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Effects of sleep and sleep loss on immunity and cytokines

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Abstract

Sleep is hypothesized to be a restorative process that is important for the proper functioning of the immune system. Severity of disordered sleep in depressed- and alcoholic subjects correlates with declines in natural- and cellular immunity and is associated with alterations in the complex cytokine network. Sleep loss has a role in mediating these immune changes as experimentally induced partial night sleep deprivation replicates the kind of sleep loss found in clinical samples and induces a pattern of immune alterations similar to that found in depressed- and alcoholic patients. Despite evidence that sleep and sleep loss have effects on immune processes and nocturnal secretion of cytokines, the clinical significance of these immune changes is not known. Moreover, in view of basic evidence of a reciprocal interaction between sleep and cytokines, further research is needed to understand whether alterations in cytokines contribute to disordered sleep in patient populations. © 2002 Elsevier Science (USA). All rights reserved.

Keywords: Sleep; Immunity; Cytokines; Major depression; Alcoholism; Sleep deprivation

1. Introduction

Sleep is hypothesized to have a restorative function on immune processes (Moldofsky, 1994; Opp & Imeri, 1999). In turn, disordered sleep and sleep loss are thought to impair host defense mechanisms and impact susceptibility to viral- and bacterial pathogens (Benca & Quintas, 1997; Dinges, Douglas, Hamarman, Zaugg, & Kapon, 1995). Few studies have evaluated the association between disordered sleep and immunity in psychiatric patient populations, even though depressed- and alcoholic patients show prominent disturbances of sleep (Benca, Obermeyer, Thisted, & Gillin, 1992)

and are at risk for infectious and other immune-related diseases (Cook, 1998; Irwin, 1999).

Increasing evidence also suggests a bi-directional communication between sleep and the immune system. In addition to the effects of sleep on cytokine expression, the complex cytokine network also influences sleep and sleep depth (Opp & Imeri, 1999; Turrin & Plata-Salamán, 2000) with inflammatory cytokines having both somnogenic and inhibitory effects depending on the cytokine, dose, and circadian phase (Krueger et al., 1995; Krueger & Toth, 1994). Translation of these basic mechanisms into the clinic has implications for answering why sleep may be disordered in psychiatric populations and for the development of novel therapies for disordered sleep (Pollmächer et al., 2000).

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2. Depression, sleep and immunity

Depression serves as an excellent model to learn more about sleep-immune interactions as depressed patients exhibit prominent abnormalities of sleep (Benca et al., 1992), dysregulation of the neuroendocrine- and sympathetic nervous systems (Irwin et al., 1991b; Owens & Nemeroff, 1991), and alterations of immunity such as a reduction of lymphocyte responses and natural killer (NK) activity (Irwin, 1999; Irwin et al., 1991a). Peripheral blood NK cell activity is an *in vitro* measure of cellular immune function that correlates with host resistance to viral illness (Trinchieri, 1989).

2.1. Relationship between subjective sleep disturbance and natural killer cell activity

Prior studies have found that severity of sleep disturbance is key in identifying those depressed patients at risk for immune alterations. In depressed patients, NK activity is negatively correlated with severity of insomnia ($r = -0.33$, $p < .05$) but not with other depressive symptoms including anxiety/somatization, weight loss, cognitive disturbance or diurnal variation. In addition, the relationships between quality of sleep and immunity remain robust even when sleep is objectively assessed by EEG. For example, in depressed patients, total sleep time, sleep efficiency, and duration of nonREM sleep positively correlate with lytic activity (Irwin, Smith, & Gillin, 1992). In other words, those depressed subjects who had the lowest amounts of EEG sleep and sleep continuity showed the lowest NK activity. Whether the secretory pattern of cytokines, or some other peptide with sleep-immune effects, is altered in depressed patients to produce coincident changes of sleep and NK activity is not known.

Similar relationships between sleep and NK activity have also been found in non-depressed groups which further supports the notion that disordered sleep affects immunity independent of a mood disorder. Even in controls who have no lifetime- or current history of a major psychiatric disorder, total sleep time, sleep efficiency, and duration of nonREM sleep are positively correlated with NK activity.

