analyses, REM sleep amounts predicted morning levels of both IL-6 and NK cell activity separate from the relative contribution of age, alcohol consumption histories, and baseline levels. These findings, along with evidence that IL-6 is elevated during REM sleep (Redwine et al., 2000), raise the possibility that greater amounts of REM sleep during the late part of the night contribute to the nocturnal rise of IL-6 in alcohol-dependent persons. Daytime elevations of IL-6 are also reported to occur in association with sleep loss (Vgontzas et al., 1999) and to correlate with fatigue (Vgontzas et al., 1997). Thus, morning increases of IL-6 may have implications for daytime fatigue in alcohol-dependent persons.

In addition to evaluating the consequences of disordered sleep on late-night and morning levels of immunity, the experimental design allowed for tests of whether cytokine abnormalities before sleep onset predicted subsequent differences in amounts of delta or REM sleep in the two groups. Again, with the use of a regression model, relations between cytokines and sleep were found. Expression of the proinflammatory cytokine IL-10 before sleep predicted 23% of the variance in delta sleep independent of age and alcohol consumption. In addition, the expression of IL-10 increases across the first part of night, during which time delta sleep is predominantly found. In comparison, the proinflammatory cytokine IL-6 inhibits delta sleep in human beings (Spath-Schwalbe et al., 1998). However, the current findings contrast with basic findings: Acute (minutes) doses of IL-10 inhibit slow wave sleep in rats and rabbits (Crum et al., 1996; Opp et al., 1995), whereas proinflammatory cytokines generally enhance delta sleep in rodents (Krueger & Toth, 1994). Although further experimental studies are needed to determine whether antiinflammatory cytokines augment delta sleep and proinflammatory cytokines inhibit delta sleep in human beings, the results of these studies seem to indicate that cytokines have a role in the regulation of normal sleep and that abnormalities of cytokines levels may contribute to disordered sleep in clinical populations such as alcohol-dependent persons.

Sympathetic mechanisms may account for the associations between disordered sleep and alterations of nocturnal measures of immunity. Disordered sleep and loss of sleep are associated with nocturnal elevations of sympathetic outflow,

with increases of norepinephrine and epinephrine having effects on immunity and cytokine expression (Felten et al., 1998; Ziegler et al., 1997). Although no data are available regarding nocturnal sympathetic activation in alcoholism, the influence of sympathetic mechanisms on T_H1/T_H2 cytokine expression and NK cell activity is well known. Results of studies, with both animals and human beings, have shown that stress and the release of sympathetic neurotransmitters shift the expression of T_H cytokines toward a T_H2 pattern and reduce NK cell activity (Irwin et al., 1991; Sanders & Straub, 2002), immune changes similar to those found in alcohol-dependent populations. It is also possible that alterations of the hypothalamic–pituitary–adrenal (HPA) axis underlie immune differences in alcoholism. Administration of oral cortisone acetate decreases the IFN-γ/IL-10 ratio greater than 70% (Petrovsky & Harrison, 1997), although alcohol-dependent persons who are abstinent for at least 3 weeks show blunted cortisol responses to stress (Lovallo et al., 2000) rather than hypercortisolemia. Alternatively, abnormalities in the nocturnal release of melatonin, such as decreases in the amount of melatonin or a delay in its release, may drive changes in sleep and in cytokine expression in alcohol dependence. Kühlwein and Irwin (2001) have found that in vitro doses of melatonin lead to decreases in the expression of the inhibitory cytokine IL-10, whereas results of other studies have shown that melatonin mediates IL-6 secretion in monocytes (Maestroni, 1998).