3. Alcoholism, sleep and immunity

Alcoholics are another patient population who deserve attention in the study of sleep-immune

interactions. Sleep disturbance in alcoholics is marked by a severe loss of sleep continuity and depth. Moreover, disordered sleep in this population persists for months and years after abstinence. Given the substantial evidence that alcoholics are at increased risk for a number of infectious illnesses including HIV, tuberculosis, and hepatitis C and that this risk is especially increased in African-American alcoholics (as reviewed by Irwin & Miller, 2000), the consequences of disordered sleep on immunity in this population was evaluated.

Severity of alcohol dependence, age, and ethnicity are all predictors of abnormal sleep in alcoholics. Recent data, for example, indicate that African-American ethnicity and alcohol dependence interact to produce a more profound loss of delta sleep as measured by polysomnographic and spectral sleep analyses than that found in Euro-American alcoholics (Irwin, Miller, Gillin, Demodena, & Ehlers, 2000; Fig. 1). Indeed, none of the African-American alcoholics had measurable amounts of Stage 4 sleep when scored by raters blind to the group status of the EEG records. Spectral analyses of the sleep EEG further confirmed the loss of delta sleep in the alcohol dependent patients. As compared to the controls, alcoholics showed significantly lower delta (0.75–

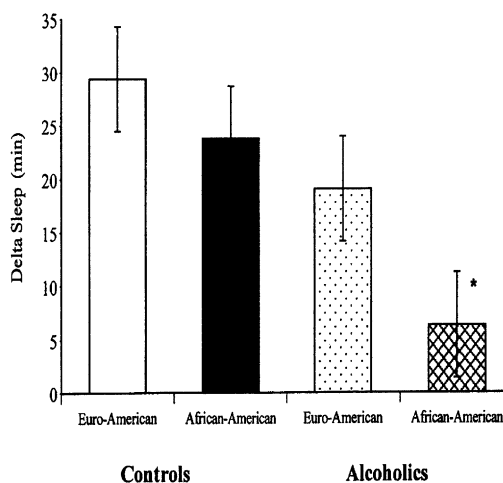


Fig. 1. Delta sleep (minutes). Data are presented as means \pm SEM. There are 17 Euro-American controls, 14 African-American controls, 17 Euro-American alcoholics, and 14 African-American alcoholics. *Planned comparisons found that African-American alcoholics showed the greatest loss of delta sleep as compared to the other three groups ($F = 4.3$, $p < .03$). (Reprinted from Irwin et al., 2000.)

4.5 Hz) activity over the whole night and especially during the first NREM period (Irwin et al., 2000).

Given the hypothesis that sleep contributes to the maintenance of the immune system, (Dinges et al., 1995; Moldofsky, 1994; Opp & Imeri, 1999), African–American alcoholics who show the most severe sleep disturbance were hypothesized to have the greatest immunological disturbances as compared to other groups. Assessment of immune function included assay of natural immunity and evaluation of levels of pro-inflammatory cytokine (IL-6) and Th-1 like (IL-2, IL-12) and Th2 like (IL-10) cytokines. In humans, two polar categories of T helper (Th) cells are described: Th1 cells secrete IL-2, IL-12 and interferon- γ (IFN) which predominantly stimulate cell-mediated responses, whereas Th2 cells secrete IL-4 and IL-10 which mainly stimulate antibody-mediated responses (Street & Mosmann, 1991).

In parallel with the increased risk of disordered sleep, African–American alcoholics had significantly lower levels of NK activity and IL-2 stimulated NK activity than the other three groups (Irwin & Miller, 2000). Furthermore, production of the pro-inflammatory cytokine, IL-6, was significantly lower in the African–American alcoholics as compared to the other three groups (Fig. 2), whereas production of the inhibitory cytokine

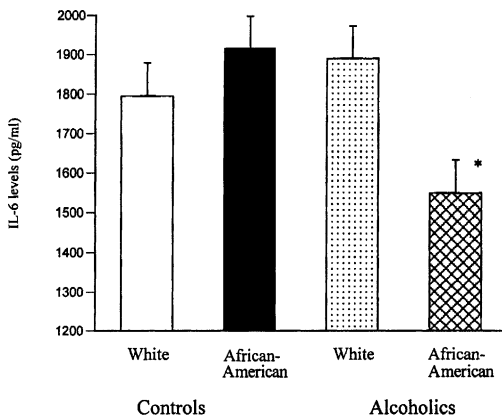


Fig. 2. Con-A stimulated production of IL-6 by peripheral blood mononuclear cells in control and alcoholic patients stratified as white- and African–American subjects. Data are presented as means \pm SEM. There are 16 white controls, 14 African–American controls, 16 white alcoholics, and 14 African–American alcoholics. *Supernatant levels of IL-6 were significantly lower in the African–American alcoholics as compared to the other three groups ($F = 7.2$, $p < .01$). (Reprinted from Irwin & Miller, 2000.)

IL-10 was significantly increased in the African–American alcoholics as compared to controls and white alcoholics (Fig. 3).

Changes in the relative expression of Th1 to Th2 cytokines, as found in the present study, may have important clinical implications in alcoholics. For example, alcoholics show a high incidence of hepatitis C (Mendenhall et al., 1993), and the chronicity of this viral infection is related to a lack of Th1 cytokine production and/or an increase in Th2 release. For example, Woitas et al. (1997) have found that hepatitis C seropositive blood donors without viremia show increased Th1 cytokine production (IFN, IL-2) in response to hepatitis C core protein, whereas seropositive donors with viremia show increases in IL-10 producing T cells.

The model put forward in this review posits an inter-relationship between sleep, and cytokine expression in which feedback systems are operating. Not only is disordered sleep thought to impact sleep, but alternatively cytokines are hypothesized to alter sleep depth and intensity. In animals, IL-1, TNF, IFN and IL-10 are involved in the physiological regulation of sleep (Krueger et al., 1995; Krueger & Toth, 1994; Opp & Imeri, 1999). For example, pro-inflammatory cytokines such as IL-1 and TNF increase delta sleep (Kapás et al., 1992; Opp, Obal, & Krueger, 1991), whereas

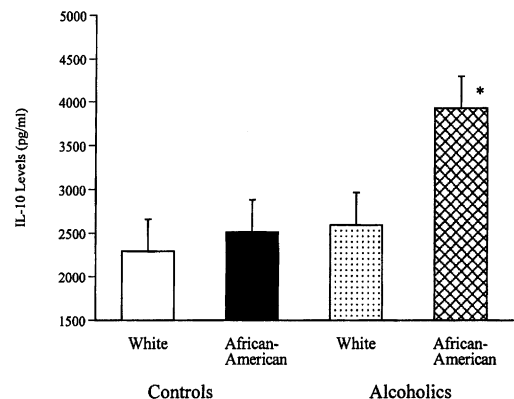


Fig. 3. Con-A stimulated production of IL-10 by peripheral blood mononuclear cells in control and alcoholic patients stratified as white- and African–American subjects. Data are presented as means \pm SEM. There are 16 white controls, 14 African–American controls, 16 white alcoholics, and 14 African–American alcoholics. *Supernatant levels of IL-10 were significantly increased in the African–American alcoholics as compared to controls and white alcoholics. ($F = 4.9$, $p < .05$). (Reprinted from Irwin & Miller, 2000.)

IL-10 inhibits slow wave sleep in animals (Opp, Smith, & Hughes, 1995). IL-6 also decreases non-REM sleep, although this action was small due to the use of a cross-species form of IL-6 (Opp, Obal, Cady, Johannsen, & Krueger, 1989). However, in humans, acute peripheral administration of IL-6 reduces delta sleep in the first half of the night when circulating levels of IL-6 are elevated (Späth-Schwalbe et al., 1998). Vgontzas have further found that daytime elevations of circulating IL-6 are associated with severity of sleepiness and fatigue in sleep disordered patients (Vgontzas et al., 1997), and that sleep deprivation leads to daytime over-secretion of IL-6 (Vgontzas et al., 1999) in which daytime plasma levels of IL-6 negatively correlate with amounts of slow wave sleep. In view of this converging evidence, it is tempting to speculate about a link between cytokines and disordered sleep in the African-American alcoholics in which cytokine abnormalities contribute the severity of sleep disturbance in these patients.

4. Partial night sleep deprivation: effects on natural and cellular immunity

4.1. Partial sleep deprivation-late night

While the findings in depressed- and alcoholic subjects studies together indicate an association between disordered sleep and immune processes, their interpretation remains obscure regarding the precise role of sleep and sleep loss. Rather than simply relying on correlational approaches, experimental strategies such as sleep deprivation are need to evaluate the effects of sleep on immunity. However, previous studies have almost exclusively used prolonged, total sleep deprivation strategies (Benca & Quinlan, 1997; Dinges et al., 1995), even though clinical samples often report symptoms of early- or late insomnia, rather than sleep loss throughout an entire night.