8. Disordered sleep and melatonin in African-American alcohol-dependent individuals

Sleep–wake activity is driven, in part, by circadian-dependent processes, and melatonin is thought to have effects on sleep. In the elderly and in patients with primary insomnia, early evening administration of melatonin has been found to decrease sleep latency and increase sleep efficiency (Garfinkel et al., 1995; Haimov et al., 1995; Jean-Louis et al., 1998; Zhdanova et al., 1995, 2001), but it has no effect on measures of sleep architecture or REM sleep (Zhdanova et al., 2001). Likewise, melatonin onset or peak (or both) values are altered in association with disturbances of sleep continuity in older adults and psychiatric populations (Beck-Friis et al., 1985; Dijk et al., 1999; Kennedy et al., 1989; Lindberg et al., 1998). Results of previous reports have shown that melatonin levels are abnormal in alcohol-dependent persons. However, conclusions are limited by the study of patients who had severe liver disease, were actively drinking, and/or had secondary depression, or by relying on a single plasma or urinary level, rather than on a profile of secretion (Fonzi et al., 1994; Majumdar & Miles, 1987; Moss et al., 1986; Murialdo et al., 1991; Schmitz et al., 1996; Wetterberg et al., 1992; Wikner et al., 1995).

To determine whether sleep continuity that would be associated with decreases or delays (or both) in the nocturnal secretion of melatonin, investigators in our laboratory have evaluated plasma levels of this hormone across the night, along with EEG measures of sleep continuity, in alcohol-dependent persons who were abstinent for 3 weeks or longer (Kühlwein et al., 2003). The secretion of melatonin changed differentially across the night in the alcohol-dependent and control groups in which the alcohol-dependent individuals showed decreases of melatonin during the early part of the night, compared with findings for control subjects, with comparable values of melatonin during the late part of the night. Additional analyses revealed that the onset of the nocturnal plateau of melatonin was significantly delayed in alcohol-dependent persons compared with findings for control subjects. On average, control subjects reached a nocturnal plateau of melatonin at 0.30 h ± 1.2 h, whereas alcohol-dependent persons did not achieve plateau of nocturnal melatonin until 1.95 h ± 1.16 h. Finally, prolonged sleep latency correlated with delay in onset of the nocturnal melatonin plateau.

The association between prolonged sleep latency and abnormal expression of melatonin supports the notion that abnormally low melatonin values or a delay in the nocturnal release of this hormone might contribute to the disordered sleep continuity in alcohol-dependent persons. It is also possible that delay of sleep onset leads to abnormal melatonin secretion, although this alternative is less likely because early night sleep deprivation does not alter the profile of melatonin secretion from that observed with uninterrupted sleep (Redwine et al., 2000). Thus, these findings represent another important step in ongoing investigations in our laboratory to determine the mechanisms underlying disordered sleep in alcohol dependence in this understudied ethnic group. Given other experimental evidence that evening administration of melatonin improves sleep quality in the elderly and primary insomniacs (Garfinkel et al., 1995; Haimov et al., 1995), a finding of abnormal melatonin expression has important clinical implications relevant to the treatment of disordered sleep in alcoholism.

9. New directions

Sleep problems are present during the active phase of alcoholism, and they extend for years after alcohol withdrawal and protracted abstinence (Brower et al., 2001). Furthermore, abnormalities of sleep predict relapse in recovering alcohol-dependent persons (Brower et al., 1998; Gillin et al., 1994), and they might also represent a risk factor for the onset of alcoholism in children of alcohol-dependent fathers (Schuckit & Bernstein, 1981).

In studies from our laboratory that are focused on African-American alcohol-dependent individuals, more profound abnormalities of sleep have been found in this understudied ethnic group than in Euro-American alcohol-dependent persons. The results of such studies indicate the need for interventions that prioritize this group of alcohol-dependent persons for treatment of their sleep complaints. Whereas

behavioral interventions have been substantially explored for the treatment of insomnia (Edinger et al., 2001; Jacobs et al., 1996) and have been accepted by the American Academy of Sleep Medicine as an efficacious therapy (Morin et al., 1999), no such study has been conducted in alcoholism. In addition, administration of melatonin may have treatment implications for disordered sleep in African-American alcohol-dependent persons as this group shows a prolonged sleep latency with a delay in the nocturnal release of melatonin. Melatonin treatment has been shown to be particularly effective in those patients with delayed sleep phase insomnia (Nowak & Zawilska, 1998). Finally, to understand the intricate connection between sleep physiology and immune elements, pharmacological trials with the use of cytokine agonists or antagonists are needed to determine whether physiologic changes in cytokines have a role in the homeostatic regulation of sleep in human beings. Such experimental approaches might have tremendous implications for the development of novel treatments of alcohol-related sleep disorders.

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