It is important to examine the effects of sleep loss using a naturalistic probe, namely partial deprivation of sleep during the late- or early part of the night, as a way of estimating further the role of sleep in altering immunity in depressed- and alcoholic populations. Indeed, partial night sleep deprivation was found to produce a significant reduction of cellular immunity as measured by NK activity, IL-2 stimulated NK activity, and stimulated production of IL-2 (Irwin et al., 1994, 1996) in which declines of IL-2 production was

driven by deficits in the function of both lymphocyte and monocyte cell populations. Born and colleagues have also shown that IL-2 production is affected by sleep; stimulated *ex vivo* production of interleukin-2 (IL-2) is enhanced during sleep as compared to wake and this effect is dependent on sleep, rather than circadian processes (Born, Lange, Hansen, Molle, & Fehm, 1997).

These findings extend previous investigations in humans on the immunological effects of prolonged- or total night sleep deprivation and show that even a rather modest disturbance of sleep produces an acute reduction of NK cell, T-cell and monocyte function. The clinical implications of reduced immune cell function following sleep loss is not known, although NK cells mediate protection against primary herpes virus infections and compromised natural immunity may be a prognostic factor for recurrence in patients with malignant disease (Trinchieri, 1989).

However, to interpret these findings in relationship to host defense function, it is useful to keep in mind that the immune parameters tested were obtained from peripheral blood. In the case of an acute stress paradigm in rats, Dhabhar and McEwen (1996) have shown that decreases of NK activity in the peripheral blood are accompanied by a redistribution of NK cells to tissues and an increase in NK function in these sites. In the present studies, changes of NK- and LAK activity were due to decreases in lytic activity per cell, not simply related to changes in the distribution of these cell types in the peripheral blood. Nevertheless, the question about whether sleep deprivation compromises host defense function remains unanswered. Dinges and colleagues have found that prolonged sleep deprivation induces leucocytosis and enhancement of NK cell function in humans (Dinges et al., 1994). Moreover, in a murine model of influenza viral infection, sleep deprivation was associated with increased levels of IL-1 and interferon- α and decreases of viral shedding in bronchioalveolar lavages (Renegar, Crouse, Floyd, & Krueger, 2000).

Although the immediate effects of modest loss of sleep on NK cell function are robust, an additional caveat requires consideration. These alterations of natural and cellular immune function following sleep deprivation are transient and return to basal levels following a night of recovery sleep. Indeed, rebound increases of slow wave sleep that typically occur following a night of sleep deprivation may underlie recovery increases of immunity (Irwin et al., 1996). Slow wave sleep

has been associated with increased serum concentrations of IL-2 in humans that in turn might stimulate NK cells during the recovery night (Moldofsky, Lue, Eisen, Keystone, & Gorczynski, 1986). Alternatively, endogenous interleukin-1 is implicated in the homeostatic recovery of slow wave sleep following sleep loss. Opp and Krueger (1994) have shown that the administration of antibodies to interleukin-1 antagonizes rebound increases of slow wave sleep in animals following sleep deprivation. Thus, release of proinflammatory cytokines such as interleukin-1 may occur before recovery sleep and coordinate the induction of increases of slow wave sleep as well as increases of NK responses and T helper cytokine production.

5. Effects of sleep and sleep loss on cytokines

Most studies have relied on *ex vivo* measures of immune function, and information about the effects of sleep on *in vivo* measures of immune function, particularly in relation to sleep activity and specific sleep stages, is rather limited. In six volunteers, Moldofsky et al. (1986) reported that the onset of sleep and slow wave sleep was associated with increases in circulating concentrations of IL-1 followed by elevations of IL-2. Another study has found that circulating concentrations of IL-2 change across the nocturnal period, with IL-2 levels increasing in the one hour period after sleep (Irwin, Thompson, Miller, Gillin, & Ziegler, 1999). Other measures of IL-2 taken during the night were comparable to awake values. In addition, sleep deprivation had no effect on circulating levels of IL-2 levels and there was no association between sleep activity and change of circulating levels of IL-2 (Irwin et al., 1999). The lack of a consistent influence of sleep on circulating concentrations of IL-2, as opposed to IL-2 production, is most parsimoniously explained by the local release of IL-2 at cellular sites where it is rapidly utilized, degraded, or bound to soluble IL-2 receptors for uptake. Thus, *in vivo* circulating concentrations of IL-2 may not reliably demonstrate the impact of sleep on the expression and release of this cytokine.

In contrast with the rather limited data linking sleep and IL-2, accumulating data suggest a robust interaction between sleep, circadian rhythms, and IL-6. Circulating concentrations of IL-6 show a periodicity with low values during daytime and maxima during the night (Bauer et al., 1994).

Other studies have found that patients with nocturnal sleep disturbance show altered circulating concentrations of TNF α and IL-6 (Vgontzas et al., 1997; Vgontzas et al., 1999) and that exogenous intravenous doses of IL-6 induce decreases of slow wave sleep and REM sleep (Späth-Schwalbe et al., 1998). However, two other studies failed to detect changes in circulating levels of IL-6 in relation to sleep deprivation and/or circadian rhythms (Born et al., 1997; Dinges et al., 1995), and it is not known whether nocturnal IL-6 concentrations are related to sleep activity or sleep stages.

To address these questions regarding the effects of nocturnal sleep and sleep loss on the nocturnal secretion of IL-6, circulating levels of IL-6 were measured during two nights, baseline and partial sleep deprivation early night (PSD-E). Sleep EEG was monitored along with sampling of circulating concentrations of growth hormone, cortisol and melatonin (Redwine, Hauger, Gillin, & Irwin, 2000). Growth hormone is thought to be sleep-dependent (Jarrett, Greenhouse, Miewald, Fedorka, & Kupfer, 1990; Perras, Marshall, Kohler, Born, & Fehm, 1999) whereas cortisol and melatonin are proposed to be driven primarily by circadian processes (Grønner et al., 1998; Youngstedt, Kripke, & Elliott, 1998). If IL-6 is sleep-dependent, the secretory profile of IL-6 would parallel that of growth hormone but not cortisol or melatonin. Change scores were calculated for each time point in relation to awake levels to evaluate the effects of sleep and sleep deprivation on IL-6, growth hormone, cortisol and melatonin levels (Fig. 4).

IL-6 showed a nocturnal profile that was similar to that found for the sleep-dependent hormone, growth hormone. Sleep onset was associated with an increase in circulating levels of IL-6, with peak values occurring 2.5 h after sleep onset. When sleep onset was delayed during partial night sleep deprivation, the nocturnal increase of IL-6 did not occur until after sleep onset at 3.00 h. In contrast, sleep deprivation had no effect on the nocturnal secretory profiles of cortisol or melatonin, which taken together suggest that sleep, rather than a circadian pacemaker, influences nocturnal IL-6 and growth hormone secretion (Redwine et al., 2000).

Levels of IL-6 were also compared between awake and different sleep stages over the nocturnal period (Fig. 5). Circulating concentrations of IL-6 were different across sleep stages in which IL-6 was higher during stages 1–2 sleep and REM

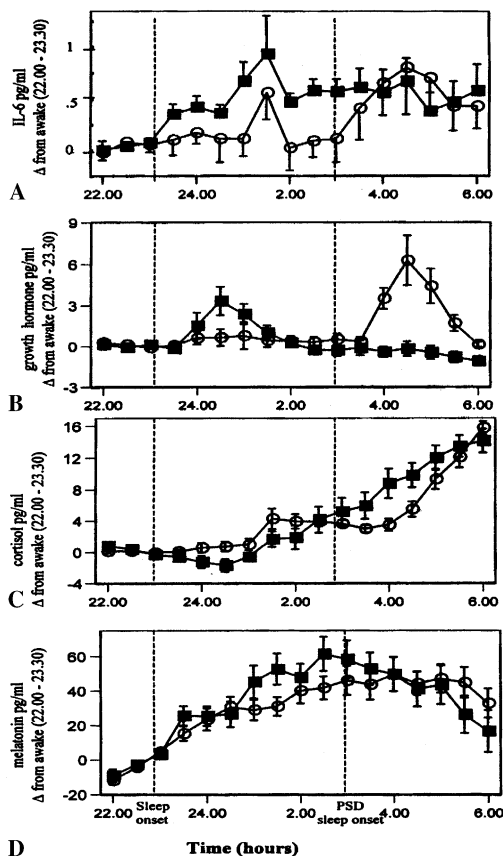


Fig. 4. Averaged change scores from awake (\pm SEM) for circulating levels of IL-6 (A), growth hormone (B), cortisol (C) and melatonin (D) in subjects during baseline (\blacksquare) and PSD-E nights (\circ). The vertical dashed line at 2300 h indicates the average time that the subjects were asleep on the baseline night; the vertical dashed line at 0300 h indicates the time that the subjects were asleep on PSD-E night. For IL-6, change in the early part of the night was elevated during the baselines- as compared to the PSD-E night ($t = 2.4, p < .05$). For growth hormone, late night change scores were elevated in the PSD-E night as compared to baseline ($t = -3.9, p < .01$). For cortisol, late night change scores were decreased in the PSD-E as compared to baseline ($t = 6.7, p < .001$). For melatonin, there were no differences between the PSD-E and baseline nights. (Reprinted from Redwine et al., 2000.)

sleep as compared to average levels during the awake period. Levels of IL-6 were similar between the awake period and stages 3–4.

The present observations linking decreases of nocturnal IL-6 to the onset of slow wave sleep are consistent with those of who found a negative correlation between slow wave sleep and IL-6

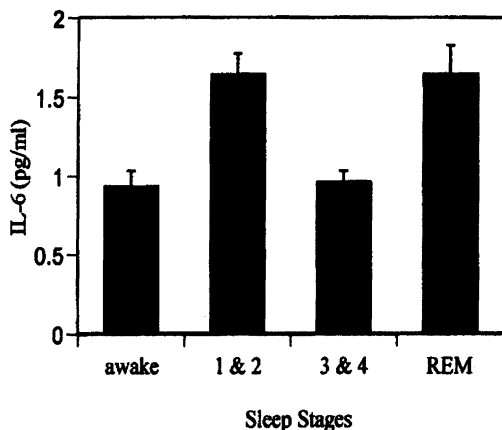


Fig. 5. Mean IL-6 serum levels across the various sleep stages. Concentrations of IL-6 were different across sleep stages ($F = 8.9, p < .001$) during the baseline night. Post hoc comparisons demonstrated that circulating concentrations of IL-6 were higher during stages 1–2 sleep ($t = 3.2, p < .01$) and REM sleep ($t = 3.6, p < .01$) as compared to average levels during the awake period. Levels of IL-6 were similar between the awake period and stages 3–4 ($t = -0.4, p = .72$). (Reprinted from Redwine et al., 2000.)

release (Vgontzas et al., 1999). Moreover, Vgontzas and colleagues found that IL-6 was decreased during a night of recovery sleep; a night of recovery sleep is typically associated with increased relative amounts of slow wave sleep (Vgontzas et al., 1999). Alternatively, as already discussed, cytokines such as IL-6 are hypothesized to have regulatory influence on sleep. Exogenous doses of IL-6 are associated with decreased REM sleep and with decreased amounts of slow wave sleep in the first part of the night followed by increases in the second half (Späth-Schwalbe et al., 1998).

There are several implications regarding the association between sleep and IL-6. Consistent with the notion that sleep has a restorative function, normal sleep is associated with enhancement of IL-6 release as well as other immune processes (Born et al., 1997). Thus, loss of sleep during part of the night may be one factor exacerbating the immunological alterations found persons who experience psychological stress or suffer from a psychiatric disorder and commonly complain of insomnia (Benca et al., 1992; Hall et al., 1998). In addition, given the association between increases of IL-6 and REM sleep, disturbances of sleep architecture may lead to abnormalities in the sleep-related secretion of IL-6. For example in conditions such as alcoholism, depression and

possibly aging where there is a relative increase of REM sleep at the expense of slow wave sleep (Benca et al., 1992), it is possible that abnormal increases of IL-6 may occur during sleep with implications for inflammatory- and cardiovascular disease risk in these populations (Musselman, Evans, & Nemeroff, 1998; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998).

6. Sleep deprivation and immune changes: possible mechanisms

Multiple pathways involving activation of the hypothalamic pituitary adrenal axis, secretion of melatonin, or release of sympathetic neurotransmitters have been postulated to mediate the relationship between depression, sleep and immune function. Both growth hormone and melatonin are secreted during sleep, and act *in vitro* to induce monocyte secretion of IL-1 and to alter cellular immune responses (Garcia-Mauriño et al., 1997; Weigent & Blalock, 1990). ACTH and cortisol release, also related to circadian rhythm, increase or suppress *in vitro* production of Th1 and Th2 cytokines depending on the stage of T cell activation (Chiappelli, Manfrini, Franceschi, Cossarizza, & Black, 1994). Finally, sympathetic tone, generally thought to decrease during the night especially during delta sleep (Irwin et al., 1999), has suppressive effects on immune function depending on the cellular target, the concentration available at the cellular, tissue, or system level, binding of α - or β -adrenergic receptors, and/or competing effects on peripheral blood immune cell traffic and cell activation (Friedman & Irwin, 1997). Production of both Th1 (IL-2) and Th2 (IL-4) cytokines is increased by sympathetic denervation (Friedman & Irwin, 1997).

Studies have begun to examine the mechanisms that mediate the effects of PSD on NK activity and have initially focused on adrenergic mechanisms. Substantial evidence has shown that the release of catecholamines and β -adrenergic receptor activation results in a reduction of *ex vivo* levels of NK activity in humans (Murray et al., 1992). The results showed that PSD was associated with increases in circulating concentrations of epinephrine and norepinephrine and that late night elevations of norepinephrine during PSD negatively correlated with change of NK activity from baseline to PSD night ($\rho = 0.48$, $p = .05$) (Irwin et al., 1999). There was no association between late night levels of epinephrine and change

of NK activity, and early night levels of catecholamines were not correlated with change of NK activity.

Among the mechanisms underlying the relation between sleep architecture and nocturnal IL-6 secretion, the release of catecholamines also needs to be considered. Catecholamines stimulate IL-6 secretion via the β -adrenergic receptor (van Gool, van Vugt, Helle, & Aarden, 1990; DeRijk, Boelen, Tilders, & Berkenbosch, 1994), and exercise-induced release of epinephrine and norepinephrine correlates with increases of IL-6 (Papanicolaou et al., 1996). Sympathetic neural activity increases during REM sleep (Somers, Phil, Dyken, Mark, & Abboud, 1993) and decreases during slow wave sleep (Irwin et al., 1999). Thus, increases of norepinephrine during REM sleep may account for the increase of IL-6 during this sleep stage. Nevertheless, as compared to awake, average levels of circulating catecholamines decrease during sleep and it not known what accounts for the average increase of IL-6 during sleep. Growth hormone and melatonin have been reported to promote pro-inflammatory and T cell function (Garcia-Mauriño et al., 1997; LeRoith et al., 1996; Lissoni, Rovelli, Brivio, Brivio, & Fumagalli, 1998), but there was no correlation between IL-6 levels and these neuroendocrine hormones in our studies.

7. Conclusions

Sleep loss is endemic in society, and loss of sleep during only part of the night is one of the most common complaints of persons who experience environmental- or psychological stress, travel across time meridians, engage in shift work, or suffer from a psychiatric disorder. The present studies indicate that only a modest amount of sleep loss impacts measures of natural- and cellular immunity and alters the nocturnal secretion of the pro-inflammatory cytokines such as IL-6. These data, together with findings in clinical samples that correlate disordered sleep with impairments in immune functioning, indicate that sleep disturbance has to be taken into account as a cause of immune alterations or as a factor exacerbating them. However, understanding the physiological- and clinical significance of these acute immunological changes observed in healthy adults requires additional research. The ultimate question about whether sleep compromises subjects' health remains unanswered. None of the studies have

employed disease specific immune measures nor intensively monitored changes in health status in relationship to administration of a sleep deprivation paradigm. Experimental approaches that involve administration of a viral challenge or biologically relevant immunization that is coupled with sleep deprivation are needed to test the impact of sleep on clinically relevant endpoints.

Partial night sleep deprivation serves as naturalistic probe to evaluate the immune changes engendered by sleep loss with minimal confounding effects due to changes in stress hormones (e.g., cortisol) or circadian phase (e.g., melatonin). Thus, partial sleep deprivation is exceedingly useful in testing the biological- and immunological responses that are linked to homeostatic drive for sleep and in exploring the reciprocal interactions between sleep and cytokines. Given the responsiveness of cytokines to disordered sleep and compelling basic evidence that pro-inflammatory cytokines are somnogenic, studies that permit more precise estimates of the temporal relationships between recovery sleep and these cytokines are needed. If changes of pro-inflammatory cytokines impact sleep and mediate deficits of sleep (e.g., loss of delta sleep) in humans, this finding could have important clinical implications in the potential use of these cytokines or their antagonists for evaluating and possibly treating disordered sleep in clinical populations.

Acknowledgments

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